Preface

Organisation

Research in Groningen

Congress

Abstracts Plenary, Oral I and Oral II

Abstracts Poster I and Poster II

Postscript
On behalf of the entire organisation of the International Student Congress Of (bio)Medical Sciences (ISCOMS) we like to explicitly thank the Healthy Ageing Network Northern Netherlands (HANNN) and Daan Bultje, director of HANNN.

ISCOMS and HANNN have worked together for many years to promote Healthy Ageing under a broad audience. Each year we strive to make our focus ‘Healthy Ageing’ more well-known. The passion of the HANNN team for Healthy Ageing is unbelievable and inspiring. Through good dialogue, we believe that this year our shared focus is even more visible. During the congress this focus will stand out within various components of the programme of ISCOMS.

A new addition is the brand new HANNN corner in the break area, the Fountain Patio. Now you can interact with colleagues from HANNN and learn more about Healthy Ageing. Of course there will also be the Healthy Ageing award, made possible by HANNN.

Without the experiences and support from HANNN this year’s edition would not have been possible. By virtue of this we devote this book of abstracts to HANNN.
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Preface
Dear participants,

It is a great pleasure to welcome you at the 26th edition of ISCOMS, the International Student Congress Of (bio)Medical Sciences.

After a year of hard work for thirty students, it is an honour to present you the tremendous programme we have put together. In response to the success of the 25th edition, when the congress was extended by a third congress day, we decided to pursue organizing a three-day congress. In 26 years, ISCOMS has grown to one of the world’s leading biomedical student congresses, where students get the opportunity to present their research on an international platform, to gain knowledge by attending a wide range of workshops and fascinating keynote lectures, and to extend their network by joining the extensive social programme we have to offer!

The focus of our congress is Healthy Ageing, which we implemented in our workshops, keynote lectures and social programme. However, to achieve Healthy Ageing, we not only need to focus on preventing and curing diseases and adopting a healthy lifestyle, we also need to take care of our planet. This year, we tried to make our congress more sustainable by for instance digitizing the Book of Abstracts.

On Monday, we will start with the pre-course, a day in which enthusiastic students can improve their research skills by attending informative masterclasses. During the following three congress days, we will welcome prof. Henning Schliephake MD DDS PhD, prof. Hein A.M. Daanen MD PhD, Nobel Laureate prof. Mario R. Capecchi PhD, and last but not least prof. Andrea B. Maier MD PhD. After the congress, thirty young and talented foreign (bio)medical students will kick-off with the ISCOMS Research Fellowships, the two-week research internships at Research Institutes of the UMCG.

Each day will end with a social programme. There will be a swinging salsa dancing workshop, the recreational evening, where you can join diverse activities, the formal dinner at the gorgeous ‘Der Aa-Kerk’ where you can meet other participants while enjoying a culinary three-course dinner, and last but not least, our one and only World Wide ISCOMS Night! On Friday, we will leave Groningen to see what more the Netherlands has to offer during the Post Congress Tour and we will visit Leeuwarden, which has been appointed as the European Capital of Culture of 2018.

On behalf of the entire Organising Committee, I wish you all a wonderful time and I hope you will enjoy the congress as much as I did organizing it!
A warm word of welcome to all guests attending the 26th edition of the International Student Congress Of (bio)Medical Sciences in Groningen (ISCOMS). This annual meeting is an exciting event organized by students from Groningen for students from all over the world.

For many years already, the ISCOMS event is one of the highlights of the University Medical Center Groningen (UMCG) academic year. We congratulate the Organising Committee for putting together yet another great scientific programme. This year’s ISCOMS edition hosts an impressive number of renowned speakers highlighting very different aspects of biomedical research. Attending lectures presented by such marvellous speakers will be a source of inspiration to all participants.

International contacts and collaborations are essential to move science forwards. The UMCG and the University of Groningen foster such international contacts, not only in their research collaborations but also at all levels of the educational system. We have strategic partnerships with many institutions across the world. ISCOMS is one of the vehicles to expand the international ties, by bringing students from a great variety of countries together and host them during a week in Groningen.

ISCOMS offers a unique opportunity to all participants to get a flavour of the best that science can offer, and for many to present their work to a friendly audience. It is also often the starting point for new collaborations and friendships for life.

So: enjoy the excellent science, the relaxed atmosphere, the intense discussions and above all the beautiful city of Groningen. Have a great conference!

Prof. Marian Joëls PhD
Dean of the faculty of Medical Sciences
Member Board of Directors UMCG
Organisation
The ISCOMS Executive Board exists of nine (bio)medical students of the University of Groningen and is formed in June 2018. Some of us were already part of the Organising Committee in previous editions of ISCOMS, but not everyone. During the intensive start of the year, we had to collaborate closely in our office next to the Faculty of Medical Sciences of the University of Groningen. In the first months, we accustomed ourselves to the functions and responsibilities and became close very quickly. During the meetings we had twice a week, we made sure every task was done and everyone was informed accurately.

Besides our professional collaboration, we also became friends. Despite the group is filled with completely different personalities, we made sure we complemented each other and helped each other in case it was needed.

We want to express our gratitude to the entire Organising Committee for their amazing effort they have put into this edition. Furthermore, we want to thank the First Year Crew, the advisory board and everyone who made ISCOMS 2019 possible.

We are honoured to welcome you to the 26th edition of the International Student Congress Of (bio)Medical Sciences at the University Medical Center Groningen and we wish you an extraordinary time!

**Eva Ensink**  
Marijn Hendriksz  
Willem Kooij  
Christa Brethouwer  
Arman Nobacht  
Berber Dantuma  
Pien de Zoeten  
Victor Moskalenko  
Carolyn Blommers
Advisory board

ISCOMS is a congress organised by and for students. Thirty biomedical students are responsible for all scientific, financial, and organisational aspects of the congress. As the congress is organised every year by a new team of students, the advisory board can assist in the continuity of the congress. They have helped organising ISCOMS for many years now. Their expertise, experience and contacts are of great support for the Organising Committee. The advisory board consists of four seniors from the University Medical Center Groningen (UMCG).

Advisory board:

Prof. Paul de Vos PhD
Full professor immunoendocrinology
at the University of Groningen
Advisor since 2009

Prof. Ruud R.M. Bos DMD PhD
Dental surgeon at the UMCG
Advisor since 2012

Matijs van Meurs MD PhD
Intensivist at the UMCG
Advisor since 2016

Robert A. Pol MD PhD
Vascular and transplant surgeon
at the UMCG
Advisor since 2018

We would like to thank the advisory board for their continuous support and useful advice.
The president, secretary and treasurer are responsible for overseeing the Organising Committee, as head of the Executive Board.

The main task of the president, Eva Ensink, is to lead the Executive Board. She is responsible for the whole organisation of the congress. Additionally, her task is to find suitable day chairs and jury members.

The secretary, Marijn Hendriksz, is the contact person of the organisation. During this year she will work closely with the president. Besides that, she will be responsible for all of the registrations, both online and during the congress. She will manage the registration desk and will be happy to welcome you.

The treasurer, Willem Kooij, is responsible for all of the budgetary aspects of the congress. As treasurer, he is in charge of the incoming and outgoing money and he will manage the budget estimate for the congress.

Furthermore, we will take care of the evaluations and statistics of our congress, to improve ISCOMS for the upcoming years.

Enjoy ISCOMS 2019!

*Eva Ensink*
*Marijn Hendriksz*
*Willem Kooij*
The Scientific Programme committee (SP) consists of six enthusiastic biomedical students, which will ensure an interesting and educative programme!

Christa is the chair of SP, her task is to coordinate the committee and she is responsible for the scientific programme of the congress. Besides this, she coordinates the abstract selection.

During the pre-course you will have the chance to improve your research skills in masterclasses and attend interesting speed-keynotes. Michelle is responsible for the pre-course.

On three congress days, internationally well-established researchers will share their knowledge and experiences with us in keynote lectures. Eline is in charge of those keynote lectures. There are also a lot of exciting workshops you can participate in, ranging from practical workshops to patient demonstrations and interactive ethical workshops. Hartger and Inez are responsible for those workshops. Additionally, you will have the opportunity to attend a patient lecture and to see a recorded operation.

For students who are interested in doing research in Groningen in the University Medical Center Groningen (UMCG), we organise the two-week ISCOMS Research Fellowships (IRF). These short internships will take place directly after the congress and will bring you into contact with researchers. The IRF are organised by Irene. Another possibility in order to meet researchers from the UMCG is the workshop “Speeddating with researchers”. This workshop will be organized during the congress and will provide you the opportunity to talk to researchers of various Research Institutes of the UMCG.

SP enjoys creating a challenging and diverse scientific programme for ISCOMS 2019 a lot and is looking forward to meeting you all in June 2019!
Sponsors and Fundraising

ISCOMS cannot take place without its financial funding. The committee of Sponsors and Fundraising takes care of the financial resources. Our committee consists of four enthusiastic, dedicated students who will make every effort to make this congress financially possible. We will do our very best to contact and inform companies in order to establish a good cooperation between the sponsors and ISCOMS.

Due to the fact that we are one of the biggest student congresses for biomedical sciences within Europe and due to the numerous national and international students attending, we have a great amount of sponsoring opportunities to offer. Hence making ISCOMS very attractive for potential sponsors.

Being a sponsor of ISCOMS allows extensive prospects for both large and small companies to create more awareness for the company, subsequently acquiring new business opportunities. Our purpose is to establish an agreement of mutual benefits. Companies can present themselves with a stand or they can choose for an appearance of their logo on for example our website or our congress bag. A new initiative that has started five years ago, is the business lunch. Selected motivated students will get acquainted with different companies during a luxurious lunch in a private space.

Apart from contacting potential sponsors, we will also subscribe several funds to support ISCOMS. Besides that, one of our committee members is going to assist the treasurer with the finances during the congress. We are also responsible for the journal subscriptions which the presenting participants can win during the congress. And last but not least, we carry the responsibility to provide the participants with a full congress bag which contains a variety of gadgets, magazines and information.
The International Contacts committee takes care of the international part of ISCOMS. Our daily responsibilities include the worldwide promotion of our congress, and helping participants who encounter problems with their registration, Visa application, or other difficulties while organising their trip to Groningen, the Netherlands.

We take care of the promotion by e-mailing, calling, and sending promotional materials across the globe. In this worldwide promotion we are supported by our highly motivated ambassadors, who were inspired by their own ISCOMS experience. Furthermore, we are responsible for the social media community of ISCOMS, including Facebook, Twitter, Instagram, Snapchat, and many more. Besides following us on social media, you can also subscribe to our monthly newsletter in order to be kept up to date about the latest progress in the organisation of our congress.

All incoming emails of students who want to submit their abstract or who are seeking additional information about ISCOMS are answered by us. We are also the committee that has contact with the embassies when aiding students in obtaining their Visa. Lastly, we are responsible for the Travel Grants for students that require financial aid in order to attend our congress.

As the International Contacts committee we are constantly looking for new contacts around the world that would like to help us with promoting ISCOMS 2019. If you believe you can help, please send an email to iscoms@umcg.nl. If you have any other questions regarding promotion, Visas, Ambassadors, Travel Grants, or anything else, please send us an email and we will be glad to help you!
The Hosting and Logistics committee is not only responsible for the social programme, but also for the accommodations, the City Tour, the Post Congress Tour and the plan of action during the congress.

The social programme is the perfect way to extend your social contacts. While enjoying dinners and informal drinks you can meet people from many different countries and cultures. On Sunday, there will be a City Tour through the centre of Groningen and a welcoming party, including a pub quiz. Monday, we will enjoy a dance workshop and on Tuesday the ISCOMS Recreational Evening will take place, which includes a cycling tour, a visit to the FC Groningen stadium, a tasting of classical Dutch cheeses, and more. On Wednesday there will be a formal dinner in the historical church: Der Aa-kerk. We will conclude the last congress day on Thursday with the World Wide ISCOMS Night. At this party you can show everyone what your country has to offer by wearing traditional clothing and bringing your national music and snacks. To finish off the congress, there will be a Post Congress Tour on Friday. On this day, we will show you a piece of our beautiful country. This year, we will go to Leeuwarden, the city of culture of the Netherlands. Together with about 100 foreign participants we will enjoy a day full of fun after an intense week of science.

As the Hosting and Logistics committee, we will also provide you with options for accommodation during the congress. One of the options is ‘Stay With a Student’. This is the perfect opportunity to experience the student life of Groningen! Furthermore, we can give you advice on ho(s)tels.

We ensure you that we will do everything to make this congress memorable. We hope you are as excited as we are, and we are looking forward to seeing you!
The Public Relations commission is responsible for the promotion of ISCOMS in Groningen and the rest of the Netherlands. We maintain contact with Dutch study associations and Dutch universities. Furthermore, we are responsible for all graphic design and the overall visual appearance of ISCOMS.

To reach as many students as possible we are in contact with all other (bio)medical faculties in the Netherlands. They help us to get a lot of attention to ISCOMS, for example, by hanging posters in their faculties and by posting information about the congress on their website. Furthermore we communicate with faculty coordinators to make sure they stimulate their students to visit ISCOMS. Besides this we are setting up a promotional campaign and communicate with the press.

Together, we are also responsible for the graphical design of all material that will be handed out at the congress and of all flyers, posters, booklets and cards that are spread all over the world by our colleagues from the International Contacts committee. Last but not least we compose and design the Book of Abstracts that will be published in our app and on the website. This book contains information about the congress and the people involved and contains all abstracts of participants who present their research at ISCOMS 2019.
The main goal of the Research & Development (R&D) committee of ISCOMS is to innovate and improve every upcoming edition of the congress. We establish this by extensive evaluation that helps us determine what we can and should change. Also, we try to think of how it could be changed. The R&D committee makes sure the improvements are implemented at the upcoming congress. Brainstorming is a great part of our committee’s task. Thinking of new ideas that will enhance the congress. These ideas come from the evaluation sheets that participants fill out and, for example, brainstorm sessions with the entire organisation that our committee organises.

A good example of innovation of ISCOMS is the application for smartphones that has been set up and launched four years ago. In the meantime, it has been updated by R&D and we will try to keep improving it every year.

Furthermore, R&D is responsible for the website. This means that, in addition to providing the website with its lay-out, we also keep the website up to date at all times to ensure you will receive the correct information.

We maintain partnerships, because these are vitally important to the improvement of medical congresses. Each year we evaluate these partnerships and look for possible new ones. As partners, ISCOMS tries to become an even more inspiring congress.

Each year ISCOMS chooses a charity to support. By organising activities our committee raises money to support this charity. This year we chose the UMCG Alzheimer Foundation. This foundation supports research in the UMCG to find out the cause, develop new treatments, and find ways to lower the risk of dementia. We have collected money for this foundation among others by organising a pub quiz and by participating in a run called the ‘Nacht van Groningen’.
The First Year Crew of ISCOMS 2019 is a team of 15 first year (bio)medical students. This team will offer assistance during the entire congress. They will be helping out the organisation with a variety of tasks, such as guiding participants to workshops and helping with the sale of merchandise. Another completely different task the First Year Crew faces is selecting and handing out the First Year Jury Award to the best plenary speaker of ISCOMS 2019. The First Year Crew will also be present during the social programme, together with the organisation.

In conclusion, you will be able to find them everywhere and they are always eager to help. The First Year Crew will also be wearing bright-coloured t-shirts during the congress, so they will be very recognisable. Do not hesitate to ask them any questions!

**Koen Eppink**  
*Nienke van der Linde*  
*Pieter Dahmen*  
*Renz Wierper*  
*Tom Lieverse*  
*Justine Zijlstra*  
*Hylke Prins*  
*Maureen Meeuwis*  
*Isa van Sambeek*  
*Gijs Stuart*  
*Sharon Groen*  
*Victoria Heijnsbroek*  
*Carien Dermer*  
*Stephanie Braunius*  
*Martijn Bouman*
The ambassadors of ISCOMS are participants or presenters from a previous ISCOMS who were so enthusiastic about the congress, that they decided to apply to become a well-respected ambassador. They play a vital role in our international promotional campaign. Each year ambassadors are selected after the congress and maintain the ambassadorship for exactly one year, until the next congress takes place. However, some ambassadors can be reselected as they provided such devotion to ISCOMS that they cannot be missed. The ambassadors start their main promotion in October. They share our social media posts and promote ISCOMS in their country by distributing posters and flyers. Some of the ambassadors even organise meetings or give presentations to explain how great their experience was at ISCOMS. The enthusiasm and excitement that we wish to bring across to everyone all around the world, is accomplished by this group of young excited scientists. We have ambassadors from over 25 countries worldwide, who we have close contact with. On the website you can find all of our ambassadors and their passion is evident in their words.

"ISCOMS was the best experience in my entire career as a medical student. The congress is a once in a lifetime experience both in terms of academics and meeting people from across the globe. Those three weeks were truly a 'Science beyond borders' experience for me. I promise, you will have a wonderful time like I did."

Rizana Riyaz
ISCOMS 2019 ambassador in India

For any question about ISCOMS, Visa applications, travelling to Groningen, or anything else, please do not hesitate to contact our ambassadors, as they will be more than happy to help you out. Their e-mail addresses can be found on our website.

If ISCOMS 2019 also excited you and makes you want to share your experience with others, you can apply to become an ambassador for ISCOMS 2020. Help us with our promotional campaign yourself! During the congress you can fill in an application form by contacting the ambassador coordinator or you can apply by sending an e-mail with a short motivation letter to iscoms@umcg.nl in days following the congress.
The Annual International Medical Students (AIMS) Meeting is an international medical congress hosted at the Faculty of Medicine of the University of Lisbon, entirely held by students every year during the month of March. With renowned national and international speakers and a huge range of practical workshops on several medical fields, this is one of the most complete and alluring congresses for students in Europe. Since it is a three-day congress, each day is based on a subject module and all the scientific lectures related to it. Besides this, there are also keynote lectures, clinical and Scientific Competitions, a Research Competition (poster, oral and plenary sessions) and a science speed dating with doctors and researchers.

It is our main purpose to promote an enriching scientific setting for learning, interaction and communication among students, health professionals and researchers alike. As we deeply value the social and cultural dimensions of the human being, the AIMS Meeting also includes a social program and a charity program for all its participants.
The Asian Medical Students’ Association (AMSA) International is a peak representative organisation for medical students from across Asia, the Asia-Pacific and beyond. Training doctors from 16 Member Nations and 11 Associate/Observer Nations combine to share knowledge, undertake activities and social services and create international and transcontinental friendships.

AMSA was officially founded in Manila, Philippines in 1985, and from this day it has been an active, dynamic and exciting student-led, not-for-profit, non-political organisation. Today, with members and friends spanning the globe AMSA has an active student-exchange program, regularly undertakes national and regional projects, provides humanitarian assistance at times of need, produces quarterly student publications and liaises with the World Health Organisation, the Association of Medical Doctors of Asia, and many other international and regional medical student organisations.

Since it was first established in 1979 and the first conference was held in Mahidol University of Thailand, the Asian Medical Students’ Conferences have been a key focus for the organisation. Now it is held biannually in January/February and July/August. These events see over 700 students from across the world to learn from each other, teach their fellow peers and develop lasting friendships.

The AMSA Vision is Knowledge, Action and Friendship. Three areas we continuously strive to in our members and peers through our organisational missions:

- **Knowledge:** We promote scientific and medical activities to increase and expand our knowledge whilst training to become the medical professionals of the future
- **Action:** As medical students, we are concerned for the community around us and endeavour to do things for the benefit and improvement of our fellow citizens
- **Friendship:** As future doctors, we aim to build and maintain a good relationship among our colleagues of the Asia-Pacific and beyond
The Antwerp Medical Students’ Congress (AMSC) is a five-day event full of promising lectures and workshops (such as a Da Vinci robot, laparoscopy and burn wounds workshop) for students, by local and international speakers.

Visit the beautiful city of Antwerp from September 10th - 14th 2019 and attend the AMSC while also getting the chance to enjoy what our diamond city has to offer!

Registrations are now open! Visit our website www.amsc.be to register.

Check out our Facebook page AMSC 2019 and our Instagram @antwerpmsc for more updates!
The Brazilian International Congress of Medical Students is an incredible opportunity for every medical student who wants to learn from renowned keynote speakers, to practice skills at hands-on workshops and to build up a network with other students from all over the world. Our scientific programme includes, also, outstanding student researchers (posters and oral presentation), presented to a professional audience. This congress also comprises sensitization activities - and, of course -, great food and social programme! We combine it all with an inspiring environment, with smart people and a lot of fun!

This congress has everything to boost your personal and medical development. You can’t spend these 3 days in a better way! Don’t waste this amazing chance, join us!

Exploring the theme “Adversities in Care: the challenging journey of becoming a doctor and making a difference”, the 8th edition of BRAINCOMS will take place in São Paulo, at UNIFESP - Universidade Federal de São Paulo, Brazil. It will happen from 19th to 21st of September.

For more information, please, check our website: http://www.braincoms.com/2019/ or send us an email: braincoms@gmail.com.

You can also find us on Facebook: https://www.facebook.com/BraincomsMedicalCongress/.
The European Medical Students’ Association (EMSA) is a politically neutral, non-governmental, non-profit and independent organization that represents students from individual medical faculties across geographical Europe. It was established in 1991 in Brussels, Belgium and is currently uniting 96 medical faculties in 24 different European countries. European Medical Students Association seeks to improve the health and quality of care of the European citizens, by acting as a conduit for increased interaction and sharing of knowledge between European medical students in the areas of medical education, medical ethics, medical science and European integration. The main objectives of EMSA are to form a network between European medical students in order to facilitate European integration and develop a sense of European identity, to represent and voice the opinions of medical students of Europe and to promote the highest standards in European medical education, science and ethics.

Our webpage: [www.emsa-europe.org](http://www.emsa-europe.org)

Official BlueMist blog: [www.bluemist.eu](http://www.bluemist.eu)
Since its foundation in 1989, the ESC has become one of Europe’s most established student biomedical conferences. It is our mission to promote the scientific exchange between students, scientists, and researchers worldwide. Every year, more than 500 participants from over 50 countries take the opportunity to attend keynote lectures by renowned experts, participate in exciting workshops, present their research, and explore the vibrant city of Berlin!

This year’s conference will be held from the 25th until the 28th of September 2019. The topic of the conference will be Future Aging – Today’s Research, Tomorrow’s Medicine, aiming to sensitise our participants to the medical challenges arising from an aging population. For more information, visit our website at www.esc-berlin.charite.de!

E-Mail: janita.mintcheva@charite.de
Facebook: www.facebook.com/escberlin
Twitter: www.twitter.com/escberlin
The International Conference for Healthcare and Medical Students (ICHAMS) is held annually at the Royal College of Surgeons in Ireland (RCSI) to allow undergraduate healthcare and medical students to present their research to peers and professionals in this field. Our mission is to create a platform for students across the globe to interact with one another in order to challenge conventional methodology and encourage innovation in medicine.

The conference includes workshops offered on a variety of topics as well as keynote speakers representing incredibly impactful realms of medicine. Centred in the vibrant city of Dublin, Ireland, we also encourage our participants to embrace the rich culture via city walking tours and traditional Irish music.

The first conference was held in 2011 and in 2013, the conference received the Irish Healthcare Award for student project of the year. As we continue to grow as an international conference, we are continuing to follow our mission of creating a global platform for innovation and medical research. The 8th edition of the ICHAMS conference will be held on the 21st until 23rd of February, 2019. For more information visit our website www.ichams.org or contact us at ichams@rcsi.ie!
ICMS – International Congress of Medical Sciences is an international event that welcomes more than 500 participants every year.

The congress gives the opportunity to students and young doctors from all over the world to present their research in a set of Preclinic, Therapy, Surgery and Public Health poster and oral sessions. We aim to inspire innovation and promote academic quality through an outstanding list of hands-on workshops and keynote lectures by world-renowned scientists and doctors.

The organizer of the forum is Association of Medical Students in Bulgaria – Sofia (AMSB-Sofia).
International Federation of Medical Students Associations of the Netherlands (IFMSA-NL) is an organisation for Dutch medical students, situated at each of the eight medical faculties. Our mission is to offer future physicians a comprehensive introduction to global health issues. Through our programming and opportunities, we develop culturally sensitive medical students, intent on influencing the transnational inequalities that shape the health of our planet. Besides being the Dutch member organisation of the worldwide federation called IFMSA, IFMSA-NL is also part of the European Medical Students Association (EMSA).

More information at:

http://www.ifmsa.nl/
The Leiden International (bio)Medical Student Conference (LIMSC) is the largest biennial student conference in the world. Founded in 1999, LIMSC strives to create an opportunity for (bio)medical students to present their research and to share knowledge whilst meeting their peers. The 10th edition in 2017 had more than 500 participants from 63 nationalities.
We believe that there is a huge need of international meetings for medical students. Such events provoke discussion, lead to mutual cooperation, provide inspiration and encourage young scientists to further endeavors. Therefore, we would like to invite you to Warsaw International Medical Congress (WIMC) 2019 edition. Students from all over the world are welcome to register and present their research, attend workshops, keynote lectures and thematic sessions.

Keynote lectures will be given by famous specialists including:

- Professor Marta Kwiatkowska, Fellow of Trinity College Department of Computer Science, University of Oxford, UK
- Professor Oliver Kurzai, Institut für Hygiene und Mikrobiologie, Leibniz Institut für Naturstoff-Forschung und Infektionsbiologie – Hans-Knöll-Institut, Jena, Germany
- Emilie Karafillakis, Research Fellow & PhD Candidate at London School of Hygiene and Tropical Medicine, London, UK

Students can choose to present their research in 29 different scientific sessions including Dentistry Session, Case Report Sessions and PhD Students Session.

WIMC offers a wide range of workshops – during the previous edition participants could choose out of 30 different fields.

The rich social programme is another reason for joining the congress – the opening ceremony, gala dinner, medical students’ party and “Warsaw by night” are events that should not be missed!

Last year there were 650 young scientists from 35 countries willing to present over 400 papers during the 14th Warsaw International Medical Congress. These numbers mean that a great event is approaching.

Please visit our website, Twitter and Facebook profile for more details:

http://wimc.wum.edu.pl/
https://www.facebook.com/warsawinternationalmedicalcongress
https://twitter.com/_wimc
WIMC video: https://goo.gl/yQ3hB1
Registration: http://wimc.wum.edu.pl/participation/registration/
The Young European Scientist Meeting (YES Meeting) is an annual international students conference which takes place at the Faculty of Medicine of the University of Porto, Portugal.

After thirteen editions, the YES Meeting still aims to provide students the opportunity to learn about groundbreaking and innovative discoveries from world-class scientists, and, more importantly, to hence their motivation in doing research! Therefore, the students have the chance to present and discuss their own research projects on Oncology & Molecular Biology, Neurosciences, Physiology & Immunology, Internal Medicine, Surgery, Public Health & Medical Informatics. You’ll also have the possibility to improve your skills with a wide variety of workshops and enjoy the beautiful city of Porto through various kinds of social programmes, where you can enjoy Porto’s great weather and its vibrant culture. We invite you all to take part in the 14th YES Meeting, which will take place between the 12th and 15th of September 2019, whether as a Presenting or a Non-Presenting student. We are waiting for you!
Zagreb International Medical Summit is a student scientific congress organized by members of EMSA Zagreb and the Students’ section of Croatian Medical Association. For 18 years in a row, as November nears its end, Zagreb becomes the meeting place of biomedical students and young doctors from all around the world. In the next 4 days, participants take part in various medical and non-medical workshops, listen to engaging lectures from esteemed professors, present their scientific work and enjoy the social program. Another special feat of ZIMS is that it is one of few congresses in Europe where the abstracts of papers presented by active participants will be published as a supplement to Liječnički vjesnik, a journal indexed in EMBASE/Index Medicus. Best works are published as full texts! It’s our aim that when it’s time to go home, you’ll be going back not only with new knowledge and practical skills, but also with great memories of your time in Zagreb and a few new friends.
Research in Groningen
The route to become a physician-scientist

Are you dreaming of becoming a physician who is trained to combine the care for patients with clinical science? The Junior Scientific Masterclass (JSM) of the University Medical Center Groningen (UMCG) presents you a unique possibility to realize this dream.

Because of the major growth in biomedical knowledge, there is a dire need for physicians who can translate fundamental insights into new clinical applications and, simultaneously, generate scientific questions based on clinical observations (i.e. translational research). In order to enforce clinical research, it is essential to immerse medical students into research during the pre-clinical phase of their curriculum. Therefore, the JSM educational programme encourages motivated students to seek research experience from the start of their medical education.

The JSM educational programme also enables medical students to apply for MD/PhD projects. The MD/PhD programme consists of clinical internships (‘co-schappen’) combined with a financed period of two extra years within the medical curriculum. This programme gives medical students the opportunity to successfully finish both their medical education (MD) and a PhD project within a period of eight years.

The JSM educational programme in the Bachelor phase, the ‘Bachelor Honours programme’, consists of two phases. The first phase entails getting familiar with research within (the Graduate School Medical Sciences of) the UMCG (GUIDE, BCN, SHARE and Kolff Institute). The second phase is meant to be a turning point and consists of a one-week course of intensive training in clinical research for a (selected) group of students, called the COMPASS week. In the second phase the students are also stimulated to choose their own line of research and apply for research grants.

The JSM programme has grown considerably since it started in 1999. In the period of 2001 until 2014, more than 850 students have been awarded Pilot Projects and 480 students an MD/PhD project. Until now, more than 200 students successfully mastered the MD/PhD programme. In 2008, the ‘Mandema-stipendium’ was introduced which enables young physician-scientists (MD PhD) to combine their specialist training with research and establish their own line of research.

The route to become a physician-scientist is challenging, but also highly rewarding. It represents an investment for a lifelong learning in the field of academic medicine.

Additional information: www.jsmgroningen.nl or j.s.masterclass@umcg.nl
The Graduate School of Medical Sciences (GSMS) trains and educates excellent researchers and promotes excellent research. The GSMS is responsible for all Research Masters and PhD education and training programmes within the University Medical Center Groningen (UMCG), including the ‘Junior Scientific Masterclass’, a special research-oriented programme (BSc Honours and (D)MD/PhD programme) for talented medical and dental students. At the GSMS we are outward-looking in our approach, working with people and partners from all over the world. All of our postgraduate programmes are conducted in English and in fact half of our doctoral students are international.

Research within the UMCG ranges from fundamental to patient-oriented (clinical) research. The UMCG has organized all its research in five Research Institutes that each have developed research programmes around specific aims and objectives. The five Research Institutes collaborate in the GSMS to educate and train research masters and PhD students for future scientific leadership. We endeavour to encourage and shape students to become critical and independent thinkers. Both PhD and Research Master students have the opportunity to tailor their programme to fit their own personal research interests.

More information for international students: www.groningenbiomed.com

Do you have questions about doing a PhD in the UMCG, and you want to ask someone with experience? Please go to www.iscoms.com/about-iscoms/research-2/research-in-groningen/

Here you will find a list of students who are from abroad and came to the Netherlands to start a PhD in the UMCG. They are happy to help and answer all of your questions!
PhD training programmes (MD/PhD, 2+2, 3 or 4 years)

The GSMS PhD curriculum has an extensive programme (choice of more than 70 courses and activities) offering each PhD student the opportunity to join courses and activities related to the Research Institute they participate in and their own specific research interest. Five Research Institutes work together to organize these courses and activities each based on their own field of expertise: 1. Behavioural and Cognitive Neurosciences (Research School BCN/Research Institute BCN-BRAIN), 2. Chronic Diseases and Drug Exploration (Research Institute GUIDE), 3. Cancer Research (Cancer Research Center Groningen), 4. Health Research (Research Institute SHARE) and 5. Biomedical Engineering (Research Institute W.J. Kolff).

The Graduate School offers different types of PhD training programmes.
1. The MD/PhD programme offers medical and dental students the opportunity to combine the last two years of the Master phase with a PhD training (two additional years of research training financed by the UMCG) to obtain a (D)MD and PhD degree upon completion.
2. The Abel Tasman Talent Programme (also see below) offers PhD Sandwich Scholarships (2+2 years). First, PhD students pursue a two years PhD education and training programme at their home university followed by a two years programme in Groningen (funded by the UMCG) where the thesis will be completed.
3. Upon successful completion of their Research Master’s programmes GSMS Research Master’s students have the opportunity to apply for a three-year PhD education and training programme within the GSMS.
4. Finally, within the UMCG regularly regular four-year PhD positions are available (offered by individual researchers or research groups) and posted on the UMCG website.

Degree awarded: PhD

Research Master’s programmes (2 years)
The Graduate School of Medical Sciences administrates three Research Master’s Programmes:

1. Behavioural and Cognitive Neurosciences (BCN/BCN-BRAIN)
The Research Master Behavioural & Cognitive Neurosciences, organised by the Research School of Behavioural and Cognitive Neurosciences (BCN), concentrates on three focal and closely related areas of particular strength within the field of neurosciences: Animal and human behaviour (B-track), Cognitive neuroscience and cognitive modeling (C-track), and Molecular and clinical neuroscience (N-track).

The programme is characterized by its interactive setting, offering the unique chance of a truly multidisciplinary neuroscience education, while becoming an expert in one specialist track. The programme is essentially tailor-made. Depending on the student’s research interest (or future career aspiration) the student can design his or her own training programme.

More information: www.rug.nl/research/behavioural-cognitive-neurosciences/education/researchmaster/
2. Clinical and Psychosocial Epidemiology (CPE-SHARE)
Clinical and Psychosocial Epidemiology (CPE) is a selective two-year research master. The programme is unique in the sense that students are encouraged to focus on their individual development as a researcher. Therefore, classes are taught in small groups. Students can choose additional courses that suit their personal interests and moreover, research will be conducted side by side with scientists who are leading experts in their field.

Mental and physical health and the reciprocal relationship between these two forms the basis of the programme. There is a strong focus on prevention, diagnosis and treatment of physical and mental health conditions. The central idea is that psychological, biological and social aspects all play a role in any physical condition. Students conduct research in several populations, including children, adults and elderly, with or without a physical or mental condition.

More information: www.rug.nl/masters/clinical-and-psychosocial-epidemiology-research/

3. Medical Pharmaceutical Drug Innovation (MPDI-GUIDE)
The selective two-year master programme Medical and Pharmaceutical Drug Innovation (MPDI) offers research-minded students small-group interactive teaching in an international and multidisciplinary environment. You will learn how to creatively apply knowledge and we will train you to become a critical and analytical scientist. You will be challenged with exciting cutting-edge research and methodologies and will learn how to critically read the literature, design novel research questions, translate hypotheses into testable research plans, and write scientific essays.

As a student you can focus on your interests and ambitions by participating in one of the following tracks after the first semester: Oncology, Medical Neurosciences and neurological diseases, Infection and immunity, Medical nutrition and metabolic diseases, Medical system biology and bioinformatics, Drug innovation.

More information: www.rug.nl/masters/medical-and-pharmaceutical-drug-innovation/

Degree awarded: Master of Science

More information:
http://www.rug.nl/research/gradschool-medical-sciences/phd-programme
http://www.umcg.nl/NL/UMCG/werken_in_het_umcg/vacatures/Pages/default.aspx

Abel Tasman Talent Programme
The Abel Tasman Talent Programme (ATTP) supports high-potential international students to excel in the field of (bio)medical or pharmaceutical sciences. Two types of financial support can be distinguished:

Financial support for students from one of our so-called ‘preferred partner universities’
Financial support for exceptionally talented students from other institutions

**Erasmus Mundus Action 2 mobility**

The European Committee's programme ‘Education and Training’ offers many opportunities to stimulate education, training and exchange of Research Master's and PhD students of the European Union and beyond. The University of Groningen participates in many of these exchange programmes.

More information:  
https://www.rug.nl/about-us/internationalization/global-focus/europe/erasmus-programme
Research Institutes

Research Institute BCN-BRAIN
Director: prof. Iris E.C. Sommer MD PhD
Central theme: Behavioural and Cognitive Neurosciences

The Research Institute BCN-BRAIN was established in 2005 and is part of the Graduate School of Medical Sciences and of the Research School of Behavioural and Cognitive Neurosciences. BCN-BRAIN promotes research that is aimed at understanding the function of the healthy brain and dysfunction of the nervous system with reference to neurological and psychiatric disorders. Research is focused on translational collaboration between lab-based (molecular- and cell biological) and hospital-based (clinical) researchers integrating different levels of neuroscience research.

Research Institute GUIDE
Director: prof. Jos G.W. Kosterink PhD
Central theme: Chronic Diseases and Drug Exploration

The main asset of the Groningen University Institute for Drug Exploration (GUIDE) is the integration of clinical, biomedical and pharmaceutical research stimulating translational research and researchers with a keen eye on the complete spectrum of biomedical research: from bed to bench to drugs. Ageing is a central theme as most chronic diseases are age-dependent. Research focuses mainly on 1. Lead discovery, development of new drugs, drug delivery and advanced formulation technology and 2. Translational research on molecular and cellular mechanisms underlying disease (etiology and pathophysiology) and on research related to treatment of disease, e.g. in the context of clinical trials and by using relevant animal models.

Cancer Research Center Groningen (CRCG)
Director: prof. Mark van Vugt PhD
Central theme: Cancer Research

The Cancer Research Center Groningen (CRCG) organizes and facilitates high-quality, oncology-related research activities within the UMCG and University of Groningen. All research activities at CRCG share the overall perspective of 'healthier and longer lives of cancer patients through improved care'. Research is performed at the fundamental, translational and clinical levels and organized in a coherent and effective manner in several research programmes to achieve fundamental, clinical and societal relevant research output. Ultimately this leads to personalized cancer therapy, thus reducing the unintended side effects of treatment on normal tissues and improving the quality of life of cancer patients.

Research Institute SHARE (Science in Healthy Ageing and healthcaRE)
Director: prof. Maarten J. Postma PhD
Central theme: Prevention in Health Research

SHARE's mission is to identify determinants and consequences of illness and Healthy Ageing, conducted within inter-/multidisciplinary programmes, in close connection with societal parties and often based on observational data. The institute investigates and evaluates factors and interventions that are population-, patient- and/or healthcare-system-related. It adds knowledge on prevention of and adaptation to disease, enhancing societal participation of patients with chronic somatic and mental disease and cost-effectiveness and efficacy of pharmaceutical, medical, life-style and psychosocial interventions. Notably,
a life-course perspective is taken, addressing research questions spanning from the preconception period, through infancy, reproductive and working ages to old age.

Research Institute W.J. Kolff
Director: prof. Yijin Ren DDS PhD
Central theme: Biomaterials

The primary objective of the W.J. Kolff Institute for Biomedical Engineering and Materials Science is to bring together pre-clinical and clinical research groups and to establish a center of expertise for the entire stage of biomedical materials science and its application involving basic materials science, medical product development and clinical evaluation that will contribute to the long-lasting well-being of patients in need of biomaterial implants and extra-corporal support systems. Research is conducted within four thematic research programmes each with their own specific theme: 1. Bioadhesion, biocompatibility and infection, 2. Nanobiotechnology and advanced therapeutic materials, 3. Restoring organ function by means of regenerative medicine and 4. Maintaining oral health and oral function.

European Research Institute for the Biology of Ageing (ERIBA)

The mission of the European Institute for the Biology of Ageing (ERIBA) is to gain more knowledge about the causes of age-related disease. Our studies are focused on the mechanisms that result in loss of cells with age and the decline in the function of old cells and tissues. We aim to develop novel strategies to prevent or combat age-related disease and to provide evidence-based recommendations for healthy ageing. Our approach is based on curiosity, communication and collaboration. Group leaders and their team working with unique model systems and technology platforms meet regularly and share their knowledge and expertise to accelerate discoveries.

ERIBA aims to become a world-class research Institute, internationally renowned for its cutting-edge basic science. It aims to attract top-level scientists of all levels of seniority. Staff scientists are expected to publish their papers in high impact journals with quality prevailing over quantity. There is ample opportunity to explore uncharted territory and embark on high-risk projects that can yield major breakthroughs. The development of novel tools and technology required to answer fundamental questions is a strategic focus. Long-term investments in developing a strong research programme are favoured over short-term activities leading to incremental results. Staff scientists define their own research agenda, but are also expected to collaborate with fellow scientists in ERIBA and its affiliated local and distant institutions.

Education at ERIBA

Research in ERIBA is strongly connected with education and training of the future generation of Biology-of-Ageing researchers. ERIBA aims to be “the place to be” for the best students by offering comprehensive training in some of the best Biology-of-Ageing laboratories in the world. We have developed a cutting-edge graduate curriculum in Ageing biology in which students will be exposed to a wide variety of model systems and approaches. The extensive training experience of the international faculty at ERIBA in other research institutes worldwide ensures an optimal educational and research environment.

Undergraduate students

ERIBA welcomes applications from undergraduate (pre-BSc and MSc) students who wish to pursue an internship in one of the ERIBA labs. Students would typically be enrolled at a biomedical, chemical, pharmaceutical, medical or bioinformatic programme at their home University or University of Applied Sciences (“Hogeschool”). Prospective students are invited to explore the different research teams on the ERIBA website, and motivate in their application the interest for the lab of their choice. Although some short-term internships may be available, we prefer rotations that last for 5 months or longer.
PhD students
ERIBA offers an exciting environment to pursue a PhD degree in the Biology of Ageing. We aim to train PhD students to become independent, creative, multi-skilled scientists. Students devote most of their time to their own research project, but will be enriched by and benefit from the complimentary research activities in neighbouring labs. A large variety of courses, all taught in English, is available for PhD students to acquire additional skills. A PhD degree from one of the ERIBA labs will optimally prepare students for the next phase in their University or corporate career. PhD students in ERIBA will be enrolled in the Graduate School of Medical Sciences and defend their thesis at the University of Groningen. PhD projects in ERIBA typically will last 4 years.

Postdoctoral fellows
We are always searching for outstanding postdoctoral candidates with a proper training in molecular or cell biology who wish to solve scientific questions in ageing science. We encourage postdoctoral candidates to directly contact one of the ERIBA Principle Investigators to explore job opportunities.

For more information, please visit www.eriba.umcg.nl
Are you a young, ambitious (bio)medical student and would you like to experience doing research in the University Medical Center Groningen? The ISCOMS Research Fellowships (IRF) give students who present their research at ISCOMS the opportunity to experience doing research in the Netherlands and, more specifically, in the UMCG.

Various Research Institutes of the UMCG are interested in welcoming young and talented foreign (bio)medical students into their institutes and giving them the opportunity to experience what doing research in the UMCG is like. As a student you will get the chance to perform research at a leading institute, meet top-researchers, and learn more about the possibilities of doing a PhD-programme in the Netherlands. The IRF are available for presenting participants on the congress only.

When your abstract is accepted to be presented at our congress, you will receive information about the IRF application. It is important to know that we only have a limited amount of thirty places for students to participate in these projects. Therefore, we have a special application procedure for the IRF-projects.

Besides a lot of biomedical projects, there are also a few Research Fellowships that focus more on the technical view of biomedical sciences. Students who study applied physics, biomedical engineering, chemistry or such, will also be able to apply for these very interesting Research Fellowships.

The fellowships take place directly after the congress, from the 10th of June until the 21st of June 2019. This makes it convenient for students to participate in the IRF. Besides this, no additional costs are charged. Accommodation and pocket money will be provided for the duration of the project free of charge.

The IRF are a challenging two week programme in which students are expected to actively participate in research at one of the UMCG Research Institutes and gather a great deal of knowledge related to the topic of research. As a student you get the chance to perform research at a leading institute, meet top-researchers and – more importantly – learn about the possibilities of doing a PhD-programme in the Netherlands. There are many foreign students who have been able to start a PhD-programme in the UMCG thanks to following a fellowship.

Unfortunately, the application period has already been closed for this year’s edition. If you are interested in the IRF of ISCOMS 2020, you can get an impression by reading about this year’s projects and apply in March 2020 for next year’s edition.
Project A: Pathobiology of lymphoma  
**Supervisor:** Lydia Visser MD PhD  
**Department:** Pathology and Medical Biology

Research in the pathogenesis of several types of lymphoma, as well as new targets for treatments can be performed. Our research group exists of pathologists, molecular biologists, haematologists and immunologists. The exact subject will be specified together with the student taking into account his or her interests. The topic will depend on what intriguing questions the team is currently working on and will depend on what is possible in the limited time.

Project B: Repair of kidneys with normothermic machine perfusion before transplantation  
**Supervisor:** Prof. Henri Leuvenink MD PhD, Cyril Moers MD PhD  
**Department:** Surgery

Organ transplantation is a lifesaving therapy for patients suffering from end-stage organ failure. Due to the growing success of transplantation more patients are on the waiting list and more donors are needed. This leads to an increasing percentage of poor quality organs. In the Surgery Research Lab researchers are trying to find new therapies to reduce or repair the injury by using machine perfusion techniques accompanied with pharmacological intervention.

The IRF student will be involved in a project in which protective treatments during perfusion will be administered to ex vivo perfused porcine kidneys. The IRF student will work together with a PhD student and will get full insight into the principles of machine perfusion. A laboratory introductory course will be part of the research stay. Depending on the progress and experience of the student, a sub-project will be designed. It is mandatory for the IRF student to follow the Transplantation Medicine Summer School which will take place in the first days of the IRF period:

http://www.rug.nl/gradschoolmedicalsciences/informationfor/summerschools/transplantationmedicine/index

Project C: Food ingredients and immunity  
**Supervisor:** Prof. Paul de Vos PhD  
**Department:** Pathology and Medical Biology

During recent year it has been shown that food ingredients are not only important for nutrition but also for keeping our immune system active. Many food ingredients such as dietary fibers are consumed by the 100 trillion bacteria in the intestine and form immune active components such as short fatty acids. This fine-tunes immune responses against pathogens. Also some food components can directly interact with the immune system. In this project you will be involved in testing food ingredients that might be instrumental in enhancing responses against pathogens or reduce the chance on ageing associated diseases.
Project D: Nephrology
Supervisors: Martin de Borst MD PhD, Jaap van den Born MD PhD
Department: Internal Medicine, Division of Nephrology

In Nephrology Department various projects are running using diverse methodologies (see 1-6). You are invited to express your interests in one of these fields (being either clinical, epidemiological, human- or animal, in vivo- or in vitro experimental) to indicate what sub-project interests you most.

1. Patients with renal disease and progressive renal function loss, are being studied with respect to the mechanisms via which the urinary protein leakage results in renal function loss. Both non-diabetic- and diabetic renal disease are studied. Most of these patients are included in clinical trials to study the efficacy of regimen to lower proteinuria and to prevent progressive renal function loss.

2. Our center also has a large population of renal transplant recipients. These patients are monitored very closely, and regimens aimed at increasing the duration of graft function as well as patient survival are being studied currently. A large database including biobanked urine and plasma is available in TransplantLines.

3. General population cohorts are studied to detect which parameters lead to initiation of progressive renal function loss and its complications. The cohorts PREVEND and Lifelines from the general population are good examples. The natural course is followed to study possible causes of morbidity and mortality in relation to renal parameters.

4. Lifestyle and the kidney. Many lifestyle factors are involved in the risk of long term renal function loss. These include smoking as well as nutritional habits, such as excess caloric intake leading to obesity and diabetes, excess sodium intake and sedentary lifestyle. The mechanisms of renal damage induced by these lifestyle factors are being studied in patients as well as experimental animals, and the effect of lifestyle intervention measures on the course of renal disease is being studied. Nutritional monitoring is part of this project.

5. Various animal (rat) models of proteinuria and progressive renal disease are being studied, in order to unravel the mechanisms of renal damage and to optimise antiproteinuric and renoprotective treatments. Focus points are the RAAS – Vitamin D – FGF23 axis; progression of structural tubulo-interstitial changes; and the interplay of proteinuria and dyslipidaemia.

6. Innate immunity and the kidney. Within this research line we try to unravel the role of innate immune system (complement system, leukocytes, chemokines) in chronic renal damage in proteinuric and transplanted kidneys. By intervention of novel heparin(oid) related drugs we aim to reduce the contribution of inflammation in chronic renal tissue remodelling. Research is largely done in vitro and in experimental models of renal disease.

Project E: Systems genetics of immune-mediated diseases
Supervisor: Sebo Withoff MD
Department: Genetics

The Immunogenetics group of prof. Cisca Wijmenga PhD (Department of Genetics of the UMCG) investigates the role of genetic variation in the aetiology of autoimmune diseases (e.g. celiac disease, inflammatory bowel disease and multiple sclerosis) and the role of the gut microbiome in health and disease.

The data used for these studies are mostly generated by next generation sequencing. The generation of the data and the analyses requires a broad range of scientific expertise. In her group, a dynamic and highly interactive environment is created in which bioinformaticians, geneticists, statisticians, molecular biologists and immunologists work together closely.
Important findings published by professor Wijmenga are (a) the shared genetics of autoimmune diseases, (b) 95% of the autoimmune disease associated single nucleotide polymorphisms (SNPs) affect gene expression rather than gene function, (c) eQTL effects of GWAS SNPs on long non-coding RNAs (lncRNAs), (d) the enrichment of ‘lymphocyte specific’ long intergenic non-coding RNAs (lincRNAs) in celiac disease associated loci, and a range of environmental factors affecting the human microbiome.

The current ongoing research is for a large part focused on the prioritisation of SNPs, genes, pathways and cell types affected in autoimmune diseases, on in vitro experiments to validate the function of the prioritised candidates (with currently a strong interest in the mechanisms of lncRNAs) and on determining how host genetics affects microbiome composition.

Depending on the interest of the student, we will design a working plan for the two-week internship.

**Project F: Personalised medicine in patients with diabetes and tuberculosis**

*Supervisor: Job van Boven MD, Jasper Stevens MD*

*Department: Pharmacology*

The department of Clinical Pharmacy & Pharmacology of the UMCG performs preclinical, translational, and clinical research. Research is focused on personalised medicine and targeted pharmacological therapy, mostly applied to diabetes mellitus type 2 (and its cardiovascular and nephropathic complications) and infectious diseases (tuberculosis (TB), HIV).

Topics within personalised medicine include optimisation of pharmacotherapy (individual response variability, therapeutic drug monitoring, pharmacogenetics, biomarkers, molecular imaging), conducting large clinical trials with investigational medicinal products, drug utilisation research (real-world outcomes such as medication adherence, safety and cost-effectiveness) and development and regulatory assessment of new drugs and dosage forms.

We offer the IRF project that will focus on drug-related issues in patients with diabetes mellitus type 2 and/or tuberculosis. Are TB drugs clinical effects affected by co-existing diabetes? Do the current TB and diabetes drug trials reflect real-world patient’s characteristics? What is needed for personalised medicine in TB and diabetes treatment? What can we do to optimise adherence to treatment? To assess these issues, you can make use of our in-house database (GIANTT, [www.giantt.nl](http://www.giantt.nl)) with anonymised patient records of over 20,000 patients with diabetes type 2, TB drug data and learn from our experienced multidisciplinary team of physicians, pharmacists, and clinical researchers.
**Project G: Development of an instrument to measure the functionality of people with prosthetic hands**

*Supervisor: Paul F.M. Krabbe PhD, Karin M. Vermeulen PhD*
*Department: Epidemiology*

In medicine, a prosthesis is an artificial device that replaces a missing body part, which may be lost through trauma, disease, or congenital conditions. Prosthetics are intended to restore the normal functions of the missing body part. Prosthetic amputee rehabilitation is primarily coordinated by a prosthetist and an inter-disciplinary team of health care professionals including psychiatrists, surgeons, physical therapists, and occupational therapists. A person’s prosthesis should be designed and assembled according to the person’s appearance and functional needs. Different types of prosthesis exist and it is not clear what type is most effective.

Health-status or health-related quality of life instruments are necessary tools to evaluate health outcomes in patients. Available instruments in the field of hand prosthesis are domain specific, lengthy, and developed from the experts’ perspective. Yet, there is not a patient-centered instrument that evaluates the perceived health status of hand prosthesis patients. We aim to develop a patient-centered compact (short) and attractive instrument that can be used to evaluate the health status or functional status in patients with a hand prosthesis.

Research question/problem definition: In this project students will first understand what patient-centered health status is and how it can be measured. Then, we will look for health items that are essential to choose for our planned instrument. Next, students will develop a graphical representation of the health items (HealthFan) and formulate a strategy to select the most relevant health items among the generated set of candidate items. Finally, the students construct a prototype of the Hand Prosthetic instrument (HealthSnApp).

**Project H: Next generation sequencing: first diagnostic one-stop show in clinical microbiology and infection prevention**

*Supervisor: Prof. John Rossen MD PhD*
*Department: Genomics*

Our research group “Personalised Microbiology” that is closely linked to Prof. Friedrich’s research group “Genomics of Infection Prevention” has successfully implemented the use of next generation sequencing for routine clinical microbiology and infection prevention. The method is used to determine the genetic relationship between pathogens (used to guide infection prevention measures) and for the molecular detection and further characterisation of (emerging) pathogens. This includes analyses for revealing (new) antibiotic resistance mechanisms and for determining the virulence of pathogens resulting in improved risk assessment and infection prevention. In addition, based on comparing whole genomes of bacteria, tailor-made diagnostic tests are developed used for specific detection of outbreak and/or virulent bacterial strains.

Nowadays we apply the method in several projects dealing with the above-mentioned topics. Our projects are not only focused on patient samples but also to animal, food and water samples. Apart from characterising the micro-organisms (including viruses) the interaction between them as well as with their host is studied.

The student will be able to participate within one of the running projects depending on his or her interests as well as on the possibilities available in June 2019.
Project I: Epidemiology and pathophysiology of heart failure
Supervisor: Prof. Adriaan A. Voors MD PhD
Department: Cardiology

Heart Failure is a syndrome defined as typical symptoms (such as dyspnea and/or impaired exercise tolerance) caused by a functional or structural cardiac abnormality. It is one of the fastest growing epidemics with a poor quality of life and a very high morbidity and mortality. The department of cardiology is a world leader in research in the epidemiology and pathophysiology of heart failure.

During a two week fellowship, the candidate can experience current projects that we are running on the use of omics (genomics, transcriptomics and proteomics) to gain a better insight in the pathophysiology of several specific phenotypes of heart failure.

Project J: Big data and deep learning in cardiology
Supervisor: Prof. Pim van der Harst PHD, Hilde Groot, Jan-Walter Benjamins
Department: Cardiology

The department of Cardiology of the University Medical Center Groningen (UMCG) performs preclinical, translational, and clinical research. One topic of interest is focused on understanding complex associations among molecular, clinical, and imaging data to enhance our understanding of the development and progression of cardiovascular disease. The electrocardiogram, molecular data and imaging data of large datasets are analysed by novel machine learning techniques to progress this field.

We are seeking students that are enthusiastic about applying deep learning techniques to create new ways for analysing big data sets of electrocardiographic, imaging, genetics, and biomarker data. You will need to become comfortable with some programming, as it touches the area of computational biology and computer science. In this project you will learn about ECG/imaging-patterns, and learn how to create deep learning algorithms to recognize these patterns. These algorithms may then be used to uncover new biological pathways and to better understand the pathophysiology of cardiovascular disease.

Project K: Regulation of hematopoietic stem cells
Supervisor: Prof. Gerald de Haan MD PhD
Department: European Institute for the Biology of Ageing (ERIBA)

The group is interested in the unique genetic and epigenetic program that distinguishes stem cells from non-stem cells. The research group of Prof Haan uses state-of-the art genomic tools to search for common molecular events in stem cells at distinct phases in hematopoietic development and aging. The team studies how stem cells can be transplanted, and which mechanisms ensure their proper homing and subsequent engraftment to the bone marrow after transplantation. Stem cells are defined by their ability to self-renew and their ability to differentiate into all lineages within a tissue. The group is addressing how stem cell self-renewal alters with age, and how enhance stem cell renewal can be exploited in stem cell expansion protocols in vivo and in vitro.

Please check our website for more information: (http://eriba.umcg.nl/groups/ageing-biology-and-stem-cells/)
Project L: Current systems of left and right ventricle unloading during extra-corporeal life support.

Supervisor: Prof. Massimo Mariani MD PhD
Department: Cardio-thoracic surgery

Patients necessitating an extracorporeal (ECLS) life support, either in the form of veno-arterial (ECLS) or in the form of an isolated left ventricular (ECLS) support, experience often left or right ventricular overloading. To prevent this problem the student will provide an overview of the existing right and left ventricular temporary unloading systems. The student will be attending clinical cases of ECLS in the UMCG, if they are available during the two week IRF-period.

Project M: Chromosomal instability in cancer and ageing

Supervisor: Floris Foijer MD PhD
Department: European Research Institute for the Biology of Ageing (ERIBA), UMCG

In each cell division, our complete genome is replicated and segregated equally over the two emerging daughter cells. Cancer cells have an intrinsic tendency to mis-segregate chromosomes occasionally, a process known as chromosomal instability or CIN. CIN results in cells with an abnormal chromosomal content, a state defined as aneuploid. Indeed, more than two out of three cancers are aneuploid, suggesting that CIN somehow contributes to the transition of normal cells into cancer cells.

Paradoxically, CIN and the resulting aneuploidy pose a growth disadvantage to non-cancer cells, suggesting that cancer cells have found ways to cope with the detrimental consequences of aneuploidy. In our lab, we try to map and understand how aneuploid cells transform into aneuploid cancer cells. We developed state of the art mouse models, in which we can provoke CIN in tissues of choice at time points of choice. Using these models, we have shown that whereas CIN is indeed detrimental for some stem cells, it is remarkably well tolerated by epidermal cells, although aneuploid mouse epidermis appears prematurely aged (Foijer et al, PNAS 2013). Furthermore, we found that CIN alone is not sufficient for cancer, but that predisposing mutations (such as p53 inactivation) are required for aneuploidy to contribute to malignancy (Foijer et al, PNAS 2014; Foijer et al, eLife 2017). The main aim of the lab is to develop new intervention strategies that can selectively kill aneuploid cells. For this, we need to better understand the biology of aneuploid cells and which (epi)genetic alterations are required to transform aneuploid cells into their malignant counterpart.

In this IRF project, you will be introduced into the exciting field of chromosome biology. This includes time lapse microscopy, cytogenetics, mouse models, pre-clinical intervention, and state of the art technology such as single cell sequencing (see Bakker et al, Genome Biology 2016) and RNA sequencing. While 2 weeks will not be sufficient to finish a full project, your IRF stay will reveal how we try to fulfil our mission to identify aneuploidy-killing compounds and we will involve you the experiments that are ongoing at that moment in time. More importantly, you will also learn whether the field of chromosomal instability is a field for you to pursue in your future research avenues. Looking forward to seeing you in June!

Project N: Bronchoscopic lung volume reduction for patients with severe emphysema

Supervisor: Dirk-Jan Slebos MD
Department: Groningen Research Institute of Asthma and COPD

Bronchoscopic lung volume reduction (BLVR) is a last resource treatment option for patients with severe emphysema. Options include both valves and coils. These treatments reduce hyperinflation, alleviating lung mechanics, resulting in less dyspnoea. However, little is known on the effects of BLVR on lung compliance and airway resistance.
In this project we want to evaluate the effect of BLVR on changes in airway resistance using resistance/volume changes, and the differences on these outcomes for valves and coils.

The way we want to evaluate this effect is through retrospective data analysis, literature review and we will be attending actual BLVR procedures.

Project O: Depression and cognition in later life: one size fits all?
Supervisor: Marij Zuidersma MD
Department: Psychiatry

Interventions according to a standardized protocol will hardly, or never, be effective for all or the majority of patients. As a consequence, it is increasingly being recognized that patient care needs to be individualized, both in general medical health care as well as mental health care settings. In contrast to this increasing thrive for more individualized patient care, the majority of studies still have a nomothetic design. That is, nomothetic studies calculate group-average estimates, thus yielding knowledge on “what is true on average”. Although nomothetic studies can be useful if one wants to make inferences about the average tendency, prevalence or risk in the population, their results will not generalize to individual patients, which might be an obstacle in developing more personalized interventions.

An alternative to the nomothetic study is the single-subject study. Instead of comparing individuals with each other, in single-subject studies individuals are compared with themselves. By using multiple assessments within one individual, an individual serves as his or her own control. In these 2 weeks you will learn more about when and why to use a single-subject study. We have time-series data of 10 older persons with depression and cognitive impairments, comprising 63 daily assessments of sleep, depression, cognitive functioning, physical activity and several other variables. You will get the opportunity to evaluate for one or all of these persons the temporal relation amongst these variables, and will compare your results to what is known from previous studies that used a group-based approach.

Project P: The effects of age, muscle size, muscle architecture, and walking environment on the variability walking patterns
Supervisor: Claudine J.C. Lamoth MD
Department: BCN-BRAIN Human Movement Sciences

Walking is an important form of daily physical activity. More than 60% of all elderly aged 80 years or older have walking or balance disorders. Impairments in walking may have several important health-related consequences. Walking impairments may reduce physical activity with serious implications for mobility, fall risk, healthcare use and mortality. Also walking impairments reduce the quality of life. Walking can thus be considered as an important predictor for health status especially in older adults.

Also, healthy aging is associated with changes in walking and mobility. Changes in walking with ageing include a slower walking speed, a decrease in stability, smoothness and complexity of the walking pattern. Underlying mechanism of these age-related changes in the walking pattern are unclear. An important change with advancing age is the reduction of muscle size, called sarcopenia. We hypothesize that age related changes in muscle mass, will contribute to the changes seen in the walking pattern of older adults. However, until now this has not been examined in previous studies. Therefore, the purpose of the project is to determine how muscle size and age are related changes in walking patterns.

In this project the walking pattern of 15 healthy young and 15 healthy older adults will be assessed.
Properties of lower leg muscles in this study will be quantified using ultrasound measurements. Changes in the walking pattern will be examined using Inertial Measurement Units (sensors that record accelerations of the movement). The walking pattern will be measured both in natural (inside/outside) and laboratory environments (treadmill walking).

Contribution / activities of fellow:
Under supervision of the PI (Claudine Lamoth) and a PhD student (Iris Hagoort) you will assist with the measurements, contribute to a literature review, and can perform a part of the data-analysis according to your specific interest.

You will participate in weekly lab meetings involving students of all levels (Bachelor, Master, PhD) and 2-weekly Healthy Ageing research meetings with staff, Master and PhD students.

**Project Q: Stem cell therapy to treat radiation-induced side effects**
*Supervisor: Prof. Rob P. Coppes MD PhD*  
*Department: Cell Biology and Radiation Oncology*

Xerostomia (dry mouth syndrome) can be caused by dysfunctional salivary glands (SG) due to aging, radiotherapy for head and neck tumours and the auto-immune diseases such as Sjögrens syndrome. About 25% of the elderly and 40% of the patients treated for head and neck cancer suffer from oral dryness leading to impaired speech, chewing, taste and swallowing, higher susceptibility for infections, and caries. These sequelae severely affect the patients’ wellbeing and quality of life. A lack of viable stem cells able to maintain glandular homeostasis underlies age and radiotherapy induced SG dysfunction. Therefore, stem cell therapy could ameliorate xerostomia. Indeed, recently we showed that transplantation of mouse or human SG stem cells can rescue murine SG from radiation damage. For patients receiving radiotherapy, collection of stem cells before cancer treatment seems feasible. However, the definitive salivary gland stem cell has not been characterized yet. This project will attempt to understand the mechanisms behind stem cell maintenance and differentiation, to allow stem cell therapy in the future.

**Project set-up**
The student will participate in the culturing and testing of salivary gland stem cells in vitro. Primary cells are obtained from mouse or human salivary glands and cultured as salispheres. Dispersed single cells selected with FACS for the expression of stem cell markers are passaged to Matrigel to form secondary spheres and organoids. The expression of genes and stem cell markers involved in the stemness of these cells are investigated. Involved signalling pathway will be manipulated to assess their role in stem cell maintenance, expansion and differentiation.

**Project R: Understanding the pathophysiology of SHOCK-mediated organ failure in order to improve the clinical care of critically-ill patients**
*Supervisor: J. Moser MD*  
*Department: Critical Care*

Every day, critically ill patients in ICUs worldwide develop failure of vital organs usually as a result of infection (sepsis) or injury (trauma or surgery). This so-called multiple organ dysfunction syndrome (MODS) leads to increased mortality among ICU patients. If patients survive MODS, their increased morbidity persists long after they have left the ICU. The incidence of sepsis is increasing worldwide mainly due to the ageing population, often burdened by multiple comorbidities, as well as the growing problem of antibiotic resistance. Unfortunately, there is currently no effective treatment beyond organ support
emphasizing the urgent need for a better understanding of the pathophysiological and molecular mechanisms in order to identify new therapeutic approaches.

One of the failing organs in septic patients is the kidney. If patients survive, they have an increased risk of developing chronic kidney disease (CKD) and/or end stage renal disease (ESRD) which can result in dialysis dependency. The underlying mechanisms of sepsis-associated acute kidney injury are still unknown. However, one of the major pathophysiological consequences is loss of microvascular integrity and exaggerated microvascular inflammation. Current research projects focus on understanding aberrant microvascular integrity and inflammation. For these studies, a variety of experimental techniques including immunostaining, western blotting, RT-qPCR and ELISA are used to analyze in vitro cell studies, kidney tissue from in vivo sepsis models and patient material. For more info: https://www.ebvdt.nl/shock-research

Project S: Gene regulation in ageing and age-related diseases
Supervisor: Prof. Cornelis F. Calkhoven PhD
Department: Biology of Ageing - ERIBA

Ageing, metabolic disorders, and cancer share common biological mechanisms. Cellular factors that are involved in sensing nutrient (food) and energy availability are decisively involved in ageing and lifespan determination, as well as in the development of age-related diseases like cancer or metabolic diseases. The primary research focus of the Calkhoven lab is determining how metabolic and other growth signals control the expression of specific sets of genes that can alter the organism's normal function or contribute to disease.

Currently, the Calkhoven lab studies a specific pathway (mTORC1-pathway) that senses if enough nutrients and energy are available to regulate cell growth through the control of protein synthesis and/or other metabolic processes. The Calkhoven lab is particularly interested in the function of mRNA control elements, protein factors and microRNAs that are involved in mTORC1-controlled processes. Using mouse models they examine the function of these elements, and other factors, on organismal health and life span determination. In addition, they study the modification of gene regulatory proteins by cellular metabolites and how this regulates cell function under different nutritional conditions. With the aim of 'translating' the fundamental research into clinical-pharmacological applications, the lab is also involved in developing reporter systems for potential compound screening strategies.

Project T: Liver transplantation
Supervisor: Aad van den Berg MD
Department: Gastrointestinal medicine

During the research period one of the following research subjects will be addressed:

1. Is muscle strength a prognostic factor for survival after liver transplantation? It has been shown that low muscle mass as assessed by CT scanning is associated with worse survival in patients on the waiting list for liver transplantation, and with inferior peri-transplant survival. We also have shown that creatinine excretion in 24H urine (reflecting muscle mass) as measured one year after liver transplantation is a strong, independent predictor of subsequent survival during the next 15 years. It is not known whether 24H creatinine excretion in these patients (i) truly reflects muscle mass, (ii) predicts survival, and if so, (iii) which factors (e.g., type of immunosuppressive regimen, original liver disease, metabolic complications) determines muscle strength in these patients. We collected a dataset of >500 measurements of muscle
strength and creatinine excretion in >300 liver transplant recipients. This database will be used to answer these questions.

2. “Minimal” immunosuppression in ultra-long survivors after liver transplantation. Patients surviving the first year after liver transplantation (>90% in our center) have a 50% chance of being alive at 20 years after transplantation. Relatively little is known about the use of immunosuppressant drugs these extremely long-term survivors. Rejection seldomly occurs in them, suggesting that a state of near-tolerance has been achieved. This study is intended to describe in detail the use of immunosuppressive drug in this population, and to investigate whether low-level immunosuppression is associated with a low incidence of immunosuppression-related side-effects (infections, cardiovascular disease, cancer, renal dysfunction).

3. Long-term effects of calcineurin-inhibitors on renal function after liver transplantation. It is well-known that calcineurin-inhibitor may have deleterious effects on renal function. Careful dosing, keeping drug levels low, is considered by many to be relatively safe at least during the first years after transplantation. However, liver transplant patients may expect very long survival (>20 years), and information about long-term renal toxicity is scarcely available. We want to study this by comparing kidney function in ultra-long surviving patients who have been treated with the calcineurin inhibitors Ciclosporin A or Tacrolimus with that of patients who never used these drugs, or only for a limited number of years.

4. Is the liver truly an immune-privileged organ? It is often stated that the liver is “different” from all other solid organs because only low amounts of immunosuppressive drugs are necessary to prevent rejection. However, good evidence for this statement is lacking. It could well be that the liver can tolerate low-grade rejection (due to relative under-immunosuppression) much better than other organs (e.g., kidney or lungs) because the liver has a much greater capacity for regeneration than these other organs. We want to study this hypothesis by comparing liver tests in liver transplant patients (receiving a typical liver transplant immunosuppressive regimen) and in patients who have received a liver plus kidney, pancreas or lung(s), (who receive the more intense immunosuppressive regimens of those other organs).

**Project U: What is the role of hypoxia in non-alcoholic fatty liver disease?**
*Supervisor: Prof. Han Moshage PhD*
*Department: Hepatology*

Non-alcoholic fatty liver disease (NAFLD) is a common condition characterized by fat accumulation in liver cells (steatosis), which may evolve to an inflammatory and fibrotic condition named non-alcoholic steatohepatitis (NASH). Transition from steatosis to NASH is not fully understood, but extracellular vesicles (EV’s) seem to play an important role. Recent clinical observations made in patients with syndrome of obstructive sleep apnea (OSA), suggest that hypoxia may contribute to disease progression through induction of the transcription factor hypoxia inducible factor 1α (HIF-1α).

Our research question is whether hypoxia modulates the release of EV’s released from steatotic hepatocytes and its role in the transition from steatosis to NASH.

**Project V: LifelinesNEXT - Introduction to scientific challenges in broad phenotyped cohorts**
*Supervisor: Prof. Sicco Scherjon MD PhD*
*Department: LifelinesNEXT*

LifelinesNEXT is a prospective birth cohort of mothers, fathers and babies, which includes extensive sample collection starting at 12 weeks of gestational age until at least the age of one year. A variety of biomaterials
is collected including blood, stool and breastmilk at multiple time points. Data on environmental, social and medical factors are collected via questionnaires at 14 time points. LifelinesNEXT offers an opportunity to relate integrated information on microbiome, metabolism, immunology, genetics, epigenetics and environmental influences. The LifelinesNEXT cohort will consist of ~1500 pregnant mothers, their newborns and partners. In this project we will introduce the student to the many scientific opportunities that occur in a broad phenotyped cohort and LifelinesNEXT in particular.

During the 2 weeks project students will get acquainted with the ongoing process of including pregnant women, the extensive data collection on mother and child, the preparation of biosamples and the first data analysis.

The course will cover three aspects of research in birth cohorts:

1. **Bio sample collection**
   Students will accompany a research nurse during their home visits to participants. Participating in the elaborate research project LLNEXT requires a lot of effort from the participants. Therefore NEXT gives ample attention to the warm contact with participants and visits them at least 4 times.

2. **Lab introduction**
   All kinds of biomaterials collected in NEXT (breastmilk, blood and stool) are processed and prepared for genotyping at the laboratories of the Genetics department UMCG. By participating in this process, students will be introduced in the fascinating world of genetics.

3. **Data analysis**
   The first data from questionnaires became available recently. Our students will perform data analysis to give insight in the inclusion process and provide a first characterisation of NEXT participants. The students will prepare a report on several topics, e.g. food intake of included newborns and characteristics of exclusively breastfed babies.

**Project W: Genetic epidemiology & genome-wide association**
*Supervisor: Peter van der Most PhD*
*Department: Epidemiology*

Genetic epidemiology is the study of the distribution of genetic traits across the population, and their influence on health and disease. One of the cornerstones of genetic epidemiological research is the Genome-Wide Association Study (GWAS), a method to find genetic variants associated with a specific phenotype, such as heart rate, kidney disease, or even education level. In the past two decades, thousands of phenotypes have been investigated by GWAS.

However, how meaningful are such population-based results for a single person? In this project, we will look at an individual genome, and test what these studies predict about the individual’s phenotype. Alternatively, we will investigate the results of a meta-analysis of GWAS. A GWAS tells us which genetic variants are associated with a phenotype, but not how. Sometimes a GWAS hit is found in a clearly associated gene (for example: a GWAS of blood pressure finds a hit in a gene associated with kidney function), but frequently this is not the case. And even if it is, it does not tell us how this variant affects the phenotype. The follow-up of GWAS is therefore an increasingly important part of genetic epidemiology. We are currently working on a GWAS of end-stage renal disease; if the results are ready in time, the student can choose this as his project.

The project will be entirely computer-based; using the software and methods applied by genetic epidemiologists. No previous experience is required, though some facility with computers will be needed.
Project X: Genome instability influencing protein quality control
Supervisor: Steven Bergink MD PhD
Department: Biomedical Sciences of Cells and Systems

Our proteomes are maintained by the cellular protein quality control pathways that include both molecular chaperones and the cellular degradation machineries. This maintenance is necessary for nascent chains (the newly born polypeptides) but also to deal with other forms of proteotoxic stress that arise due to internal or external stimuli. Alteration of the genetic code will impact the proteome and may in fact cause proteotoxic stress as well. However, how somatic mutations affect our proteomes and which cellular pathways are dealing with this presumed link is currently unclear. Currently we are investigating this link in more detail and this will be the focus of this project.

Project Y: Recharging the heart: can we harness the power of ketones
Supervisor: Daan Westenbrink MD
Department: Cardiology and Thorax Surgery

Heart Failure (HF) remains a devastating disease that is characterized with severe symptoms, frequent hospital admissions and a grim prognosis. New strategies to treat or prevent HF are therefore urgently needed.

In HF patients, the cardiac capacity to oxidize fats and sugars is severely diminished, making the heart resembles an "engine out of fuel". This causes exercise intolerance, which is one of the earliest and most debilitating consequences of HF and often used to diagnose HF.

Ketones function as a cardiac super fuel and are used by athletes to boost exercise performance. We believe that they may also be beneficial for HF patients. We are currently testing if a simple sports drink containing ketones or drugs that stimulate ketone production can improve exercise performance in HF patients. To test this we use advanced magnetic resonance spectroscopy which allows us to detect ATP-production during exercise.
The Medical Sciences Summer School programme of the University Medical Center Groningen (UMCG) and the University of Groningen consists of several Summer Schools including a wide range of medical disciplines. The aim of these Summer School programmes is to give international students the opportunity to get an introduction to – or deepen their knowledge of – (bio)medical research in specific research fields.

A hallmark of all Summer Schools is the combination of clinical practice and research. In addition, participating in a Summer School is an excellent opportunity to broaden your horizon and meet other international and ambitious medical students.

The diverse programmes leave students with many opportunities for furthering their career in medical research and practice, by enhancing connections to the Graduate School of Medical Sciences, as well as creating new connections with individual (international) guest speakers and professors.

- Biobanking 17 - 21 June 2019
- Bone, Joint & Tendon Care 3 - 12 July 2019
- Cardiovascular Regenerative Medicine 2 - 12 July 2019
- Global Health 3 - 12 July 2019
- Health and Human Rights 8 - 12 July 2019
- Healthy Ageing 8 - 12 July 2019
- Innovation in Medicine 2 25 - 30 August 2019
- Pediatrics 3 - 12 July 2019
- Transplantation Medicine 10 - 13 June 2019
- Translational Neurosciences ‘Ageing Brain’ 3 - 12 July 2019
- Data-Driven Prevention Policy in Public Health 19 - 30 August 2019
- What About the Family? 12 - 18 August 2019
- Persistent Physical Symptoms 15 - 18 June 2019

An overview of the Medical Sciences Summer School Programme 2019:
Attending one of these programmes could be combined perfectly with your attendance to ISCOMS and will give you the opportunity to increase your knowledge even further.

For general information about the Medical Sciences Summer Schools Groningen, please visit their website (http://www.rug.nl/research/gradschool-medical-sciences/summerschools/) or e-mail them at summer.schools@umcg.nl.
Congress
Programme ISCOMS 2019

Sunday 2nd of June - Welcoming Night

19:30-21:00 City tour
21:00 Pub quiz

Monday, 3rd of June - Pre-course

08:15-09:00 Registration
09:00-09:30 Day opening
09:30-11:10 Course 1
11:10-11:50 Break
11:50-13:20 Science Elective
13:20-14:30 Lunch
14:30-15:00 Your Future at the UMCG
15:00-16:00 Speed keynote lectures
16:00-17:30 Course 2
19:00-23:00 Social Programme

Tuesday, 4th of June - Congress day 1

07:45-08:30 Registration
08:30-09:30 Opening ceremony
09:30-10:30 Keynote lecture: Prof. Henning Schliephake MD DDS PhD
10:30-11:35 Poster session I
11:35-12:20 Break
12:20-13:35 Workshops I
13:35-14:50 Lunch
14:50-16:15 Oral session I
16:15-16:45 Break
16:45-17:45 Keynote lecture: Prof. Hein A. M. Daanen MD PhD
17:45-18:00 Closing ceremony
19:30-22:30 Recreational evening
### Wednesday, 5th of June - Congress day 2

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<tr>
<td>08:30-09:00</td>
<td>Registration</td>
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<tr>
<td>09:00-09:15</td>
<td>Opening ceremony</td>
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<td>09:15-10:15</td>
<td>Keynote lecture: Prof. Mario R. Capecchi PhD</td>
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<td>10:15-11:20</td>
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<tr>
<td>11:50-13:05</td>
<td>Workshops II</td>
</tr>
<tr>
<td>13:05-14:05</td>
<td>Lunch</td>
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<tr>
<td>14:05-15:20</td>
<td>Patient Lecture</td>
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<tr>
<td>15:20-16:20</td>
<td>Plenary session I</td>
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<tr>
<td>16:20-16:35</td>
<td>Closing ceremony</td>
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<tr>
<td>19:00-23:00</td>
<td>Formal Dinner</td>
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### Thursday, 6th of June - Congress day 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>08:30-09:00</td>
<td>Registration</td>
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<tr>
<td>09:00-09:15</td>
<td>Opening ceremony</td>
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<tr>
<td>09:15-10:15</td>
<td>Keynote lecture: Prof. Andrea B. Maier MD PhD</td>
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<tr>
<td>10:15-11:15</td>
<td>Plenary session II</td>
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<tr>
<td>11:15-11:45</td>
<td>Break</td>
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<tr>
<td>11:45-13:00</td>
<td>Workshops III</td>
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<tr>
<td>13:00-14:00</td>
<td>Lunch</td>
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<tr>
<td>14:00-15:25</td>
<td>Oral session II</td>
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<tr>
<td>15:25-15:55</td>
<td>Break</td>
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<tr>
<td>15:55-17:15</td>
<td>Operation</td>
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<tr>
<td>17:15-18:00</td>
<td>Award &amp; closing ceremony</td>
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<tr>
<td>19:00-22:00</td>
<td>Buffet</td>
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<tr>
<td>22:00-02:00</td>
<td>World Wide ISCOMS Night</td>
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### Friday, 7th of June - Post Congress Tour

<table>
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<tr>
<td>8:30-20:30</td>
<td>Post Congress Tour</td>
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Prof. Yijin Ren DDS PhD is a professor and head of the Department of Orthodontics at University Medical Center Groningen (UMCG). She is the programme director for specialist training in orthodontics, which is a 4-year full-time programme to train dental clinicians, qualified after a 6-year dental training, to become an orthodontist. It is one of the only two specialty training in dentistry, and Groningen is one of the only three training institutes in the Netherlands. Clinically professor Ren keeps an active practice within her department mainly on patients with cleft lip and palate and other craniofacial anomalies. She is a consultant orthodontist in the Cleft Lip and Palate Team of Northern Netherlands.

Professor Ren is also Director of the W.J. Kolff Institute of Biomedical Engineering and Materials Science, named after the godfather of biomaterials implants and devices, such as kidney dialysis or the artificial heart, Dr. W.J. Kolff. The Kolff Institute (KOLFF) is the only engineering-centered institute that is embedded in an academic hospital in the Netherlands. Recently, in line with the new UMCG Research Strategy and emerging health problems and clinical needs, KOLFF has been under profound reorganization, with the main focus on the development and application of innovative biomedical techniques and technologies, including novel bio(nano)materials to improve quality of health care and to realize a sustainable healthcare.

Professor Ren her research interests include biofilms and biomaterials-associated (oral) infection, novel alternatives to antibiotics, application of 3D imaging, workflow and 3D printing and manufacturing in clinical practice and outcome evaluation.

Together with two other collaborating PIs in KOLFF, professor Ren has recruited 20 sandwich PhD students in collaboration with two Chinese partners, - Nankai University, funding based on Major International Collaboration Grant from National Natural Science Foundation of China (NSFC); and Suzhou University, funding based on Suzhou University Funding scheme for Biomaterials for Healthcare. These PhD projects run in the period of 2015-2022 and focus on promising responsive nanoparticles and nanostructured surfaces for bacterial adhesion and biofilm control harnessing their unique features such as biofilm penetration and eradication, photo-thermal effects, photo-induced ROS production, increased antibiotic housing and extremely low possibility of generating resistance. Given that antibiotic-resistance amongst infecting bacteria is becoming a global threat, the outcome of this line of research is expected to have significant impact particularly in the biomedical fields. Professor Ren is also consortium member for a COFUND from MARIE SKŁODOWSKA- CURIE ACTIONS on novel tailor-made antimicrobials and delivery strategies (2016-2020).
Prof. J.M.C. van Dijk MD PhD is chair of the department of Neurosurgery in the University Medical Center Groningen, the Netherlands. His main surgical specialties are Neuromodulation, Neurovascular Surgery, and Skull Base Surgery. Professor van Dijk started his neurosurgical training with Raph Thomeer in Leiden in 1994. After the graduation in 2000, professor van Dijk was admitted to do a prestigious clinical and research fellowship in Toronto, Canada. As such, he had the opportunity to work closely with world-leading neurovascular specialists, Karel Ter Brugge and Chris Wallace, in The Western Hospital. During the Toronto experience, professor van Dijk was fascinated by the dural arteriovenous fistula, a rare and peculiar neurovascular disorder, of which he collected a large database that resulted in several hallmark papers and ultimately in a PhD-thesis.

Once returned to the Netherlands in 2002, he was appointed as staff neurosurgeon and clinical director in the Leiden University Medical Center. Despite this demanding position, he managed to obtain an additional master degree (MSc) in neurovascular diseases at the Université de Paris-Sud under the guidance of Pierre Lasjaunias. In 2006, professor van Dijk was invited to join the neurosurgical staff in the University Medical Center Groningen. This appointment gave him the unique opportunity to further broaden his experience as a teacher on the European platform (EANS), as well as to learn the fine arts of neuromodulation covering the full spectrum from the deep brain stimulation to the microvascular decompression of cranial nerves in the cerebello-pontine angle.

Because of his multifaceted academic profile, professor van Dijk was offered a tenure-track position that resulted in the appointment as a university tenure-track professor on the topic ‘Ageing Brain’. Besides the fact that this topic is closely related to the motto ‘Heathy Ageing’ of the University of Groningen, the focus on the ageing brain also gives rise to the unique opportunity to bundle the efforts of multiple clinical and preclinical academic disciplines, instead of the traditional monodisciplinary research. Being a true bridgebuilder, professor van Dijk’s firm belief is that by merging skilled knowledge and efforts a range of new and groundbreaking indications for neuromodulation is ready to be identified. Therefore, treatment or at least modulation of societal issues such as epilepsy, dementia, arterial hypertension, morbid obesity, tinnitus, and psychiatric disorders might be well within reach.
Prof. Joost M. Klaase MD PhD works as a hepatobiliary surgeon at the Department of Hepatobiliary Surgery and Liver Transplantation in the University Medical Center Groningen. He is engaged in minimally invasive pancreatic and liver surgery and is professor in Surgery at the University of Groningen. Until recently he was Chairman of the Dutch Liver Surgery Working Group and Chairman of the Scientific Board of the Dutch Hepatobiliary Audit. Currently, he is Chairman of the Managed Clinical Network HPB Surgery North East Netherlands. His research topic is optimisation of perioperative care in hepatobiliary surgery. His main interest is in prehabilitation. This means improving physical capacity and functional reserve of patients before surgery or start of treatment with chemotherapy and/or radiotherapy.

According to data from our national audits (www.dica.nl), the chance of development of minor or major complications after complex abdominal surgery for cancer is respectively 10-20% and 20-30%. The impact of postoperative complications is high. A complicated postoperative course leads to decrease in quality of life, not only during or directly after hospital admission but also on the long term. Complications, especially in the elderly patient with multimorbidty, could lead to dependency and eventually death. Complications after hepatobiliary surgery are responsible for a 2-3 times increase in hospital admission costs and account for an unplanned readmission rate as high as 25%. The cause of postoperative morbidity is multifactorial. In the last years, care has been taken to improve care processes and structure issues in hospitals. National audits, centralisation of surgical procedures, ‘enhanced recovery after surgery’ programmes and the introduction of laparoscopic surgery to diminish surgical tissue trauma, are all examples of quality improvement programmes, and have already been implemented. However, we could see the patient as a possible modifiable risk factor as well. The patients themselves have high influence on surgical outcome by factors as muscle mass, muscle quality and fitness level.

At this moment we are implementing a multimodal prehabilitation program, focussing at six domains, fitness, frailty, nutrition, anaemia, psychological resilience and intoxications (smoking and use of alcohol). This programme will allow us to embrace and make targeted use of the waiting time for surgery to optimise physical capacity and physiological reserve of our patients before they start treatment, in order to improve postoperative outcome and quality of live on the short and long term.
Prof. Marian J.E. Mourits MD PhD (1956) is a Professor in Gynaecological Oncology at the University Medical Center Groningen (UMCG). She went to medical school at the Radboud University Nijmegen and was trained as a gynaecologist at the UMCG in Groningen. Here she also did her fellowship in Gynaecological Oncology and wrote her PhD thesis on ‘Tamoxifen and the female genital tract’. Since then, she has been working in the UMCG as a gynaecological oncologist, which she combines with teaching, training and doing research. For 10 years she was programme director of the gynaecology training in Northern Netherlands. She has a keen interest in talent development, leadership and diversity at all levels.

After her PhD thesis, her research focuses on clinical aspects of hereditary gynaecological cancer, with special interest in risk assessment, quality of life and sexual functioning. Women with a BRCA1-2 mutation have to deal with this hereditary trait and prophylactic measures, such as prophylactic surgery at a young age. The short- and long-term side effects of early surgical menopause are subject of her research. She does most of her research in close collaboration with other researchers, which adds to the quality of her work.

She underlines the fun and joy of close multidisciplinary co-operation between different medical disciplines, such as gynaecologists, geneticists, surgeons, epidemiologists, pathologists and psychologists in the UMCG and abroad. Together with her collaborators and PhD students she has delivered valuable input for new clinical guidelines which aim to improve the surveillance and treatment of women with a hereditary cancer trait.
Professor Jan-Luuk Hillebrands PhD is a medical biologist and professor of Experimental Vascular Pathology. He is Principal Investigator at the Pathology section, Department of Pathology & Medical Biology University Medical Center Groningen. His main research interest is the development of accelerated cardiovascular disease (including atherosclerosis and vascular calcification) with focus on the biology of kidney disease- and diabetes-induced cellular and functional changes in the vascular wall. His expertise is on the interface of basic/translational/clinical vascular and renal research. Furthermore, he is an inspired lecturer involved in teaching students of Medical Sciences, Dentistry, Life Sciences and University College Groningen (UCG). He co-edited the Dutch histology textbook “Functionele histologie”, 14th (2014) and 16th (2019) edition. He is UMCG coordinator of the International Research Training Group GRK1874 “Diabetic Microvascular Complications” (collaboration University of Mannheim/Heidelberg, Germany, and the University of Groningen/UMCG). Subsequently, he was a member of the Scientific Advisory Board of the Dutch Kidney Foundation from 2012-2018.
Professor Barbro N. Melgert PhD is an associate professor in Pharmaceutical Immunology. She is a pharmacist and basic scientist who focuses on immunological processes in respiratory diseases such as asthma, pulmonary fibrosis and chronic obstructive pulmonary disease (COPD). In particular, she focuses on the role of the innate immune system and its cells, especially the macrophages. Macrophages are the most abundant cells in the respiratory tract and they can have strikingly different phenotypes within this environment. These different phenotypes and their functions in the lung are not well understood, but they appear to be linked to the protection of gas exchange against microbial threats and excessive tissue responses. Phenotypical changes of macrophages within the lung are found in many respiratory diseases including asthma, COPD and pulmonary fibrosis.

The topic of her research in her lab is how these changes relate to disease development, which is still unclear. In addition, her lab develops novel therapies that aim to change the macrophage phenotype in the lung to change the course of these respiratory diseases.
emProf. Cees Th. Smit Sibinga MD PhD is a clinical haematologist and specialist of Transfusion Medicine. He is special professor of International Development of Transfusion Medicine at the University of Groningen. He was involved in the development of Transfusion Medicine, and quality systems and management in developing economies since 1980 through his work with the World Health Organization (WHO). There he has been regional coordinator of the global Quality Management Project for the Europe region. For 25 years, he has served as the Managing Director of Sanquin Division Blood Bank North Netherlands in Groningen. From 1993 until 2005 the Blood Bank incorporated the WHO Collaborating Centre for Blood Transfusion and the WFH International Hemophilia Training Centre in Groningen.

emProf. Smit Sibinga is the founder of the Dutch Blood Bank Inspection, the Accreditation Programme and the Hemovigilance system. Besides this, he is the founder of the Academic Institute for International Development of Transfusion Medicine at the UMCG. This institute used to provide a post-academic Master in Management of Transfusion Medicine, which is now part of the Master programme of the University of Groningen Graduate School of Medical Sciences.

emProf. Smit Sibinga is still intensively involved in transfusion medicine, related health sciences education and research focused on developing countries. He serves WHO Eastern Mediterranean Region as a Lead Technical Adviser in their Strategic Framework for Blood Safety and Availability 2016-2025 and its priority interventions.
Currently Noor is a fifth year medical student at the University of Groningen. For her medical clerkships she is located at the Deventer Ziekenhuis. Two years ago she was the president of ISCOMS 2017, after she was a part of the organisation of ISCOMS 2016 in the Research & Development committee. Besides organising the congress in 2017, she has been involved with a research at the department of Obstetrics and Gynaecology of the UMCG. In her spare time, Noor loves to enjoy the company of friends and aims to see as much as possible of the world.

“I hope that all of the visitors will enjoy ISCOMS as much as I did all these years. I think this congress is a great experience to get to know more about doing research and the possibilities within the biomedical sciences. Make use of the opportunity to talk to as many cultures as possible and learn from each other. As for the Organising Committee of ISCOMS 2019, you can be very proud of yourself for organising such a big event. The last thing I want to share is the most valuable lesson for me: do something that makes you happy!”
Martin Beukema MSc is a PhD-student at the Medical Biology department at the UMCG, working under supervision of prof. Paul de Vos PhD. The research group of prof. Paul de Vos PhD focuses on food induced modulation of the intestinal immune barrier. The topic of his PhD project is about the role of the dietary fiber pectin on intestinal immune responses. In collaboration with the department of Food Chemistry at the Wageningen University, he would like to unravel which specific chemical structures of pectins are responsible for direct interactions with immune cells or which pectin structures are used as fuel for intestinal microbiota. Moreover, his project is part of the Carbokinetics Consortium from the partnership between the Carbohydrate Competence Center and the Dutch Organisation for Scientific Research.
Koen Wijsman, Organising Committee of the Leiden International (Bio)Medical Student Conference (LIMSC)

Koen Wijsman is currently in his third year of medical school in Leiden, the Netherlands. Because of the great variety of standards and procedures in healthcare systems all over the world, Koen believes that it is extremely valuable to exchange this knowledge on an international scale. Recent technologies have made the borders of science more and more fluid, and (bio)medical students should make use of the opportunities that this offers. (Bio)medical students are the doctors and researchers of the future, and therefore it is of significant importance that they start sharing their knowledge early on in their career.

Being inspired by this, Koen decided to take part in the Leiden International (Bio)Medical Student Conference (LIMSC) as president of the Organising Committee. This conference took place in March 2019. It was an eye-opening experience for Koen that 800 young and ambitious students from all over the world came together in Leiden to exchange knowledge with their peers. Having organized this 11th edition of LIMSC, Koen has come to value the importance of student research more than ever. ISCOMS is an incredible student conference that offers a wealth of opportunities for the doctors and researchers of the future. For that reason, it is his pleasure to be a jury member of the 26th edition of ISCOMS.
Plenary awards
Students who are selected to present their research during the plenary sessions, have a chance of winning one of the three plenary awards. The first prize consists of €1250,-, the second prize of €750,-, and the third prize of €250,-. You can spend this money on visiting biomedical congresses of your choice. All of these winners will also receive a one-year online subscription to Nature. The winners will be selected by a jury of renowned medical scientists and (bio)medical students.

Plenary presentation: Audience award
The winner of this award will be determined by the audience. The presenter most appreciated by the audience will receive a cheque of €150,- to spend on visiting a biomedical congress of his or her choice.

Plenary presentation: First Year Jury award
This is a special award, as the jury consists of first year (bio)medical students only. Despite not having much research experience, they will judge the plenary sessions open minded and with great care. The winner of this award will receive €150,- and a goodie bag from the journal Disease Models & Mechanisms.

Oral Research award
This prize is awarded to the best orally presented research selected out of all the oral sessions, judged by the ISCOMS session supervisors. The winner will receive a one-year online subscription to the New England Journal of Medicine.

Poster Research award
This prize is awarded to the best research presented in a poster session, judged by the ISCOMS session supervisors. The winner will receive a one-year online subscription to the New England Journal of Medicine.

Oral Performance award
This prize is awarded to the best oral performance selected out of all the different oral sessions. The winner of this award will be selected by the ISCOMS organisation supervisors. This award focuses on the aspect of good presentation skills. The winner will receive a one-year subscription to the New England Journal of Medicine.

Poster Performance award
This prize is awarded to the best poster performance selected out of all the different poster sessions. The winner of this award will be selected by the ISCOMS organisation supervisors. This award focuses on the aspect of good presentation skills. The winner will receive a one-year subscription to the New England Journal of Medicine.

Best Abstract award
The best abstracts will be awarded with either an abstract award for the clinical sciences or the basic sciences. Our official jury will select two winners out of all different topics. Winners will receive a cheque of €150,- to spend on visiting a biomedical congress.

Session winners
In each poster and oral session the best presentation will be selected. All session winners will receive an official certificate.
World Health award
To stimulate and acknowledge students in the research of global health issues and their contribution to global health in general, the WHO supported World Health consists of a one-year online subscription to the Eastern Mediterranean Health Journal (EMHJ). This means that either the presenter comes from a developing country or the subject of the research affects developing countries.

HANNN award
The aim of the HANNN Healthy Ageing Award is to promote research that has a positive impact on society because it achieves one of the goals mentioned on the next page. The HANNN Healthy Ageing Award will be rewarded to the participant who has performed the research with the highest positive impact on Healthy Ageing in society. This year the winner of the HANNN Healthy Ageing Award will receive a €500,- grant.

Please note, all of the prizes which include money, should be claimed within a maximum of three years after this 26th edition of ISCOMS. The awards can only be spent on visiting (bio)medical congresses, and only the travel costs and the costs for the congress itself can be declared.
Welcome to the Northern Netherlands; a Four Star Healthy Ageing Region!

The Healthy Ageing Network Northern Netherlands (HANNN) is proud to welcome you in our region. Recently the European Commission reaffirmed that the Northern-Netherlands region leads the pack in the field of Active and Healthy Ageing. They did so by awarding us a Reference Site-status with the highest possible score of 4 stars. What Michelin stars are for restaurants, the Reference Site-stars are for Healthy Ageing ecosystems. So: bon appetit!

The four stars are the result of broad cooperation between dozens of companies (in the field of Food, Medical Technology, Life Sciences, Healthy Lifestyle, ICT), knowledge institutions (University Medical Center Groningen, University of Groningen, 4 Universities of Applied Sciences), Care & Cure organisations, and local authorities on solutions for staying healthy longer. Healthy Ageing is a lifelong process, starting before birth and is aimed at adding healthy years to life. The objective is to develop new products, services, and concepts contributing to prevention, the recovery process, better health care, and self-management. HANNN is the umbrella organisation for these activities in the Northern Netherlands.

HANNN is a longtime supporter of ISCOMS, first of all because we think it is an awesome conference organised by a very talented group of young people. But also because we believe the participants will play a major role in shaping the future of health in the world, and we need the future of health to be aware that they are part of a bigger ecosystem. Cooperation between regional and local government authorities, cities, hospitals, care organisations, industry, start-ups, research and innovation organisations, and civil society, are key.

So if you’re open to that idea, you’ve come to the right place! Have fun, strengthen your network and remember us when you’re shaping the future of health.

www.hannn.eu
Twitter and Facebook: @healthyageingeu
Instagram: healthyageing
Focus: Healthy Ageing

ISCOMS has been enriched with the focus ‘Healthy Ageing’, which we share with the University Medical Center Groningen (UMCG). During the congress, this focus will stand out within various components of the programme of ISCOMS.

Healthy Ageing in the University Medical Center Groningen
The UMCG has a pivotal focus on healthy ageing in patient care, education, and research. Healthy Ageing is a lifelong process, which already starts before conception with parents passing on their genes and with them the risks and opportunities for a healthy lifespan. External factors, such as lifestyle, food patterns, and environmental factors also influence the development of health. However, new knowledge is required about the influences of these factors, and how they interact with one another.

Basic knowledge about the ageing processes and understanding of what is necessary for prevention, diagnosis and treatments of age-related, chronic diseases as well as for improved care for the elderly, will also contribute to healthy ageing. A multidisciplinary approach is thus necessary for research into ageing, extending from fundamental biological and (pre)clinical research through to applied research into social-societal effects of disease and health.

The strength of the UMCG’s efforts in the area of healthy ageing is largely due to Lifelines: a large-scale cohort study that follows 167,000 people for a minimum of 30 years and will record the course of their life and health developments. The unique, three-generation approach is being used to study the extent to which heredity and the circumstances of life plays a role in the occurrence of chronic diseases. Fundamental scientific research into ageing processes and diseases related to ageing is performed in the European Research Institute for the Biology of Ageing (ERIBA). In Groningen, a brand-new building was erected, which contains all the facilities needed for top-level research. Since 2011, leading international researchers are working in this new building.

Lifelines and ERIBA complement and enhance one another and produce new insights and solutions. Other examples of Healthy Ageing-related initiatives within the UMCG are: Technology for Ageing People, Ageing Brain, UMCG Center for Geriatric Medicine, Healthy Ageing at work, and Proton therapy.

The patient perspective on healthy ageing
In patient care the UMCG increasingly focusses on healthy ageing and ‘better in, better out’. This concept generates increasingly generates evidence that exercising before, during and, after treatment benefits the patient. It reduces complications and advances the results of treatment. In several patient populations this concept has been introduced and proven effective. In 2017, the UMCG introduced a lifestyle check through which patients can get free and voluntary advice with regard to their lifestyle (exercise, food habits and smoking). The importance of health literacy among patients is evident; already multiple departments have a strategy in place. A corporate effort is introduced in the UMCG to get health literacy higher on the agenda of all departments and via numerous channels of communication (waiting rooms, doctor/patient conversations, arts route aimed at getting patients out of bed, etc.).
Prof. Henning Schliephake MD DDS PhD works in the field of ear, nose, and throat medicine. His main focus is on reconstructive surgery. In the field of experimental research, he develops modern methods of hard tissue reconstruction in the craniofacial region using growth factors and osteogenic cells. Henning Schliephake received his training as a research associate in Oral Maxillofacial Surgery and Facial Plastic Surgery from 1989 to 1996 at the department of Oral and Maxifacial Surgery of the Hannover Medical School. He continued at the Hannover University and finished his PhD degree on in-vivo cultivation of bone in 1995. After that, he became a senior physician at this department. In 1997 he was officially appointed. In 2000 he was appointed associate professor of Oral and Maxillofacial surgery. He became full professor and chair of the Department of Oral and Maxillofacial Surgery at the Georg August University in Göttingen in 2001.

Prof. Schliephake has chaired several national scientific associations such as the German Association for Oral Implantology (DGII) and the German Society of Dental, Oral and Craniomandibular Sciences (DGZMK). He is a member of the National Academy of Sciences and is currently President of the German Society of Oral and Maxillofacial Surgery (DGZMK) and 1st Chairman of the Maxillofacial Surgery Association. He is Editor in Chief of the “Oral and Maxillofacial Surgery” and is member of the editorial board of a couple of scientific journals such as Oral Oncology and the International Journal of Oral and Maxillofacial Surgery. He has won several prices in Germany, Switzerland and the United Kingdom for his contributions in the field.

The focus of prof. Schliephake’s clinical work and research is reconstructive surgery in the context of ablative tumour therapies and the treatment of craniofacial malformations – especially cleft lip and palate. His focus in the field of experimental research lies in the development of modern processes of hard tissue reconstruction in the craniofacial area using growth factors and osteogenic cells. Prof. Schliephake has made important contributions to the development of controlled release techniques for osteogenic growth factors. Individually formable templates are produced from resorbable polymer materials, which should be used for anatomically adapted new bone formation. In further work, he developed innovative steps for the biofunctionalization of endosseous implant materials with growth factors in order to achieve a secure bony anchoring of implants in the bone, even under unfavourable circumstances, such as after radiation or in osteoporosis.
Prof. Hein A.M. Daanen MD PhD was born in Mierlo, the Netherlands, in 1958. He completed a study in Human Movement Sciences at the Vrije Universiteit of Amsterdam. Afterwards, he obtained a degree as teacher in medical-biological sciences. Professor Daanen completed a PhD at the Vrije Universiteit of Amsterdam. His thesis was called: “Central and peripheral control of finger blood flow in the cold”. Professor Daanen has been involved in electromyography research from 1985 – 1990 in Leiden. In 1990 he started working for TNO, a company specialized in applied scientific research. In 1995 he spent a year in Canada and the U.S. for military research in thermal physiology and anthropometry. He was a research coordinator of the Workplace Ergonomics Group and of the Thermal Physiology Group. He was head of the department of human performance from 2003 until 2008. From 2003 until 2016 he was adjunct professor in thermal physiology at the Faculty of Behavioural and Movement Sciences at the Vrije Universiteit of Amsterdam. In addition he has been working as a professor at the Amsterdam Fashion Institute. Since 2016 he is a full professor in (environmental) exercise physiology and director of master education in Human Movement Sciences at the Vrije Universiteit of Amsterdam.

The research of professor Daanen focusses on thermal strain of the human body during exercise, with special relation to body dimensions. During exercise it takes a while before heat loss mechanisms are activated and therefore body core temperature rises. High body temperatures are related to a reduced power delivery during endurance exercise and precooling mechanisms are investigated to reduce the increase in body temperatures. These mechanisms include external cooling using garments or ice vests, but also body core cooling using ice slurry ingestion prior to exercise. For athletes body temperature is important for optimal performance. The vigilance of racing drivers in a Formula 1 car, for instance, is reduced when the driver is very hot. Pre-cooling thus tends to have a positive effect on the physical performance of athletes. Pre-cooling creates a thermal buffer where one can store body heat. The performance improvement is undisputed in endurance athletes who have participated in studies that made use of pre-cooling techniques. Many athletes are pre-cooling prior to competition nowadays.

Many questions remain such as how the temperature of water affects swimming performance? How can the thermal physiological knowledge be implemented in sports practice? How can we reduce heat strain in soccer players?
Prof. Mario R. Capecchi PhD was born in Verona, Italy, in 1937. He moved with his mother to the United States after the Second World War. Prof. Capecchi received his Bachelor of Science in chemistry and physics in 1961 from Antioch College in Ohio. Prof. Capecchi came to MIT (Massachusetts Institute of Technology) as a graduate student intending to study physics and mathematics, but during the course of his studies, he became interested in molecular biology. He subsequently transferred to Harvard to join the lab of James D. Watson, co-discoverer of the structure of DNA. Prof. Capecchi received his PhD in biophysics in 1967 at the Harvard University, with his doctoral thesis completed under the tutelage of Watson. He was a Junior Fellow of the Society of Fellows at Harvard University from 1967 to 1969. In 1969 he became an Assistant Professor in the Department of Biochemistry at Harvard Medical School. He was promoted to Associate Professor in 1971. In 1973 he joined the faculty at the University of Utah. Prof. Capecchi has also been an investigator of the Howard Hughes Medical Institute since 1988.

He has won numerous awards, including the Kyoto Prize in Basic Sciences (1996), the Franklin Medal for Advancing Our Knowledge of the Physical Sciences (1997), the Feodor Lynen Lectureship (1998), the Rosenblatt Prize for Excellence (1998), the Baxter Award for Distinguished Research in the Biomedical Sciences (1998), the Helen Lowe Bamberger Colby and John E. Bamberger Presidential Endowed Chair in the University of Utah Health Sciences Center (1999), lectureship in the Life Sciences for the Collège de France (2000), the Horace Mann Distinguished Alumni Award, Antioch College (2000), the Italian Premio Phoenix-Anni Verdi for Genetics Research Award (2000), the March of Dimes Prize in Developmental Biology (2005).

Prof. Capecchi is known for his work on the development of gene targeting in embryo-derived stem cells of mice, creating mutations in any desired gene and giving freedom to manipulate the DNA sequence. In 2007 he won the Nobel Prize in Physiology or Medicine for this research, which he shared with prof. Oliver Smithies PhD and prof Martin Evans PhD. His current research interests include the molecular genetic analysis of early mouse development and production of mouse models of human genetic diseases.
Professor Andrea Maier (1978) was born and raised in Aurich, Germany. She graduated in Medicine at the Martin-Luther University Halle-Wittenberg and the Medical University Lübeck (Germany in 2003. She registered as a specialist Internal Medicine-Geriatrician at the Leiden University Medical Centre (the Netherlands) in 2009.

In 2013, she was appointed as full Professor of Gerontology at the Vrije Universiteit Amsterdam (the Netherlands). She was the youngest professor in internal medicine to be appointed in the Netherlands. During her childhood she received piano lessons from a 90 year old teacher, and during her study in China she received Tai chi lessons by a vibrant old lady. These are examples of what fascinates her about getting older in a healthy way. Since February 2016, she is Divisional Director of Medicine and Community Care at the Royal Melbourne Hospital and Professor of Medicine and Aged Care at the University of Melbourne (Australia).

She wrote her thesis on cellular senescence in vitro and organismal ageing. These senescent cells are older cells, mostly seen in people aged 60 years or older with a lot of diseases. People who become older in a vital manner appear to have less of these senescent cells. Experiments in mice show that if you remove these senescent cells that the health and the mortality will significantly improve. Her research is driven by her passion to unravel ageing mechanisms and the interaction of ageing and age-related diseases, with a particular focus on sarcopenia. Sarcopenia is loss of muscle mass and muscle force caused by ageing. This deterioration starts from the 30th life year, and from that moment onwards you lose 1% muscle mass a year. So a human will lose half of its muscle mass after 50 years so between the 30th and 80th life year. A simple solution to make this deterioration go slower is to stay active and use your muscles a lot. There are already antibodies towards substances that cause muscle deterioration. Experiments in lab animals show promising results.

During the last ten years, she conducted multiple national and European observational studies as well as clinical trials and published more than 190 peer-reviewed articles in international journals. Her innovative, multidisciplinary @Age research team works in the Netherlands (@AgeAmsterdam) and in Australia (@AgeMelbourne). She is an invited member of several international research and health policy committees to eventually increase the visibility, quantity and quality of ageing research. She also has been in various tv-shows in the Netherlands like Pauw & Universiteit van Nederland. Furthermore, in 2017 she published her first book in Dutch: ‘Eeuwig houdbaar’ which translates to eternally tenable. It is about the unknown future potential of our bodies.
Every year more than 60,000 patients with traumatic brain injury (TBI) are admitted to emergency departments in the Netherlands. TBI incidence world-wide is estimated at more than 200/100,000, making TBI one of the most frequent neurological disorders. TBI represents a heterogeneous patient population of all ages, from infants to the elderly, with large variability in injury severity, pathophysiology, (long term) outcome and post-traumatic sequelae. TBI is the leading cause of death and disability among children and young adults in the Western world and incidence numbers in the elderly are rising. In a report on neurological disorders the World Health Organization (WHO) concludes that there is a silent and neglected epidemic of TBI, even more prominent in developing countries, with devastating consequences. The outcome after TBI varies across the different TBI severity categories. In mild TBI mortality is low (about 1%), but in severe TBI the mortality rates can be as high as 40%.

TBI results from an abrupt external mechanical force acting upon head and brain. The impact and successive energy of the force transfer cause (temporary) injury to the skull, brain and adherent tissues. The main causes of non-penetrating or blunt head injury are, predominantly represented in the younger population and road traffic related (more than half of all cases): motor vehicle accidents, injuries of cyclists and pedestrians. The second category of trauma mechanisms is of falls, especially the elderly are at a higher risk: fall from standing height or from stairs. Assaults and head injuries related to sports represent the smaller incidence groups.

In this patient lecture on Wednesday the 5th of June, a patient that suffered or still suffers from TBI will join the teacher to illustrate the consequences of TBI.
On Wednesday the 5th of June a business lunch is organised, which will give you the opportunity to make contact with different companies in a casual environment. During this business lunch you will find out about different career opportunities and what companies can offer you in the future. Meanwhile, the lunch offers companies the chance to spot talented future doctors or biomedical engineers and to promote their brands in a face-to-face manner. This business lunch takes place during the regular lunch and a workshop round.

Companies attending the lunch will be from diverse sectors, which will make it interesting for all kinds of students. Parties that confirmed their presence are: Health Hub Roden, Polyganics and the Groningen Transplantation Centre.

Health Hub Roden is centered in the world of medical technology and healthy ageing. The company forms a so-called ‘hub’: a connection between businesses, knowledge institutes and government bodies.

Polyganics is a medical technology company with multiple versatile polymer platforms. The company develops, manufactures and commercializes innovative bioresorbable medical devices that facilitate tissue repair and regeneration.

The UMCG Transplantion Center is a place where all forms of transplantation are conducted: heart, liver, lung, kidney, pancreas and stem cell. All these transplantations programmes work together with the UMCG Transplantation center. The credo of the Transplantation center is ‘Shared care for shared organs’.

There will be a selection procedure since there are only a few spots available. The selection procedure will be based on your motivation letter. We will let you know by e-mail if you are selected.

Please note: the selection for the business lunch has already closed.
The operation: a kidney transplantation

Organ transplantation is a lifesaving therapy for patients suffering from end stage organ failure. The UMCG is the largest transplant centre in the Netherlands and is the only centre performing transplantation of all solid organs. Transplantation is a multidisciplinary treatment in which a team of specialists work closely together. To ensure optimal patient outcome, organ-specific knowledge in terms of both physiology and anatomy is essential. In addition, knowledge about donor management and optimization, donor organ preservation, post-transplantation (ICU) management and quality of life are all relevant aspects that require continuous research and development.

On average there are about 1000 kidney transplantations a year in the Netherlands, of which 180-200 are performed at the UMCG. About half of these transplanted kidneys come from a living donor. Currently 719 people are waiting for a donor kidney in the Netherlands. The number of kidney transplantations is increasing, mainly due to an increase in living donors and new operations on previously transplanted kidney recipients.

This increase in available organs is inter alia determined by the introduction of machine perfusion techniques. This technique allows assessment and resuscitation of otherwise rejected organs. With this innovative organ preservation technique, developed in the UMCG, it is possible to make more kidneys suitable for transplantation.

The impact of an organ transplant on patients is enormous. Their quality of life as well as their life expectancy increases significantly after the transplantation. With the innovative technique of machine perfusion, more organs become available for transplantation and therefore more people can be treated, waiting lists can be shortened, and maybe eventually make the lists belong to the past.

If you want to know more about the transplantation and perfusion techniques, visit the ISCOMS operation on Thursday the 6th of June.
During ISCOMS you are able to participate in a great variety of workshops. It does not matter whether you are interested in practical skills, biomedical technology, movement sciences, dentistry or ethical issues. There will surely be a workshop fitted for your wishes.

This year’s workshops will be:

- Augmented reality to treat phantom limb pain: the phantom motor execution program
- Advances in organ preservation for transplantation
- An introduction in treating life-threatening situations in the ICU
- Basic life support: heroes aren’t born they are trained
- Crime scene or no crime scene?
- Dental implants in the aesthetic zone
- Dissection of the human brain
- Emergo train system
- Exoskeleton
- Fast motor actions, cognition and adaptations
- Fix an mandibular fracture yourself
- Guided tour in the central animal facility of the UMCG
- How to perform IV injections
- How to perform tracheal intubation
- Inside the psychotic experience: a conversation with a patient
- Lab-on-a-chip
- Liver transplantation with machine perfusion
- Suturing
- Macro- and microscopic suturing
- Onco-pathology: diagnose a biopsy
- Pandemic – Let’s safe the world together
- Plastic surgery: How does a tissue expander work? How is a detailed exam of the hand performed?
- Positive energy in cancer treatment
- Practical ultrasound
- Real sounds sent out by your ear
- Simplicity in complex woundcare
- Surgical anatomy of the heart and surgical treatment of heart failure: LVAD
- Surgical anatomy of the heart and hybrid treatment of arterial fibrillation
- Speeddating with researchers
- Labvisit with PhD students
- The miracle of giving birth
- Transgenders: A debate with the UMCG genderteam and a patient
- Transesophageal echocardiogram (TEE)

The different workshops will be explained in more details on the next couple of pages.
**Advances in organ preservation for transplantation**

Department: Groningen Transplant Center, UMCG  
Supervisors: Cyril Moers MD PhD  

Machine preservation of donor organs is becoming more common by the day as a standard technique to preserve and transport organs. It creates possibilities to improve the quality of organs and test the viability. More importantly, machine perfusion can increase the number of available donor organs. During this interactive hands-on workshop, you will receive expert insights from specialists about this innovative way of donation and transplantation. Additionally, you can work under the supervision of surgeons to connect a (porcine) kidney to a hypo- and normothermic machine. This workshop gives you the opportunity to network with young medical and biomedical students who are active in the clinic or research area. Besides, these students can teach you how to take biopsies properly. The spaces in this workshop are limited, so make sure to sign up so you don’t miss out!

**An introduction in treating life-threatening situations in the ICU**

Department: Department of Critical Care, UMCG  
Supervisors: J.C.C. van der Horst, MD PhD  
Dinald Maatman  
Nursing Staff  

The workshop will be about the implementation of interdisciplinary teams in the ICU to provide care in often life-threatening situations, and about focused attention on the relevance of leadership behaviour. Effective, coordinated, and safe patient care challenge even the most experienced ICU teams daily. Leadership behaviour is defined as the process of influencing others to understand and agree about what needs to be done and how to do it, and facilitating individual and collective efforts to accomplish shared objectives. Simulation training is useful for teaching team-based crisis management skills and is now considered essential in developing and maintaining competencies for ICU workers.

In our high fidelity simulation center, participants of the workshop will become familiar with some stepwise elements of the treatment, such as resuscitation and airway management of critically ill patients. The non-technical skills such as leadership, communication, and cooperation are also emphasised. The experiences may contribute to the development of knowledge and skills in decision-making and teamwork during the treatment of critically ill patients.
Dissection of the human brain

Department: Anatomy, UMCG
Supervisors: Gerben Ruesink BSc, Sussan Quinten MSc

Dissection of the human body in general and of the brain in particular is an underexposed part of the average medical curriculum. In this context, the workshop “Dissection of the human brain” will address this omission. The workshop will be organised in the dissection room of the Anatomy Department of the UMCG and is especially intended for students with a special interest in the brain.

The workshop will start with inspection of the external parts of the human brain. The morphology of meninges, blood vessels and neocortical areas are central topics. Subsequently transversal and horizontal sections of a fixated human brains will be used to inspect the inner parts of the brain. Attention will be paid to the three-dimensional location of the cortical, extrapyramidal and limbic structures.

At the end of the workshop students will have gained a better insight in the structure and function of the human brain.

Augmented reality to treat phantom limb pain: the phantom motor execution program

Department: Rehabilitation Medicine, University Medical Center Groningen, the Netherlands
Supervisors: Prof. C.K. van der Sluis

Phantom limb pain (PLP) is a condition, which is difficult to treat and is experienced by about 30-80% of people with an amputation of a limb. The most recently developed treatments use virtual environments to treat PLP. In the latter, the reality is increased or adjusted. The Phantom Motor Execution (PME) program, developed in Sweden, uses augmented reality to treat PLP. The patient sees himself through a webcam on a computer screen, where a virtual arm is projected over his stump. The patient has electrodes on his arm, with which he can control the virtual arm. In this way, the patient gets the idea that he can actually move his phantom arm, reducing phantom pain and phantom feelings. Recent research into the effectiveness of the PME treatment showed that six months after finishing the treatment, half of the participants had significantly less PLP.

During the workshop a patient with an upper limb amputation will demonstrate the PME treatment. Furthermore, participants of the workshop can try to control an upper limb prosthesis themselves by utilizing prosthesis simulators.
**Basic life support: heroes aren’t born they are trained**

Department: Wenckebach Training Institute, UMCG

Supervisors:  
Wim J.C. Grimberg, Docent-Instructor  
ERC / NRR CPR-Instructor  
Monique Timmer, Instructor ERC / NRR  
CPR-Instructor

During this workshop you will be invited to engage with fellow students (3-4 people) to show us a perfect resuscitation (with AED) and continue the resuscitation for some time (5-7 minutes). The students who do not participate in the cardiopulmonary resuscitation-action (CPR) are invited to assess this resuscitation: what is going well and what could go better. If you are working as a doctor, it is necessary to take the leadership on a resuscitation team and to have the ability to coach your CPR-team. A good observation of skills is a requirement of a doctor in order to make the CPR procedure perfect. During the CPR-action it is important to push hard (5-6 cm), push fast (100-120/minute), and minimise interruption. At the end of this workshop you can exercise your CPR skills with the AED. The workshop will end with a certificate of participation in the workshop: “heroes aren’t born, they are trained” given by the Wenckebach Training Institute of the UMCG. To prepare for this workshop you can find the international guidelines for CPR on the site of the ERC: www.erc.edu. Furthermore, you can find a link about an international campaign for reanimation awareness: life-saver.org.uk.

**Crime scene or no crime scene?**

Department: Community Health Service (GGD) Groningen

Supervisors:  
Taco van Mesdag MD forensic medicine  
Tatjana Naujocks MD forensice medicine

Finding a dead person requires further investigation. In the first place it is necessary to be sure a person is dead indeed and in the second place it is important to find out whether a person died from natural causes or not. Last but not least, declaring a person dead and signing the death certificate requires certainty about the identity of the person you want to declare dead. Making mistakes in these situations creates a lot of problems for the ‘living-dead’ person.

During this workshop we will present two crime scene investigations, not the ones you can see on TV, but the ones we see in real life! Questions like: what, when, why and to whom did it happen, will have to be answered and the students will have the opportunity to participate.

Real forensic investigators will be present to join us in the investigations. The bodies – of course – won’t be real, but will be represented by two LOTUS-volunteers. LOTUS is an organization that participates in all kinds of training where casualties/victims are needed, dead or alive. They do a perfect job by playing their roles lifelike, or in our cases dead like.
**Dental implants in the aesthetic zone**

Department: Oral Maxillofacial Surgery, UMCG Prosthetic Dentistry, UMCG

Supervisors: Prof. Henny J.A. Meijer DMD PhD  
Prof. Gerry M. Raghoebear DMD PhD  
Wim J.W.A. Slot DMD PhD  
Charlotte Jensen DMD PhD  

Losing one or more teeth in the aesthetic zone has a great impact on a person. Inserting root-form dental implants and restoring them with ceramic crowns has proven to be a reliable method to solve the problem. The dental literature shows excellent survival rates of single-tooth restorations on dental implants, varying from 96.1% to 98.9% after 7.5 years in function. Studies that address aesthetics and patient satisfaction reveal it is a very sensitive method in the eye of the professional, but that patients are generally very satisfied. This workshop comprises a lecture with the possibilities of dental implants, different treatment steps and aesthetic results. The second part of the workshop is a hands-on training in which the participant places a dental implant in a model, imitating the surgical part of the treatment. The workshop is supported by Nobel Biocare Netherlands.

**Emergo Train System**

Department: Acute Health Care, University Medical Center Groningen

Supervisors: Jaap de Geus

Emergo Train System (ETS) is a simulation system used for education and training in emergency and disaster management. It is used worldwide and can test and evaluate your incident command system, disaster preparedness, the effect on the medical management system, and resilience within your organization. It’s all about communication, organisation, collaboration, and to experience which atmosphere arises in crisis situations.
Exoskeleton

Department: Technical University Delft
Supervisors: Non Nominatus

Giving back full mobility to people with a Spinal Cord Injury to fully participate in daily activities and in this way contribute to quality of life is what Project MARCH is about. They work this out by designing and building an exoskeleton for people with a spinal cord injury. The exoskeleton is an essential step to a future where there are no more wheelchairs on the streets. The ultimate goal is to make an exoskeleton that is accessible and available for everyone who can benefit from it. A lot of the needed technology already exist. However, there is also research required about new technologies and their application in this project. It is up to us to combine these different technologies in one possible implementation: a new and improved exoskeleton. We already made several successful exoskeletons, yet we still dream of a better exoskeleton that is for example self-balancing. With this feature, a person with a spinal cord injury can walk independently with a natural gait and without crutches. Together with the government and health insurances, we want to make a future where everyone who benefits from the suit can use it.

Fast motor actions, cognition and adaptations

Department: Human Movement Sciences University Medical Center Groningen (UMCG)
Supervisors: Prof. Egbert Otten PhD

Many of the fast motor actions that we perform in everyday life have become automated and are performed using rules that escape higher cognition. That makes them fast, and unloads parts of the brain that are used for different functions. In order to demonstrate this, several experiments will be conducted that include different loads, movement directions, pointing tasks that interfere with balance, and body mapping using both the visual system and the proprioceptive system. These experiments demonstrate our implicit assumptions about the task at hand and that these assumptions may be wrong. They also show our inability to compensate for the given errors, using higher cognition. This has direct consequences for motor learning of fast actions and the design of environments and devices in which reliable motor actions are required. The experiments also demonstrate strong and weak mappings of the sensory system onto the motor system. These mappings make sense if we reflect on the biological functions for which they appeared in evolution and developed during ontogeny. The results of the experiments may be surprising, which is an important condition and driving force for scientific research.
Fix an mandibular fracture yourself

Department: Oral and Maxillofacial Surgery, UMCG
Supervisors: Prof. Ruud R.M. Bos DMD PhD
Baucke van Minnen MD PhD

The treatment of mandibular fractures has evolved greatly over the past 50 years. Biomechanical principles that have been developed in laboratory models are applied to clinical practice in order to allow for immediate mobilization and rehabilitation of the injured part.

The goal of this workshop is to give insight in the widely accepted treatment modality of mandibular fractures: internal fixation with mini plates and screws. After a short introduction of the principles of mandibular fracture treatment, the participants will perform an osteosynthesis of mandibular fractures in a polyurethane mandible with mini plates and screws.

Guided tour in the Central Animal Facility of the UMCG

Department: Research Support Facility – Central Animal Facility
Supervisors: Catriene Thuring, DVM, PhD
Annemieke van Oosten, PhD

Many major findings in the field of human medicine have been established following animal experiments. To date, animal experimentation is still a very important way to gain data and knowledge mandatory to develop new procedures in modern human medicine.

Within the UMCG all animal experimental work is organised in the Central Animal Facility. The workshop consists of a guided tour in this facility. During the tour the current status of laboratory animal experimentation within the UMCG will be presented to you.

Please note:
For permission to participate in the tour it is important that you have not had contact with rodents or rabbits in the 24 hours prior to the tour. In this way we want to prevent unwanted transmission of pathogenic micro-organisms to our laboratory animals.
**How to perform IV injections**

Department: Anaesthesiology, University Medical Center Groningen

Supervisors: Two anaesthesiology residents

Anaesthesiologists are perioperative medical specialists who provide medical care to patients before, during, and after surgical procedures. Airway management, intraoperative life support, and pain control are essential skills. Besides their work in the perioperative field as physicians and nowadays often as managers as well, anaesthesiologists are involved in Intensive Care Units, Postoperative Anaesthesia Care Units, Pain Clinics, and last but not least emergency medicine including the helicopter Mobile Medical Team. Besides their clinical work anaesthesiologists are involved in teaching and research. In the University Medical Center Groningen (UMCG) residents and staff members are trained in an ultramodern Skills Lab where all kinds of situations can be simulated. Research in the UMCG is focused on pharmacokinetics (what the body does to a drug), pharmacodynamics (what a drug does to the body), neuroscience, hemodynamics, and blood coagulation.

This anaesthesiology workshop provides a basic approach to patient care. Participants will deal with various aspects of vascular access.

**How to perform tracheal intubation**

Department: Anaesthesiology, University Medical Center Groningen

Supervisors: Two anaesthesiology residents

Anaesthesiologists are perioperative medical specialists who provide medical care to patients before, during, and after surgical procedures. Airway management, intraoperative life support, and pain control are essential skills. Besides their work in the perioperative field as physicians and nowadays often as managers as well, anaesthesiologists are involved in Intensive Care Units, Postoperative Anaesthesia Care Units, Pain Clinics, and last but not least emergency medicine including the helicopter Mobile Medical Team. Besides their clinical work anaesthesiologists are involved in teaching and research. In the University Medical Center Groningen (UMCG) residents and staff members are trained in an ultramodern Skills Lab where all kinds of situations can be simulated. Research in the UMCG is focused on pharmacokinetics (what the body does to a drug), pharmacodynamics (what a drug does to the body), neuroscience, hemodynamics, and blood coagulation.

This anaesthesiology workshop provides a basic approach to patient care. Participants will deal with various aspects of airway management. Participants will have to solve different ventilation problems. You will be assisted by trained anaesthesiologists to keep the patient safe and sound.
Inside the psychotic experience: a conversation with a patient

Department: Psychiatry, UMCG
Supervisors: Frank D. van Es MD

Psychosis is a generic psychiatric term for a mental state often described as loss of contact with reality. Patients experiencing psychosis may report hallucinations (seeing or hearing things that are not there) or delusions (false beliefs about what is taking place or who one is). The combination of both can cause an often severe disruption to perception, thinking, emotion, and behaviour. Depending on its severity, a psychotic episode may thus be accompanied by unusual or bizarre behaviour, as well as difficulty with social interaction and, impairment in carrying out daily life activities. As a result, patients with psychosis are caught in a hostile environment. They are therefore in need of your dedication and medical skills: how can you meet their needs? How can you avoid stigma and promote health and social recovery?

During this workshop you will be able to ask questions to a psychiatrist and a patient who has suffered from psychosis.

Lab-on-a-chip

Department: Research Institute of Pharmacy
Supervisors: P.P.M.F.A (Patty) Mulder MSc, Prof. E.M.J. (Sabeth) Verpoorte PhD

Over the past couple of decades Lab-on-a-chip technologies made inroads into laboratories focusing on the development of fast chemical and bioanalytical analyses using minute volumes of sample. Micro- and nanotechnologies are used to construct interconnected microchannel networks in planar substrates, forming microfluidic devices to replace more conventional chemical vessels such as beakers, and columns to achieve ultra-small-volume (10-6 to 10-15 µL) liquid handling. Small handheld analysers are one result, suitable for medical diagnostic, agricultural, environmental, and other applications.

The last fifteen years, lab-on-a-chip technologies have also found increasing application for cell biological studies, as cell microenvironments can be exquisitely engineered to mimic in vivo environments. It becomes possible to think about assembling tissue constructs or actual tissue samples in physiological configurations in specially designed lab chip systems, so-called “body-on-a-chip” or “human-on-a-chip” system. This may lead to an improved capability to study in vivo processes in vitro. Organ interactions can be revealed in these systems, giving insight not only into drug toxicity but also into more subtle regulatory pathways between organs.

This workshop will give a short glimpse into how a laboratory is actively involved in the realisation of lab chip systems for sensing/analytical chemistry and cell culture and analysis. Participants will see the fabrication of those devices and the basic principles of microfluidics. Besides that, they have an opportunity to discuss about other possible medical uses of the lab-on-a-chip technologies with researchers in the lab.
Liver transplantation with machine perfusion

Department: Surgery
Supervisors: O.B. van Leeuwen

Every year in the Netherlands one out of three donor livers are not used for transplantation. With an ageing population with a rising BMI, more and more donor livers are expected to be declined for transplantation in the coming years.

The University Medical Center Groningen is leading in the field of organ preservation. Every declined liver in the Netherlands is currently tested in Groningen by using a perfusion device. Many of the previously declined livers are now actually transplanted with very good results.

In this hands-on workshop, you will learn the difficult anatomy of the upper abdominal region and you will practice preparing (porcine) donor livers for ‘transplantation’ and machine perfusion. You will cannulate the aorta and the portal vein and close all arterial branches of the hepatic artery. Hereafter, you can test whether you performed these procedures in a waterproof manner as your liver will be connected to the perfusion machine.

After this workshop, you will not only be an expert in the hepatobiliary and pancreatic anatomy, but also in suturing and knot tying.

Suturing

Department: Surgery, UMCG
Supervisors: Non Nominatus

Get a head start on learning a fundamental surgical skill. Our suturing workshop provides you with the training and materials to practice a variety of suturing methods (simple interrupted, simple continuous and, subcutaneous) on real porcine skin. The workshop consists of two parts. The first part is a theoretical outline of several aspects of wound closure, illustrated with pictures and short animations. The second part is a practical session that features the guidance of an attending surgeon, allowing personal instruction for every participant. By the end of the workshop, students leave with basic skills necessary to practice basic suturing and achieve mastery.

Please note: The practicing will be on real pig’s legs.
Macro- and microscopic suturing

Department: Research Support Facility – Central Animal Facility

Supervisors: Annemieke van Oosten, PhD
            Catriene Thuring, DVM, PhD

Microsurgical techniques have gained importance in recent years. The more delicate and sophisticated a surgical technique is, the more it requires training and education. The purpose of this workshop is to teach the students the proper way to handle their surgical instruments, how to tie a suture in the correct way, and to provide an opportunity to test their hands in the fine art and skill of micro suturing.

Please note:

For permission to participate in the workshop it is important that you have not had contact with rodents or rabbits in the 24 hours prior to the workshop. In this way we want to prevent unwanted transmission of pathogenic micro-organisms to our laboratory animals.

Onco-pathology: diagnose a biopsy

Department: Oncology, UMCG

Supervisors: Prof. Harry Hollema MD PhD

Despite the introduction of sophisticated techniques in modern pathology, macroscopic interpretation of resection specimens remains a cornerstone in the daily practice of surgical pathology. After a short introduction regarding the role of pathology in oncologic patient care and basic terminology the participants will be asked to interpret five macroscopic specimens from surgical resections. Questions will be focused on the most likely diagnosis, carcinogenesis and, T stage in relation to prognosis and therapy. Four pathologists will be present to assist and answer questions during the workshop.
Positive energy in cancer treatment

Department: Radiation Oncology, UMCG
Supervisors: Hiske van der Weide MD, Roel Kierkels MS, Stefan Both FAAPM PhD

Radiation oncology is a rapidly evolving field where innovative technology, physics, and medicine merge and enhance one another. Pencil beam scanning (PBS) is a relatively new radiation therapy technique that involves protons instead of traditional X-rays. PBS offers new opportunities for cancer patients, who benefit from significant reduction of radiation exposure to normal tissues. In certain patients this may lead to less side effects and consequent irreversible late complications of treatment.

During this workshop, you will have the opportunity to participate in our ‘radiotherapy operating room’. In an interactive manner, you will experience the processes of radiation treatment planning and radiation delivery. You will be part of discussion on patient selection including ethical issues and cost effectiveness, and ongoing scientific investigations to compare PBS to other radiation therapy techniques.
Plastic surgery: How does a tissue expander work? How is a detailed exam of the hand performed?

Department: Plastic Surgery, UMCG
Supervisors: Vera van Aalst, plastic surgeon
Sophie Post, resident plastic surgery

Plastic surgeons perform a variety of different reconstructive and aesthetic procedures. These vary from basic wound care to extensive reconstructions after tissue loss or removal due to trauma or disease, like cancer. At the University Medical Center Groningen (UMCG) we collaborate with many different medical specialists. Considering the high incidence of breast cancer (more than 1 in 8 women will have breast cancer in their lifetime), a large part of our practice focuses on breast reconstruction after cancer removal. For this reconstruction, we not only have the option of using patients’ own tissue, but also implants. A tissue expander is a temporary implant which we use to expand soft tissue to create a pocket for a permanent implant.

Another focus of our practice is hand surgery. To be able to make a correct diagnosis and choose appropriate (surgical) treatment it is important to perform a detailed and comprehensive exam of the hand.

There are two main goals of this workshop. First, to familiarize participants with different treatment options available for breast reconstruction. Specifically, they will learn how to use (and fill) a tissue expander. Secondly, participants will learn how to perform a detailed and comprehensive hand exam.

Practical ultrasound

Department: Medical Imaging Centre (MIC), UMCG
Supervisors: Theo Kok MD PhD

Medical ultrasonography (sonography or ultrasound) is a diagnostic imaging technology used to visualise internal organs, their size, structure, and any pathological lesions using high frequency sound. (Humans can only hear in the range of about 30 to 20,000 cycles per second while ultrasonography frequency falls in the megahertz range: millions of cycles per second). Ultrasound is different from x-ray because it uses mechanical sound energy rather than radiation to produce images. Furthermore, ultrasound provides a thin tomographic slice (similar to CT), rather than a flat plane projection like x-ray or fluoroscopy. It also has the advantage of being real-time rather than static and it can display not only images, but Doppler information as well. This is very useful in assessment of blood flow.

For ultrasound imaging, a hand-held probe (called a scan head) is placed directly on the abdominal wall. Acoustic gel is used to couple the probe to the body, because the high frequency sound waves do not travel well through air.

After a short introduction (physics and clinical examples), the students are able to practice ultrasound on each other. The normal anatomy of several intra-abdominal organs and vascular structures will be visualised.
**Real sounds sent out by your ear**

Department: Otorhinolaryngology, UMCG  

Supervisors: Bert Maat MSc  

72% of healthy human ears are emitting acoustic energy just below the hearing threshold. This phenomenon is called Spontaneous Otoacoustic Emission (SOAE). The origin of this acoustic signal lies within the cochlea. Outer hair cells (OHC’s) in the cochlea are believed to play a key role in generation of Otoacoustic Emissions (OAE’s). OAE’s have been found in other mammals, as well as in non-mammals as well, such as lizards, frogs, and birds, sharing this fundamental biophysical mechanism. What can we learn from this fundamental mechanism, do they interact with incoming sounds, why do they exist, and can we make use of OAE’s in diagnostics? But the bigger question is: do you have SOAE’s? In this workshop you will find out.

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**Simplicity in complex woundcare**

Department: Dermatology, UMCG  

Supervisors: M. Ruettermann (plastic surgeon) MD  
M.J. Wiegman (dermatologist) MD  

An undisturbed primary wound healing proceeds according to a number of phases (hemostasis, inflammation, regeneration, maturation). A large number of factors play a role in these phases. When one factor is missing and a phase cannot be fully completed, the healing process stagnates and a complex wound arises. Wound care is therefore a lot more complex. In addition, the extensive range of wound care products on the market also plays an influential role. Factors that play a part in the choice of the suitable product are: purpose of the wound care (moist, dry, cleaning, protection, comfort, etc.) based on evidence, best practice and, cost effectiveness. A tool to determine your goal is to use the international classification model TIME. By approaching a wound in a systematic way your goal becomes clear. Then choose the product based on your goal. On the basis of case studies, you learn to classify a wound and thereby choose the most suitable material to treat the wound efficiently and cost-effectively.
Surgical anatomy of the heart and surgical treatment of heart failure: LVAD

Department: Cardiothoracic Surgery, UMCG
Supervisors: Michiel Erasmus MD PhD
            Prof. Massimo Mariani MD PhD

Heart failure is an increasing problem. Until recently, heart transplantation was the only effective option to prolong survival of patients with end-stage heart failure. Nowadays it can be treated by implantation of a left ventricular assist device (LVAD). In this workshop the problem of end-stage heart failure, the relevant cardiac anatomy, and concepts of different types of left ventricular assist devices will be discussed (emergency implantation and destination therapy). The implantation technique of an internal LVAD used for destination therapy will be shown on a cadaver. Four randomly selected students will assist in this operation and the rest of the participants will follow the implantation closely on a live video stream, supervised by a cardiothoracic surgeon. After this workshop, medical students will understand the entity of heart failure and the concepts and problems related to LVAD therapy.

Surgical anatomy of the heart and hybrid treatment of arterial fibrillation

Department: Cardiothoracic Surgery, UMCG
Supervisors: Michiel Erasmus MD PhD
            Prof. Massimo Mariani MD PhD
            Wobbe Bouma, MD PhD

Coronary artery disease affects millions of patients worldwide and is highly related to the western lifestyle. It is a disease that develops slowly and affects both the cardiac morphology and function over the years. This workshop will focus on the morphology of ischemic hearts and the surgical strategies to prolong survival when significant stenosis causes serious complaints. Lectures are combined with a live stream coronary artery bypass graft (CABG) operation on a beating-heart model in a human cadaver. Four randomly selected students will assist the operation. The rest of the participants will follow the operation closely via a live video stream, supervised by a cardiothoracic surgeon.
Speeddating with researchers

Department: UMCG
Supervisors: Non Nominatus

During this workshop you will get the chance to get in touch with researchers from the different Research Institutes of the UMCG (more information about the UMCG Research Institutes can be found under “Research in Groningen” on our website). The researchers will tell you everything about their current research projects, their departments and what it is like to do research (at the UMCG). You can choose the research (sub)topics of your own interest! Therefore you have to the chance to meet the expert in the UMCG in your field of expertise.

This workshop is meant for presenting students interested in (doing) (PhD-)research at the UMCG. Everyone will be able to talk to three different researchers. You might want to exchange some contact information during that time for any future correspondence. Do not underestimate the possibilities of what these short introductions and first impressions can offer you. Please note that research in the UMCG is performed mainly by PhD/master students and covers the entire range of (bio)medical sciences. Research involving patient contact and/or performing a residency is very difficult.

You will receive detailed information about the researchers and departments participating in this workshop several weeks before the congress. Afterwards, you can get a list of all the email addresses for you in order to contact the Research Institute of your choice in the future. The registration for this workshop stops at the 14th of April. This is in order for us to find the best match between you and a researcher from the UMCG.

Labvisit with PhD students

Department: Laboratory facility, UMCG
Supervisors: Non Nominatus

During this workshop you will get the opportunity to visit research laboratories in the UMCG. You will get a guided tour from a PhD student. Meanwhile you can ask this student anything you want to know about doing research in Groningen. Also, they will show the kind of research that is performed in the labs, and tell their own experiences with doing research here.
The miracle of giving birth

Department: Clinical Training Center, UMCG

Supervisors: Marco A.C. Versluis MD PhD
Dennis Beekhuis MD

General childbirth, also known as labour, is an unique event showing the miracle and power of nature. Although it is a physiological event of itself, childbirth is one of the most fascinating aspects of medicine, which mostly deals with pathophysiological processes.

Childbirth is the culmination of the gestation and pregnancy period with the expulsion of one or more newborn babies from a woman's uterus into a completely different environment. At that particular moment, being disconnected from the mother’s circulation after cutting the umbilical cord, the newborn faces a very serious and complicated adaptation of his own circulation to the onset of his own respiratory system.

The process of a normal vaginal human childbirth is categorised into four stages. Stage 1: The onset of birth is initiated by a metabolic change in the infant which causes the release of the hormones needed for uterine contractions. Stage 2: The process of shortening and dilation of the uterine cervix is caused by uterine contractions. This process facilitates the head of the infant to enter into the birth canal. Stage 3: The continuation of uterine contractions with the help of the mother's pressing, pushing the baby through the birth canal into the baby’s new world. Stage 4: The delivery of the placenta. The expulsion of the placenta mostly starts spontaneously approximately twenty minutes after the occlusion and the cutting of the umbilical cord.

During this workshop more details will be given on monitoring labour, pain control, and problems that may happen before and during delivery including the therapeutic possibilities if these problems occur. You are also given the opportunity to deliver a baby using a mannequin, simulating the real situation.

Transgenders: A debate with the UMCG genderteam and a patient

Department: Genderteam UMCG (gynaecology and plastic surgery)

Supervisors: Tim R. Middelberg MD PhD
Tallechien M.T. Tempelman MD
M. van den Berg MD
Marga Tjallingii MSc

Transgender people experience a mismatch between their gender identity or gender expression and their assigned sex. Transgender is an umbrella term, because in addition to including trans men and trans women (whose binary gender identity is the opposite of their assigned sex), it may also include gender queer people (whose identities are not exclusively masculine or feminine, for example: bigender, pangender, genderfluid, or agender).

Since the late 70’s the University Medical Center Groningen (UMCG) in the Netherlands offers a treatment programme for transgenders, according to the professional standards of the World Professional Association of Transgender Health (WPATH). Once patients have been diagnosed with genderdysphoria by the psychiatrist, the ‘real life phase’ starts. This includes living their gender
identity and cross sex hormone therapy. When the ‘real-life phase’ has been followed through with success, one can apply for sex reassignment surgery. After these operations, lifelong continuation of cross sex hormone therapy is needed to maintain secondary sex characteristics of the desired gender.

What does the transition contain and cause physically, mentally, and socially and how can we guide the patients in this process? During this workshop you will be able to ask questions to a member of the UMCG Genderteam and a transgender patient.

**Transeosophageal echocardiogram (TEE)**

Department: Anesthesiology, UMCG

Supervisors: Jayant Jainandunsing MD  
Nini E.M.E. Craenen MD

Anaesthesiologists are medical specialists who provide medical care to patients before, during, and after surgery. Our main tasks are airway management, intraoperative life support, and pain. The field of Anaesthesiology is not only restricted to the operating room. Anaesthesiologists are involved in Intensive Care Units, Postoperative Anaesthesia Care Units, Pain Clinics, and Emergency medicine including Mobile Medical Trauma Team.

In the University Medical Center Groningen (UMCG), residents and staff members are trained in our state of the art Skills Lab where all kinds of medical and/or peri-operative situations can be simulated.

The training to become an anaesthesiologist consists of a 5-year program. The main pillars of anaesthesiological training are physiology and pharmacology. After residency, additional training can be done to become a super-specialist such as cardiac anaesthesiology, paediatric anaesthesiology, intensive care, pain management or emergency care.

Cardiac-Anaesthesiologists are involved in cardiac and lung surgery, one of the tools used to assess cardiac function is transesophagaeal echocardiography (TEE). TEE is one of the essential tools during cardiac surgery to asses function and provide the surgeon with additional information. In this workshop you will get an introduction into TEE. After a short introduction you will be challenged to make a TEE yourself on a virtual reality simulator. Another clinical assessment tool is the bronchoscope. During lung surgery, the use of a bronchoscopy is necessary to asses positioning of the airway tube and to see whether tracheal suture lines are properly made. In this workshop you will get a hands-on experience on our bronchoscopy simulator.
On Monday the 3rd of June, the pre-course will take place. The pre-course is organised for international students, and aims at improving your research skills. To master your research skills, several masterclasses are organised. In addition, a lecture about Your Future at the UMCG, two speed keynote lectures, a Science Elective and to finish the day, a spectacular salsa workshop is organised to improve your dancing!

**Monday, 3rd of June - Pre-course**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>08:15-09:00</td>
<td>Registration</td>
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<tr>
<td>09:00-09:30</td>
<td>Day opening</td>
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<tr>
<td>09:30-11:10</td>
<td>Course 1</td>
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<tr>
<td>11:10-11:50</td>
<td>Break</td>
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<tr>
<td>11:50-13:20</td>
<td>Science Elective</td>
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<td>13:20-14:30</td>
<td>Lunch</td>
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<td>14:30-15:00</td>
<td>Your Future at the UMCG</td>
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<td>15:00-16:00</td>
<td>Speed keynote lectures</td>
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<td>16:00-17:30</td>
<td>Course 2</td>
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<tr>
<td>19:00-23:00</td>
<td>Social Programme</td>
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Marthe Walvoort PhD is an assistant professor of Chemical Biology at the Stratingh Institute for Chemistry at the University of Groningen. She combines her expertise in (organic) chemistry and biochemistry to unravel the impact of sugars in health and disease.

Sugars are naturally present in many molecular shapes and forms, and not limited to the sugar sucrose that is currently blamed as the next bad thing in our food. Sugars are crucial mediators of many human cellular processes like cell-cell interactions, signaling and the immune response, and are also heavily involved in host-pathogen interactions. For instance, bacteria display a diverse array of exotic sugars that are absent from humans. These sugars play a crucial role in infection and bacterial survival. Using inhibitor development, protein expression and enzyme activity assays, a solid chemical biology research line dedicated to bacterial glycobiology is being established. Enzymes involved in bacterial glycoprotein synthesis, and the biosynthetic machinery to make bacterial carbohydrates are central to this research line. We are currently investigating the glycoprotein synthesis machinery from Haemophilus influenzae, Pseudomonas aeruginosa and Neisseria meningitidis, to understand their molecular mechanism as a basis for novel antibiotic therapies. And as the production of oligosaccharides is still far from straightforward, especially when compared to peptides and nucleotides, several projects in the Walvoort group are devoted to the development of novel methods to synthesize oligosaccharides, based on chemical, enzymatic and automated methods. We aim to synthesize oligosaccharides inspired by the ‘healthy’ sugars found in human milk and on probiotic bacteria, and use them in biological studies to understand their structure-function relationship.

Marthe Walvoort obtained her PhD degree in 2012 (cum laude) at Leiden University (the Netherlands) on the organic chemistry of carbohydrates. Her research included the investigation of the mechanism of glycosylation of mannuronic acids, and she led the automated synthesis of β-mannuronic acid alginates and hyaluronan using a second-generation solid-phase oligosaccharide synthesizer. This was followed by a postdoctoral period of 3 years in the group of Prof. Barbara Imperiali PhD at Massachusetts Institute of Technology (Boston, USA). There she led the development of phosphoglycosyltransferase inhibitors inspired by nucleoside antibiotics, and was involved in a collaborative effort to link a bacterial infection to biomarkers in multiple sclerosis by producing N-linked glycoproteins. In November 2015, Walvoort joined the University of Groningen as Assistant Professor and Rosalind Franklin fellow in the Chemical Biology division at the Stratingh Institute for Chemistry, which is headed by Prof. Adriaan J. Minnaard PhD. She was awarded with a VENI grant in 2016. Also, Walvoort is one of the founding members of the Young Academy Groningen, which is a recently established group of talented early-career researchers across all disciplines. She is active in the Netherlands Research School on Chemical Biology. Further information can be found at www.chemicalbiologygroningen.nl
Simeon Ruiter is working as a technical physician at the University Medical Center Groningen, in the Department of Hepatobiliary Surgery. His focus on both clinical work as well as research includes (percutaneous) thermal ablation of liver tumors. In collaboration with the University of Twente and a mechatronic company, they developed a robotic arm for percutaneous needle placement for the treatment of liver tumors. Simeon Ruiter will share his experience of developing and introducing this new technique in clinical practice.
Doctor Sietske Berghuis is working as a post-doctoral researcher in the Department of Pediatrics at the University Medical Center Groningen. She is interested in Pediatric Environmental Health, including the impact of environmental chemicals on child development.

Several chemical compounds are resistant to degradation and end up in the food chain. One group of these chemicals are polychlorinated biphenyls (PCBs), i.e. used as plasticizers. Although PCBs have been banned since 1985, 17 years later they were still detectable in all pregnant women and showed to transfer to the fetus, in a Dutch cohort study. This raises the important question whether this prenatal exposure can influence the development of the child.

Doctor Berghuis is the project leader of the follow up study at adolescence, aiming to determine whether exposure to chemicals is associated with pubertal development, neuropsychological status, thyroid hormone homeostasis, and metabolic status. She will present the results of the longitudinal cohort study, including the finding that higher exposure to PCBs during pregnancy is associated with advanced pubertal development in both boys and girls.
How to make a research poster?
Erik A.M. Veschuuren MD PhD
Prof. Tjip S. van der Werf MD PhD

After you have been busy with your research for months to years, it is finally finished! You now would like to share your work with the rest of the world and send your abstract to a congress. One of the ways to present your work is through a research poster.

Research posters are widely used in the academic world. Most of the congresses give presenting-participants the opportunity to present their work with a poster presentation. The research posters will summarize the research you’ve done and will help to generate a discussion about the topic.

A research poster is usually a mixture of a short text with pictures, graphs, tables, etc. During the congress, the presenter stands by the poster display while other participants of the congress can come, view the presentation and interact with the presenter.

During this interactive course you will assess a number of posters and discuss this with the other participants. You can discuss the points of improvement and you will learn how an excellent poster differs from a good poster.

Medical statistics
Johannes G.M. Burgerhof MSc
Sacha la Bastide-van Gemert MD

In 90 minutes, an overview of statistical techniques will be given. Together with the participants several questions will be answered including:

• What is the link between probability theory and statistics?
• Why is it important to use descriptive statistics?
• What is a statistical test and when do we use which test?
• How do we calculate a sample size?

Based on the article of Phung et al. (2002) on risk factors for low birth weight, we will go through several steps of the statistical process. Starting with descriptive statistics, refreshing the theory of univariate tests and confidence intervals, we will end up making and interpreting several regressions models: linear, logistic and Cox regression for survival.

Emphasis will not be on formulas and mathematics, but on understanding the logic behind the statistical tools. Depending on the interest of the participants, more time can be spend on elementary or advanced statistics.
Critical Reading  
Prof. Pieter U. Dijkstra PhD

Medical students are supposed to read an enormous amount of information in textbooks, on the internet, and in medical journals. Research is progressing fast and textbooks often contain dated information. Recent manuscripts provide up-to-date information. However, are we certain that the presented information is valid and should be implemented in patient care? Critical appraisal of a manuscript enables the assessment of the validity of the study results. In this pre-course class, participants will be provided with a general approach to critically appraise clinical research papers and assess research design, identify selection bias, information bias, and confounding factors. Different research designs will be presented, and strengths and weaknesses will be discussed. Participants will assess a paper critically. The results of the assessment will be discussed in the masterclass.

Preparing oral presentations  
Prof. Anton J.W. Scheurink PhD

This masterclass will provide strategies for preparing interesting and engaging presentations. The essence of an effective presentation is engaging the audience, capturing their interest by posing an intriguing question, spelling out a methodology for addressing that question and then answering it. A successful presentation provides the audience with cues and information in an orderly structure, allowing them to form expectations on what they will hear and when they will hear it. Tips for doing so, along with tips on what not to do, will be supplied. The presenter will engage participants in a highly interactive format by crafting storylines and structures from material that they provide. The main focus of this masterclass will be on oral presentations but at the end we will give some do’s and don’ts on poster presentations as well.

Famelab  
Bart J. van de Laar MD

X-factor, The Voice, MasterChef, you name it. Talent scouting is a big thing and results in prize winning television. However, do we embrace science communication talent just as passionately as we embrace young singers and chefs? Or is science communication too important to be in the hands of young talents? On the other hand, they do shape the future of science.

FameLab is the number one international science communication contest, inviting scientists, mathematicians and engineers across the globe to take part. The FameLab contestants only have three minutes to convey a scientific concept of their choice to a professional jury. It is not allowed to use a PowerPoint or any other tool to facilitate the clarity of the presentation. All contestants are judged on the three C’s: content, clarity and charisma. An unforgettable presentation might make one the winner of a national or international FameLab competition someday. Moreover, you’ll learn to master an essential skill for a PhD-student or post-doc to engage future research partners, funders and all sorts of audiences.

This hands-on masterclass challenges participants to prepare and present a three minute presentation according to the FameLab rules. The masterclass is convened by Bart van de Laar, Dutch FameLab pioneer and regular local/national convenor, together with the winners of this year’s Groningen FameLab heat.
Scientific Integrity
Els L.M. Maeckelberghe PhD

50 shades of scientific integrity: a VIW (a Very Interactive Workshop)
Scientific integrity is an important topic in research, but what does it actually mean? What is ethically sound behavior? Are there any guidelines for scientific integrity, including plagiarism?

There is no clear definition of what ‘scientific integrity’ is supposed to mean. However, it is acknowledged that scientific integrity should be guarded, warranted and monitored at both individual and institutional levels. Fraud, Falsification and Plagiarism (also known as FFP) are probably the most well-known violations of scientific integrity.

Els L.M. Maeckelberghe PhD, lecturer of ethics at the UMCG, will host a masterclass on scientific integrity. A film about a PhD student at the beginning of her doctoral research will serve as a guide in this course. The audience decides how to respond to realistic scenarios where there is potential for misconduct. The participants will discuss the options and decide together what to do in these specific cases. It is promised to be an interesting and informative masterclass on Scientific Integrity!

An abstract: the invitation to your research
Prof. Marianne G. Rots PhD

The scientific abstract is one of the most important parts of a scientific paper or grant application as it presents the features of your research and with that immediately shows the quality of the paper. Your abstract can therefore be an invitation for fellow researchers to find out more about your research. This workshop is all about the writing of a convincing scientific abstract. The learning objectives are directed towards the structure of the abstract as well as towards effective and comprehensible formulation of complex problems and research constructions. The course will consist of a short lecture followed by assignments in groups and discussions.

How do scientific reviewers review your article?
Prof. J.A. Lisman PhD

After years of meticulous study design, data analysis and perfecting your article, there is only one task left; getting your article published!

How do you choose the right scientific journal for your manuscript, and what happens after the submission of your article to your journal of choice? Which features render your paper attractive to the editor and how do you increase the likelihood that your manuscript will be sent out for review? What will convince the reviewers that your work is good and how do you respond to their comments? How do you react to a rejection by the editor, would you accept it or fight for your article?

Prof. J.A. Lisman PhD will help you to find the answers of all these questions in this very interactive Masterclass.
If you want to know more about PhD positions and research at the University Medical Center Groningen (UMCG), come to Your Future at the UMCG! The director of the Graduate School of Medical Sciences (GSMS) Martin J. Smit PhD, will give a detailed presentation about the possibilities of doing research and the opportunities to gain a PhD position at the UMCG. The session will be concluded with a personal story from a PhD graduate.
The Science Elective will be held between the masterclasses. Besides the educational parts of the day, the Science Electives are meant to be a fun part of the day! You can choose between a patient lecture, a debate, thinking critically about the approach of House MD and listening to a fascinating Triple-B lecture.

In the patient lecture, a patient who has suffered from psychosis will tell you everything you want to know about the disease and the influence it has on the patient’s life, together with Frank D. van Es MD.

This year, the debate will be about ethics considering organ donation. The leading statement during this debate will be: ‘People with a healthy lifestyle should be placed higher on the waiting list for donor organs’. Two experts will set the stage for a thorough reflection on the ethical challenges facing us.

During the interactive lecture of House MD, a doctor specialised on the subject will analyse an episode of the fascinating House MD series and discuss the myths and facts of doctor House.

A new subject this year will be the Triple-B lecture. Triple-B stands for ‘from Bed to Bench and Back’. In the Triple-B lectures the emphasis will be on the relationship of scientific research (bench) with the clinical practice in the hospital (bed). The Triple-B lecture of this year will be about pre-eclampsia and will be given by Prof. Sicco Scherjon PhD.
**Patient lecture**

*Frank D. van Es MD*

Psychosis is a generic psychiatric term for a mental state often described as loss of contact with reality. Patients experiencing psychosis may report hallucinations (seeing or hearing things that are not there) or delusional beliefs (false beliefs about what is taking place or who one is). The combination of both can cause an often severe disruption to perception, thinking, emotion, and behaviour.

Depending on its severity, a psychotic episode may thus be accompanied by unusual or bizarre behaviour, as well as difficulty with social interaction and, impairment in carrying out daily life activities.

As a result, patients with psychosis are caught in a hostile environment. They are therefore in need of your dedication and medical skills: how can you meet their needs? How can you avoid stigma and promote health and social recovery?

During the patient lecture you will be able to ask questions to a psychiatrist and a patient who has suffered from psychosis.

**Debate on organ donation**

*Els L.M. Maeckelberghe MD*

*Machlon Huiting*

A transplant is the replacement of a poor functioning or completely non-functional organ/tissue of a patient, usually by a donor organ. Organs that can be transplanted include the heart, lungs, kidneys, pancreas, small intestine, cornea and liver. Parts of organs and tissues such as skin, liver or bone marrow are also transplanted. The difference between an organ transplant and a tissue transplant is that an organ transplant can be lifesaving, while a tissue transplant is not necessarily. Many lives have already been saved through the possibility of transplantation. Yet some ethical questions arise around organ donation.

Currently more donor organs are needed than there are available. This raises the question what measures can be taken to solve this discrepancy. During the pre-course debate, we will address the statement: ‘People with a healthy lifestyle must be placed higher on the waiting list for donor organs’. Possible ethical questions one could ask are: Does someone who has obesity have as much right to an organ as someone who has a healthy weight? Does an athlete have the same right to an organ as someone who hardly moves? Dr. Els L.M. Maeckelberghe and Machlon Huiting will lead this debate.

Dr. Els Maeckelberghe, ethicist at the UMCG, will lead the debate and will challenge the audience to think about what today and the future holds in stock for us. She will invite everybody to engage in setting an agenda for responsible engineering of life. Machlon Huiting, transplantation coordinator at the UMCG, can tell us everything about organ donation.
House MD

In this Science Elective we will analyze an episode of the fascinating House MD series. During this Science Elective, a specialist on the topic of the episode will discuss the facts and myths of a House MD episode. Doctor Gregory House is not known for his commitment and empathy towards his patients, staff or interns. These characteristics often place him, his colleagues and patients in problematic situations. However, to what extent is an episode realistic? Are the disease characteristics of the patients similar to those in real life? And are the used diagnostic tools actually suitable? What can we actually learn from this television programme?

These questions will be answered during this interactive course, where participants will be able to judge and discuss the authenticity of a House MD episode.

Triple-B lecture

Triple-B stands for ‘from Bed to Bench and Back’. In the Triple-B lectures the emphasis will be on the relationship of scientific research (bench) with the clinical practice in the hospital (bed). The Triple-B lecture of this year will be about preeclampsia and will be given by Sicco A. Scherjon MD PhD.

It takes two to tango: maternal-fetal immune interactions

Pre-eclampsia, affecting 3-8% of all pregnancies, is one of the main pregnancy complications of which the pathophysiology is only partly understood and treatment is given when the baby is delivered. It is worldwide responsible for a majority of maternal morbidity, fetal and neonatal mortality and (neurodevelopment) morbidity. In this presentation we will discuss epidemiological arguments why the immune system is involved in the pathogenesis, elucidating the extreme value of unique clinical observations, resulting in fundamental research approaches in the field of (reproductive) immunology. The importance of T-cell regulation, the need for cellular recognition and induction of T cell tolerance mechanism are resulting in the start of innovative intervention trials at the UMCG. They will show how research and patient care benefits from bedside to (lab) bench interaction and translation of findings at the laboratory to clinical study protocols.
Social Programme

Sunday 2nd of June 2019
If you are already in Groningen on Sunday, you can participate in the city tour we organise on Sunday evening. We will walk through the historic city centre of Groningen and show you the most beautiful and fun spots in the city. The tour will end at ‘De Drie Gezusters’, a famous restaurant & bar in the city centre, where the welcoming night will take place. At this bar, we will join a pub quiz together while enjoying a few drinks. It is a good opportunity for you to meet other participants, the ISCOMS Organising Committee and the First Year Crew! You are always welcome to join the welcoming night, regardless of your participation in the city tour.

Monday 3rd of June 2019
Most of the presenting participants will arrive on Monday. On this day, the pre-course of the congress will take place. Registration for the pre-course is required. You can also choose to discover our beautiful city and have a look in the UMCG on your own occasion. When the educational programme is finished, the Organising Committee will guide you to ‘Het Platformtheater’ the location where we will have dinner together. Afterwards, you have the opportunity to participate in a salsa dancing workshop! The perfect chance to blow off some steam and show everyone your dancing skills!

Tuesday 4th of June 2019
On Tuesday, the ISCOMS Recreational Evening will take place. The evening will start with a BBQ, organised at a ‘De Drie Gezusters’. Afterwards, everybody is going to the activity they have chosen beforehand: bike cycling through Groningen, playing billiards with other participants, bowling, a typical Dutch cheese tasting at a local Cheese Shop ‘De Kaaskop’, a yoga workshop and a tour through the football stadium of our local club FC Groningen.

Wednesday 5th of June 2019
On Wednesday, we will have a formal dinner at one of the most prestigious places of Groningen: the historical “Der Aa-Kerk”. This church will be transformed into a fancy dining room with a capacity of 350 people! An outstanding three-course dinner will be served, among which you can choose between meat or vegetarian dishes. You will have the opportunity to get to know the other ISCOMS participants and to meet some of the professors who will be present at the formal dinner. Bring your most elegant dress or best suit to look amazing that night!

Thursday 6th of June 2019
After the last congress day and the closing ceremony, we will go to ‘Huize Maas’ where the World Wide ISCOMS Night will take place! We are going to start with a delicious buffet. Afterwards, the great party will begin. This night is all about the traditions of the different countries represented at ISCOMS. Dress up in traditional clothes and bring a traditional snack of your country. We would love to play music specifically from your country! A few weeks before the start of the congress, a WeTransfer link will be available through which you can submit your favourite music from your country. The DJ will take care of the rest and make sure you have an unforgettable night!
To finish off our great congress, there will be a Post Congress Tour (PCT) on Friday the 7th of June. On this day you will be able to enjoy a typical Dutch afternoon with 100 other participants and the Organising Committee of ISCOMS 2019.

Every year the PCT consists of the perfect balance between experiencing the unique Dutch culture, relaxation, and enjoyment. It will give you the perfect opportunity to blow off some steam after the intense congress days. This year we will visit the beautiful city of Leeuwarden. We will travel by bus from Groningen to Leeuwarden, which will take about one hour.

Leeuwarden is the capital of the province of Friesland. As is the case with all old city centres in The Netherlands, the old centre of Leeuwarden is compact and can easily be explored on foot. Furthermore, Leeuwarden is strongly characterized by its culture. And for that reason Leeuwarden also became the European Capital of Culture 2018.

During the PCT you will get to see the city and its culture by a augmented reality walking tour. In addition, we will visit the frisian museum, which exhibits the history of the Frisian people, so you can see how its inhabitants lived in the old days!

The Post Congress Tour will ultimately end the wonderful experience of ISCOMS 2019. This day will be spent with members of the Organising Committee and other participants that will guarantee you a lovely day. See you there!
Plenary sessions

Presenters

Freitas, T.R. (Thaís)
García-Bellido, SGB (Sara)
Hamelink, T.L. (Tim)
Hassanipour, M. (Mahsa)
Kristen, M.K. (Marleen)
Tauer, ST (Sebastian)
Vijaya Mohan, S.V.M (Sivanesan)
Zhang, B.Z. (Boyan)
Simulation in health education: development of a simulator for ultrasound-guided vascular access

Freitas, T.R. (Thaís)¹, Carvalho, V.B. (Vinícius)¹, Estrutti, C.M. (Carolina)¹, Moura Neto, A.C (Antonio)¹, Vasconcelos, V.T. (Vladimir)¹, Carneiro Junior, F.C.F (Francisco)¹, Amorim, J.E. (Jorge)¹, Guedes Neto, H.J (Henrique)¹, Flumignan, R.L.G (Ronald)¹, Nakano, L.C.U (Luis)¹

¹ UNIFESP, Vascular and Endovascular Surgery, São Paulo, Brazil

Introduction

Although the simulation for health care education has been used since the eighteenth century, this method has been responsible for a true revolution in the training and development of health professionals. Simulation allows more repetition and practice for the student at the same time of avoid unnecessary procedure-related patient risk. The big barrier to the popularization of such teaching methods is the high cost of simulators which the Universities cannot afford for implementation. The weight of this burden increases every day and the University’s role is to find ways to modernize the learning within the economic reality that the country faces. In this setting the Division of Vascular and Endovascular Surgery of a Federal University has created a development and researching center in the realistic training area for health care students and professionals specializing.

The aim of this study was to develop realistic simulators for professional training and health care improvement that have as premises low cost, easy reproduction and easy handling. This specific work shows development of a simulator for ultrasound-guided vascular access.

Materials & Methods

The simulator basis was made with injectable polyurethane foam in an human neck format. The internal jugular and subclavian veins were made from latex with taps that enable filling with colored liquid to simulate blood and facilitate the puncture’s visualization. After the study of different substances to evolve the simulated vessels, the ballistic gelatine provided the best ultrasound visualization.

Results

Four simulators were tested and demonstrated improvement of catheterization success rate from 43% and 55% before to 100% after simulation training for senior medical students and residents, respectively. The both students’ and residents’ acceptance for ecoguiated central venous access training was of more than 90%. The final production cost of the manufactured simulator was 72 euros versus 7200 euros of a similar industrialized simulator.

Conclusion

A high quality and low-cost simulator, reproducible and with easy handling proved to be feasible for students’ and residents’ training. The affordable production cost enables the knowledge dissemination through all students’ and residents’ training services in the country that have been facing a lack of resources to innovations.
Genetic screens in Drosophila identify genes suppressing neurodegeneration

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Introduction
Neurodegenerative disorders such as Alzheimer’s Disease (AD), Parkinson’s Disease and Huntington’s Disease are rapidly increasing in prevalence as population grows older. These late-onset, age-dependent diseases result from progressive, aberrant protein accumulation in different brain areas, leading to neuronal dysfunction and death clinically manifested with cognitive and motor impairment, dementia etc. Although studied for decades, the fundamental physiopathology of neurodegeneration is still poorly understood, and no effective, disease-modifying treatment is available for the majority of neurodegenerative disorders.

Most preclinical AD research aimed at identifying therapeutic targets have employed cellular/in vitro assays focused on the amyloid precursor protein processing. However, clinical trials following this approach have been unsuccessful so far.

An alternative strategy is to abandon preconceived notions and search for new therapeutic avenues using forward, unbiased, genetic screens together with behavioral assays to identify target genes that reduce nervous system dysfunction.

Materials & Methods
We used genetically modified Drosophila melanogaster strains expressing the human genes for β-amyloid and tau proteins specifically in neurons using the elav-Gal4 driver. These fruit flies develop characteristic AD neuropathology – amyloid plaques and tau neurofibrillary tangles – and a late-onset, age-dependent neuronal dysfunction leading to motor impairments. We quantified motor performance using a video system and software to analyze several movement metrics – speed, direction, number of falls –. Then, each candidate gene was down-regulated using siRNAs and was classified as not impacting disease, enhancer or suppressor comparing the down-regulated phenotype with a disease control, a wild-type control and a modifier control. Neuronal phenotypes and protein accumulation were also measured in Drosophila neurons.

Results
The genetic screen approach was successful and could identify modifier genes that ameliorate or enhance neuronal dysfunction in Drosophila AD models. We also investigated the subjacent mechanism, specifically if modifier genes modulate β-amyloid and tau protein steady-states levels, which would be especially attractive from a therapeutic point of view.

Conclusion
High-throughput genetic screens in the Drosophila nervous system are able to identify modifier genes that drive or ameliorate neurodegeneration, targets that could be further investigated for therapeutic purposes. Although this study was made on AD, the same approach can be applied to other neurodegenerative disorders.
Ex-vivo normothermic perfusion of a porcine kidney with three different perfusion solutions

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Introduction

In the Netherlands, hypothermic machine perfusion (HMP) is clinically used to preserve deceased donor kidneys. Normothermic machine perfusion (NMP) could comprise an even better preservation strategy. It provides the opportunity for pre-transplant organ diagnostics and interventions during kidney preservation to improve post-transplant renal function. At this time, a suitable perfusion solution has to be established for NMP. This study evaluated three different normothermic perfusion solutions in a porcine kidney model. The purpose of this study was to determine which perfusion solution is most suitable for NMP.

Materials & Methods

Porcine kidneys and autologous blood were obtained from a local slaughterhouse. Warm ischaemia time was standardised at 20 min and subsequent HMP with UW-MP for 2-3 hours. Next, kidneys underwent NMP at 37°C during 7 hours in a recirculating circuit with autologous red blood cells (RBCs) and 3 different perfusion solutions (n=5 per group). Group 1 consisted of RBCs and a perfusion solution based on Williams’ Medium E (WME). Group 2 consisted RBCs, human albumin and an outbalanced electrolyte composition. Group 3 contained RBCs and a medium based on a British clinical NMP solution. Vital parameters were monitored during NMP and perfusate and urine samples were taken regularly for analysis. Biopsies were taken to assess renal histology.

Results

During perfusion all kidneys were functional and produced urine. Injury markers aspartate aminotransferase (ASAT) and lactate dehydrogenase (LDH) increased during perfusion with highest end-levels in group 3. N-Acetyl-β-D Glucosaminidase (NAG) levels were significantly lower in group 2 in comparison with group 1 (p = 0.02) and group 3 (p = 0.01). All groups histologically showed glomerular dilatation, tubular dilatation and acute tubular necrosis, consistent with ischemic injury in this donation after circulatory death model.

Conclusion

In conclusion, perfusion of porcine kidneys with three different perfusion solutions proved feasible. However, the group 2 perfusate, based on human albumin and a balanced electrolyte composition, showed the lowest levels of injury markers, indicating that this perfusate is probably most suitable for NMP of a porcine kidney.
The effects of metformin on morphine-induced analgesic tolerance in mice: role of nitric oxide

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Introduction
Morphine and related medications in opioid pharmacologic category are the most effective options for treatment of severe pain. Chronic consumption of opioid drugs is accompanied by dependence or analgesic tolerance. Different mechanisms are involved in these phenomena such as nitric oxide (NO) pathway. Metformin has been used for pharmacotherapy of type 2 diabetes mellitus. Metformin possesses protective effects in neural disorders. Data revealed that NO mediates neuroprotective effects of metformin. Current study investigates the possible involvement of NO in the beneficial role of metformin against morphine-induced antinociceptive tolerance.

Materials & Methods
Male NMRI mice were used in our studies based on institutional Guideline for the Care and Use of Laboratory Animals. Animals were divided into following groups: 1: Normal (treated with normal saline), 2: Morphine (treated with morphine), 3, 4, and 5: Animals treated with both morphine and metformin with three doses (1, 10 and 50 mg/kg), 6 and 7: Morphine-dependent animals treated with metformin and nitric oxide synthase (NOS) inhibitors. For analgesic tolerance induction, morphine was injected intraperitoneally three times a day with intervals of 3 and 5 hours with doses of 50, 50 and 75 mg/kg for 5 days. Hot plate test was performed on first, third and fifth days of the study. Metformin was administered, 45 minute before morphine on the last day of study (5th day). In order to study the involvement of NO, L-NAME, a non-specific inhibitor of NOS (5 mg/kg) and aminoguanidine, a selective inhibitor of inducible NOS (iNOS) (100 mg/kg), were administered intraperitoneally 30 minute before metformin on the fifth day of experiment in dependent animals. Data were analyzed by One-way analysis of variance (ANOVA) and Tukey’s multiple comparisons.

Results
Administration of morphine for five continuous days induced analgesic tolerance (P<0.001). Metformin 10 mg/kg could prevent analgesic tolerance and analgesic thresholds (in hot plate test) were significantly higher than of morphine-treated groups (P<0.001). Acute administration of L-NAME and aminoguanidine augmented the protective effects of metformin (all P<0.01) in dependent mice.

Conclusion
Metformin, possibly through inducible NOS inhibition, alleviated analgesic tolerance that was induced by chronic consumption of morphine.
Tailored Microfiber Scaffold Fabrication for Renal Replacement Therapies

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Introduction
End-stage renal disease (ESRD) patients require life saving renal replacement therapies (RRTs). The most common RRT, haemodialysis, is time-consuming and is unable to take over important renal functions like sufficient blood clearance of protein-bound waste products. Consequently, uremic toxins can accumulate and damage organs in ESRD patients. Within the kidneys, proximal tubule epithelial cells (PTECs) are responsible for 65-80% of reabsorption and the only cells that can actively remove uremic toxins. Consequently, PTECs are a good candidate to include and thereby improve existing RRTs. Previous research showed that extracellular architecture is essential for cell maturation and function. Melt electrowriting (MEW) is able to produce highly porous fibre scaffolds with controlled architecture with medical grade polymers (PCL). Therefore, we used MEW to produce scaffolds with different geometries to evaluate the effects of scaffold geometry on PTECs and vascular cells. We aimed to find ideal scaffold geometries for these cells to investigate a tissue-engineering approach to improve RRTs.

Materials & Methods
This research is an in vitro study comparing endothelial and epithelial cell behaviour on different MEW fabricated PCL scaffold geometries that were non-coated or L-DOPA coated. DAPI, E-Cadherin, and phalloidin immunofluorescence stainings were used to compare cellular morphology across scaffold geometries. ANOVA with Tukey HSD post hoc analyses was used to evaluate the differences in quantitative immunofluorescence measures compared to a random scaffold control.

Results
We obtained MEW parameters that resulted in a stable MEW jet and fibre deposition. We could fabricate PCL fibre scaffolds with squared, rectangular and crosshatched geometries with dimensions smaller than shown before (≤150 μm fibre spacing, 4-6 μm fibre diameters). We demonstrated by immunofluorescence monolayer and network formation of both epithelial and endothelial cells on 120x120 μm square scaffolds. Moreover, monolayer formation was more pronounced in L-DOPA coated fibre scaffolds.

Conclusion
We showed that epithelial and endothelial monolayers can be obtained on PCL scaffolds with predefined geometry scaffolds with coated and non-coated fibres. Continuation of this research could aid the kidney tissue-engineering field in the future.
Continuous External Negative Pressure improves Lung Mechanics in an experimental model of Acute Respiratory Distress Syndrome

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Introduction
External negative pressure ventilation has been used long before the advent of positive pressure ventilation (PPV), but was mostly left due to the rapid development of the latter. Despite its ability to support gas-exchange, PPV may cause ventilator-induced lung injury (VILI) by volutrauma and atelectrauma. Recent experimental data suggest that full body continuous external negative pressure (CENP) may stabilize alveoli in dependent lung zones reducing VILI. However, the use of full body CENP is cumbersome in clinical practice. We hypothesized CENP, as obtained with a thoraco-abdominal shell-ventilator (Pegaso Vent, Dima Italia, Italy), improves lung function and mechanics in anesthetized pigs.

Materials & Methods
After approval of the protocol by the local authorities, 5 pigs (German Landrace, 47-57kg) were anesthetized, orally intubated and mechanically ventilated using Airway Pressure Release Ventilation. Arterial and venous vascular access was established and a pulmonary artery catheter was installed. Intrapleural pressure sensors were placed by video-assisted thoracoscopy to compute the local transpulmonary pressures. Experimental acute respiratory distress syndrome was induced by eight saline lung lavages. Pigs were ventilated with combinations of positive end-expiratory pressures (PEEP) of 0, 7 and 15 cmH2O with steps of CENP from -40 to 0 cmH2O with the shell in predominantly thoracic and predominantly abdominal positions. Electric impedance tomography (EIT), esophageal pressure, hemodynamics and blood gas analyses were recorded periodically.

Results
After CENP initiation, the ratio of arterial partial pressure of oxygen and inspired fraction of oxygen increased up to 339.5 mmHg (P<0.0001), with the strongest effects at a PEEP level of 7 cmH2O. Cardiac output decreased with lower CENP levels. In thoracic position, CENP of -40 cmH2O caused a significant increase of respiratory system compliance by 4.520ml/mbar compared with zero CENP (P<0.0001). Compared to traditional ventilation, CENP led to a shift of the aeration towards dependent zones (P<0.0001).

Conclusion
In anesthetized pigs, the lung mechanics was significantly improved by local (non whole-body) CENP, resulting in better oxygenation, but dose-dependent impairment of hemodynamics.
Nasal washings: a novel and non-invasive tool for the detection of nasopharyngeal carcinoma (NPC)

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Introduction
Nasopharyngeal Carcinoma (NPC) is a cancer arising from the epithelium of the nasopharynx. NPC pathogenesis is associated with the Epstein-Barr virus (EBV). Patients are often diagnosed at late stages due to inaccessibility of primary tumour site. Nasal washings (NW) is obtained through the administration of saline into and out of the nasal cavity through the nostrils. This non-invasive method allows the assessment of the cells and biofluid from the nasopharynx. MicroRNAs (miRNA) are a class of small non-coding RNA that are dysregulated in various cancers and have been extensively studied as biomarker due to their stability in various biospecimens. The aim of this project is to evaluate the load of EBV DNA and dysregulated miRNAs as potential biomarkers to detect NPC.

Materials & Methods
Forty-six NPC and 73 non-NPC patients were included in this study. EBNA1 gene and the BAMHI-W region of the EBV genome, were evaluated by real time PCR (qPCR) to quantify EBV DNA load. Twenty-seven human and EBV miRNAs shortlisted from Gene Expression Omnibus datasets were validated using high-throughput reverse transcription qPCR. Mann-Whitney U test was used to compare means between groups. Receiver operating characteristic (ROC) was used to determine area under the ROC curve (AUC) to evaluate the individual performance of these biomarkers as classifier for NPC. Multiple logistic regression (MLR) was performed to determine if the combination of these biomarkers will lead to a classifier panel with improved accuracy.

Results
EBV DNA loads and levels of seven miRNAs (miR-21, miR-26a, miR-29c, miR-93, miR-205, miR-375, and miR-421) were significantly higher in NPC samples compared to controls (p<0.05). AUC for EBV DNA and all significantly upregulated miRNAs were above 0.7 indicating that these biomarkers are good classifier in discriminating NPC cases from non-NPC cases. MLR showed that combination of EBNA1 and miR-21 produced the best AUC of 0.860 with 80.0% sensitivity, 84.4% specificity, and 83.3% accuracy

Conclusion
This study shows that EBNA1 and miR-21 levels in NW are good classifiers for NPC. This non-invasive sampling method with less rigorous storage requirement makes it ideal to be conducted at rural areas where NPC rates are high and laboratory and healthcare facilities are limited.
A CRISPR-engineered swine model with COL2A1 mutations recapitulates human abnormally early bone and cartilage development.

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Introduction
The COL2A1 encodes the type II collagen which is found primarily in cartilage, a tough but flexible tissue that makes up much of the skeleton especially during early development. Mutations in COL2A1 could lead to abnormal skeletal growth. Different location of mutation could cause various kinds of phenotypes. To study this kind of disease generated by the mutation of COL2A1, we chose swine as an experimental animal because swine model is a powerful tool for elucidating the pathogenic mutations. Using CRISPR/Cas9 and somatic nuclear transfer technology, we successfully established a novel swine model with a point mutation of COL2A1.

Materials & Methods
We designed Cas9/sgRNA targeting vectors and transfected them into the pig fetal fibroblasts by electroporation. Pig fetal fibroblasts were isolated and selected after PCR sequencing. By using somatic cell nuclear transfer (SCNT) technology, we established a pig model with COL2A1 mutation. Western bolt was taken to measure the expression of COL2A1.

Results
We identified 3 positive cell clones by screening 96 fetal pig fibroblast cell clones transfected with Cas9/sgRNA vectors. We selected a cell clone for SCNT and obtained 916 embryos. After transferring the embryos into the 5 surrogate pigs, 3 of them became pregnant and yielded some miscarried fetuses and 7 naturally delivered piglets. All 7 piglets exhibited typical appearances which are short noses, flat face, enlarged tongue, short arms and legs. The expression of the COL2A1 in cartilage was lowered than normal piglets.

Conclusion
The mutant swine model with COL2A1 mutation exhibits typical phenotypes which are short limbs, facial deformity, and enlarged abdomen. Their death after birth in a very short time implies COL2A1 mutation not only affects the cartilage in long bones of limbs but also tracheal cartilage which is vital to life. The swine models of human diseases could better simulate the abnormal cartilage development than other smaller experimental animals such as rabbits, rats and mouse. This model provides scientists with more opportunities to study the function of the COL2A1 gene and the development of cartilage.
Oral session 1
Cardiology I

Chair
Herman H.W. Sillje MD PhD

Presenters
Fu, S (Shan)
Mehdizadeh, Ms (Mozhdeh)
Mirmaksudov, M S (Mirakhmadjon)
Pandhi, P. (Paloma)
Prins, F.M. (Femke)
Rocha, J.P. (Josemara)
ROS is essential for mesodermal and cardiac differentiation during cardiac induction of human embryonic stem cell

Fu, S (Shan)

Introduction

Human pluripotent stem cells (hPSCs) can be induced to differentiate into cardiomyocytes in vitro due to their property of pluripotency, which provides us a powerful tool for disease modeling and drug screening, and holds tremendous promise for cell-based therapies for heart diseases. Although various differentiation protocols have been developed and optimized over the past decade, the yield and purity of hPSCs-derived cardiomyocyte still can not meet the requirement of cell therapy because the mechanisms underlying the cardiac differentiation of hPSCs are not fully understood. In this study, we focused on the effect of ROS on cardiac differentiation of human embryonic stem cells and found elevated ROS level favors cardiac and mesodermal differentiation.

Materials & Methods

ROS levels were measured by FACS using DCFH-DA staining; mRNA and protein levels were detected by qPCR and Western Blotting; the percentage of cTnT+ cells was used to evaluate cardiac differentiation efficiency by flow cytometry. All data are expressed as means ± SEM and compared by Student's t test for single comparisons. P value <0.05 was considered significant.

Results

We found that intracellular ROS level sharply increased immediately after cardiac induction and peaked at day 2~4, then decreased but maintained at fairly high level. The expressions of FOXO3a, a key redox regulator and its downstream target catalase antioxidant enzyme changed insistent with ROS level but delayed. Then we added ROS scavenger (NAC) or pro-oxidant (BSO) to different cardiac induction groups to decrease or increase intracellular ROS level. qPCR results showed that ROS level reduction significantly decreased expression level and delayed expression peak of mesodermal markers including T, GATA4, MESP2, HAND1 and HAND2 during early cardiac differentiation. However, ROS level elevation up-regulated the expression of these markers. At the end stage of cardiac differentiation, FACS analysis showed NAC treatment resulted in lower percentage of cTnT+ cells and cell yield compare to control group, while BSO group showed opposite results.

Conclusion

ROS is essential for mesoderm and cardiac differentiation of human ES cells. FOXO3a may be a regulator through modulation of ROS level.
Polymeric nanoparticles designed to achieve targeted drug delivery to cardiomyocytes

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Introduction
Cardiac arrhythmias and ischemic heart disease are a major health problem in the developed world. Available therapies for these conditions have many limitations, including adverse effects and insufficient efficacy. Therefore, finding novel therapeutic approaches for these diseases is urgently required. A promising strategy is targeted drug delivery to heart tissue that provides specific accumulation of therapeutic agents in cardiac cells, with minimal off-target effects. A cardiac-targeting peptide (CTP) has been described, consisting of a specific 12 amino acid sequence reported to be able to target cardiomyocytes. Thus, using this peptide as a targeting agent for polymeric nanoparticles (NPs) can provide an effective way for designing a novel drug delivery system for heart diseases.

Materials & Methods
CTP was synthesized with solid-phase peptide synthesis (SPPS) method and characterized by reverse-phase high performance liquid chromatography (HPLC) and MALDI-TOF Mass spectroscopy. Synthesized peptide was purified by preparative HPLC to obtain highly purified peptides. PLGA-PEG-MAL copolymer was conjugated to CTP through a thiol–maleimide reaction. CTP NPs were synthesized by single-step nanoprecipitation with different percentages of CTP-conjugated targeting polymer. A fluorescent dye (DiD) was incorporated into the CTP-NPs to facilitate tracking NPs in cells. Synthesized NPs were characterized in size via Dynamic Light Scattering (DLS). To confirm internalization of CTP NPs, neonatal rat cardiomyocytes were cultured and treated with CTP NPs. The cells were incubated with CTP NPs for 3 hours.

Results
The main peak in mass spectrum was at the expected molecular weight for CTP, validating a successful synthesis and purification of the molecule. The formation of polymer – peptide conjugate was confirmed by H-NMR spectroscopy. The obtained CTP NPs with single step nanoprecipitation possessed acceptable particle sizes with narrow size distributions. Confocal Microscopy analysis showed the internalization of NPs in neonatal rat cardiomyocytes.

Conclusion
We have successfully performed the initial steps towards the construction and testing of NPs designed for targeted delivery to the heart. Designing cardiac-targeted NPs will contribute to developing novel drug delivery systems with precisely targeted therapeutic agents such as small molecules, peptide and nucleic-acid constructs directly to cardiomyocytes.
EFFECT OF CARDIOPROTECTOR QUERCETIN ON REVERSIBLE DYSFUNCTION AND TIME OF MYOCARDIAL REPERFUSION IN ST ELEVATION ACUTE MYOCARDIAL INFARCTION

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Introduction
The aim was to study the effect of cardioprotector quercetin on reversible dysfunction and the time of myocardial reperfusion in ST elevation myocardial infarction.

Materials & Methods
The study included 268 patients with STEMI. Patients admitted within 3 hours of the onset of pain syndrome. All patients underwent reperfusion therapy: primary PCI or thrombolytic therapy. Patients were divided into 2 groups: 1st group (quercetin group): 132 patients with STEMI, whom reperfusion was performed against the background of intravenous administration of quercetin; 2nd group (control group) of 136 patients with STEMI, reperfusion was performed against the background of standard therapy. According to duration of onset of the disease, age, the main risk factors and standard therapy, both groups were randomized. After the stabilization of condition, on the 3-5 day of the disease, low dose dobutamine stress-echocardiography were carried out to verify the myocardial viability. Also, the analysis of the ST segment dynamics based on 24-hour ECG monitoring was performed and the symptom to reperfusion time was evaluated.

Results
According to results of low dose dobutamine stress-echocardiography, reversible dysfunction was found on the average 5.0 ± 0.2 segments in quercetin group, and 4.2 ± 0.2 in the control group (p <0.05). A mild negative correlation was observed between number of stunned segments and the symptom to reperfusion time (r = 0.5, p <0.05) which were determined in low dose dobutamine stress echocardiography. A positive average correlation was also found between the wall motion abnormality index and the symptom-to reperfusion time (r = 0.43, p <0.05);

Conclusion
Thus, quercetin, due to its antioxidant, cardioprotective properties in myocardial reperfusion in patients with STEMI, reduces the additional damaging effects of reperfusion, favorably affects the formation of reversible dysfunctioning zones of the myocardium in which the contractile function improves after a certain period of time.
The value of discharge bio-ADM as a marker of residual congestion, discharge loop diuretic doses and clinical outcomes in acute heart failure patients

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Introduction
Plasma bio-adrenomedullin (bio-ADM) levels are elevated in conditions characterised by fluid overload, such as acute heart failure (HF). An increase in bio-ADM levels is the result of a feedback response to limit further oedema and vascular leakage, by maintaining vascular integrity. Recently, bio-ADM, was implicated to be a congestion marker in acute HF patients. Therefore, bio-ADM levels at discharge could provide additional information on (residual) congestion status, titration of loop diuretics and outcomes.

Materials & Methods
We evaluated the associations between discharge bio-ADM levels and clinical variables, congestion status and discharge loop diuretic doses. Furthermore, we investigated the combined value of bio-ADM and loop diuretic doses to predict the risk of rehospitalization and mortality. Plasma bio-ADM levels were measured in 1,236 acute HF patients at discharge in the randomized controlled PROTECT trial. Clinical congestion score (CCS) was defined as the composite score of jugular venous pressure, orthopnoea and peripheral oedema (range 0 to 8).

Results
Median plasma bio-ADM concentration was 33.7 pg/mL [IQR 21.5-61.5] at day 7 or discharge. Patients with higher discharge levels of bio-ADM had a longer length of hospitalization, signs and symptoms of congestion, higher BNP levels, and a poorer diuretic response (all P<0.001). Bio-ADM was the strongest predictor of residual congestion at discharge (defined as CCS>3) (OR=4.35, 95%CI: 3.37-5.62, P<0.001). In a multivariable regression model, edema at the time of discharge was one of the strongest predictors of bio-ADM levels (β=0.240, P<0.001). Higher discharge loop diuretic doses were independently associated with a poorer diuretic response during hospitalization (β=0.187; P<0.001) and higher discharge bio-ADM levels (β=0.084; P=0.020). High bio-ADM levels combined with higher use of loop diuretics at discharge were independently associated with greater risk of 60-day HF rehospitalization (HR=4.02, 95%CI: 2.23–7.26; P<0.001), but not 180-day mortality.

Conclusion
Elevated discharge bio-ADM levels reflected residual congestion and were associated with higher discharge loop diuretic doses. Patients with higher bio-ADM levels and higher loop diuretic doses at discharge had an increased risk of HF rehospitalization. Assessment of bio-ADM at discharge could therefore be a readily applicable marker to identify patients with residual congestion who are at higher risk of early hospital re-admission after discharge.
Increased levels of interleukin-6 are associated with reduced risk of cardiovascular disease

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Introduction
Inflammation has been proved to play an important role in the development of cardiovascular disease (CVD). The cytokine interleukin-6 (IL-6) is involved in these inflammatory processes. However, the exact effects of IL-6 levels on cardiovascular outcomes remain to be elucidated. As a tool to study IL-6 levels, genetic variation caused by single nucleotide polymorphisms (SNPs) can be used. This study investigated the associations between IL-6 levels and cardiovascular outcomes using SNPs as a proxy for IL-6 levels.

Materials & Methods
Data from participants of the UK Biobank cohort were used. Unrelated individuals of white British descent with available genetic data were included. Five SNPs known to affect IL-6 levels were selected (rs4845371, rs7529229, rs12740969, rs657152, rs11804305) and used for logistic and linear regression analyses on cardiovascular (health) outcomes, longevity, hemodynamic traits, and blood count. To adjust for multiple testing, the Bonferroni correction was used. Statistical significance was considered as a 2-sided P value less than 2.00·10^-4.

Results
Of the 436,683 participants included, 236,530 (54%) were female and the mean age was 57 ± 8 years. Increased IL-6 levels were significantly associated with reduced risk of CVD variables, with odd ratios of 0.96 (95% CI 0.95-1.06) for atherosclerosis, 0.77 (95% CI 0.75-1.33) for thrombosis, 0.90 (95% CI 0.87-1.15) for heart failure and 0.95 (95% CI 0.94-1.07) for hyperlipidemia. In addition, elevated IL-6 significantly increased cardiovascular health (OR 1.05, 95% CI 1.03-0.97), increased longevity (β=.028; SE 0.006) and increased number of thrombocytes (β=.78; SE 0.15), monocytes (β=.007; SE 0.001), lymphocytes (β=.005; SE 0.001) and neutrophils (β=.03; SE 0.004).

Conclusion
Increased IL-6 levels were associated with a reduced risk of CVD. Since IL-6 functions in different pathways, the exact mechanisms causing IL-6 elevations should be further explored. However, this study serves as a starting point for future studies focusing on unraveling the exact pathway of IL-6 in CVD and investigating potential therapeutic targets.
Increased B-type natriuretic peptide level is related to inspiratory muscle weakness in asymptomatic community-dwelling nonagenarians

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Introduction
Cardiorespiratory diseases are strong contributors to the burden of disease in longevity. Early diagnosis is essential. However, nonagenarians can be asymptomatic until they reach critical functional impairment levels. B-type natriuretic peptide (BNP), marker of heart failure, is a predictor of mortality for all causes. However, it is not routinely used and its relationship with respiratory health in community-dwelling nonagenarians has not been tested yet. We investigated the relationship between BNP and inspiratory muscle strength in community-dwelling nonagenarians.

Materials & Methods
Observational cross-sectional study including 96 community-dwelling nonagenarians, who were independent walkers (including mobility aids), without exacerbated chronic disease. Logistic regression analyzes were performed to test the chance of presenting inspiratory muscle weakness (maximum inspiratory pressure <70% of expected, measured by manuvacuometry) related to BNP level, adjusting or not for sociodemographic, Mini-Mental State Examination (cognition), cardiometabolic diseases, free time activities, cardiorespiratory signs and symptoms, lung function, and how ease was to perform activities of daily living.

Results
Normal BNP level (<100 pg/mL) in comparison to abnormal level was protective against IMW in three regression models: unadjusted (OR 0.349, 95%CI 0.150-0.809, p=0.014), adjusted initial model (OR 0.277, 95%CI 0.086-0.888, p=0.031) and final adjusted model (after systematically removing of the variables with p>0.05) (OR 0.196, 95%CI 0.067-0.574, p=0.003). Cardiorespiratory symptoms were not related to IMW. Other variables independent related to IMW in the final model were: diabetes mellitus (OR 0.205, 95%CI 0.046-0.926, p=0.039), mean arterial blood pressure (OR 0.940, 95%CI 0.904-0.978, p=0.002), ease to perform activities of daily living (OR 0.894, 95%CI 0.816-0.980, p=0.017) and cognition (OR 0.860, 95%CI 0.745-0.993, p=0.040).

Conclusion
Increased BNP level is related to IMW in community-dwelling nonagenarians, regardless of sociodemographic and clinical variables, including cardiorespiratory symptoms. If new studies reinforce the finding, BNP may be an outpatient routine screening as an indicator of pulmonary and cardiac condition, besides predictor of mortality.
Cell Biology + Breaking News

Chair

Prof Cor F. Calkhoven MD PhD

Presenters

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Uncovering the Lgr5 interactome using peroxidase-based proximity labeling

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Introduction
Wnt signaling is crucial for stem cell maintenance, and aberrant activation of this pathway is frequently observed in colorectal cancer (CRC). Leucine-rich repeat-containing G-protein coupled receptor (Lgr5) is an intestinal stem cell marker also expressed in cancer stem cells. Lgr5 and its homolog Lgr4 potentiate Wnt/β-catenin signaling. However, the mechanisms underlying Lgr5 regulation are not completely understood. We set out to find novel Lgr5 interactors that will help elucidate how stem cells react to signals and explain its oncogenic role in CRC.

Materials & Methods
We set up an APEX2 proximity-based approach that covalently labels proteins in close proximity to either Lgr4 or Lgr5, in cells expressing an APEX-tagged version of the receptors. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) identified the purified proteins and two-sample T-test analysis determined the proteins significantly associated with either of the interactomes.

Results
The APEX2-proximity labeling followed LC-MS/MS identified several proteins as putative interactors of either Lgr4 or Lgr5 only, or both receptors. Protein kinases previously related to the Wnt signaling that could potentially regulate Lgr4 and Lgr5 internalization. The detection of a number of components of the cargo-selective complex retromer indicate that sorting of Lgr5 to the trans-Golgi network and the plasma membrane is regulated by the retromer and WASH multiprotein complexes. In addition, the identification of several autophagy-related proteins as putative Lgr5 interactors suggests a connection between Lgr5 and autophagy, a cellular process that is thought to be essential for maintenance of intestinal stem cells. Finally, the E3-ubiquitin ligases Nedd4 and Nedd4L that were previously reported to regulate Lgr5 were further studied. Immunofluorescence and biochemical assays confirmed that Nedd4 and Nedd4L specifically downregulate Lgr5 protein levels.

Conclusion
We demonstrate that the APEX2-proximity labeling efficiently identifies complex protein association networks. Our data shows putative shared interactors of both Lgr4 and Lgr5, as well as proteins that may uniquely interact with stem cell marker Lgr5. Although results need to be validated with further in vitro and in vivo assays, our data could help us understand better understand how Lgr5 function and dynamics are controlled in normal and cancer stem cells.
Change in the levels of oxidative stress markers in saliva of the patients with mobile dentures

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Introduction
Even though it's been almost 33 years of knowing the concept of oxidative stress, it's still one of the most researched topics in every branch of medicine, including dentistry. It's been proven that the level of oxidative stress markers can be used to determine whether a tissue was damaged and to which extent. The aim of our study was to see if mobile dentures can cause significant oxidative stress in patients' oral cavity by detecting change in level of oxidative stress markers in patients' saliva.

Materials & Methods
Study was conducted with 40 patients who needed mobile denture and haven't used any other prosthodontic appliance. Denture was made of acrylic material. Oxidative stress markers that we measured were level of malondialdehyde concentration (MDA), level of advanced oxidation protein products concentration (AOPP) and level of enzyme catalase activity (CAT) in patients' saliva. Two millilitres of saliva were collected using Eppendorf tubes, frozen on –80°C and unfrozen right before biochemical analysis. Five measurements were done: before the treatment (control group), right after receiving the mobile denture, 24 hours, 7 days and 30 days after. RM ANOVA was used to trace effect of time on changes in levels of measured markers.

Results
Levels of MDA and AOPP reached maximum on 7th day after receiving mobile denture) when compared to control group (MDA=15,63±2,34 nmol/mg of protein vs. MDA=10,19±2,49 nmol/mg of protein,p<0.05;AOPP=59,00±6,31 µmol/mg of protein vs. AOPP=36,42±7,27 µmol/mg of protein,p<0.001). After receiving the denture level of CAT decreased, and minimum of was reached on 7th day when compared to the control group (22,57±4,37 U/mg vs. 37,02±6,30 U/mg of protein,p<0.001). On 30th day measured levels of all parameters almost normalized (MDA=11,19±1,70 nmol/mg;AOPP=42,84±5,44 µmol/mg of protein;CAT=29,80±3,50 U/mg of protein).

Conclusion
The levels of MDA and AOPP increased by 7th day and decreased by 30th, as the level of CAT decreased by 7th and increased by 30th day. The levels changed during the course of measurement and by the 30th day, they came close to the ones of the control group. Our results prove that there was significant change in the levels of oxidative stress markers in saliva of patients' with mobile dentures.
Angiogenic Properties of Dehydrated Human Amniotic Membrane using in-vivo Model of Skinfold Chamber

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Introduction

Dehydrated human amnionic membrane (dHAM) has been utilized in regenerative medicine as a scaffold and for various allografts. It exhibits comparable features with fresh human amnionic membrane (fHAM) including vascularizing ischemic or recombinant organs, improving wound-healing by reducing scar formation, and immunoregulatory features. Moreover, it possesses antimicrobial properties as well as longer shelf-life. This study aimed to investigate the angiogenic properties of dHAM compared to fHAM on both mesenchymal and epithelial sides. Dorsal skinfold chamber model was chosen to provide dynamic monitoring of angiogenesis.

Materials & Methods

Dorsal skinfold chamber was performed on male rats under general anesthesia. After 48 hours recovery, dHAM and fHAM were implanted from both epithelial-side-up and mesenchymal-side-up positions which embeded mesenchymal-side and epithelial-side in contact with opposite skin’s fascia respectively. Intra-vital microscopy and image recording was done on the first and 10th day after implantation. Samples with any signs of inflammation or infection were excluded. Microinvital angiogenesis was analyzed by ImageJ. Recently formed capillaries were defined along with 3 branches before their origins and the length of sprouts was measured in 10-12 different fields per sample. Capillaries of dHAM on each side were separately compared with fHAM and the control group.

Results

The mean (SD) length of newly vessel sprouts increased significantly in mesenchymal-side of dHAM, mesenchymal-side of fHAM and epithelial-side of dHAM respectively compared with the control group: 74.8 (6.9); 70.7 (6.9); and 59.1 (7.5) versus 42.6 (8.1), p<0.01. There were no significant statistical differences between capillary growth of dHAM and fHAM on their mesenchymal-side. Capillary growth on mesenchymal-side of dHAM was significantly more than its epithelial-side; p<0.05. The mean (SD) length of newly vessel sprouts in epithelial-side of fHAM was significantly less than the control group: 23.67 (9.31), p<0.01.

Conclusion

This study showed that dHAM had angiogenic properties on both mesenchymal-side and epithelial-side, although the length of new vessel sprouts on epithelial-side of dHAM was less than the mesenchymal-side. While the mesenchymal-side of fHAM promoted angiogenesis, the epithelial-side of fHAM exhibited anti-angiogenic effects. Therefore, dHAM could have numerous utilities by inducing side independent angiogenesis in ischemic tissues.
Unraveling the molecular mechanisms of Muscular Dystrophy: identifying novel regulatory genes

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Introduction
Muscular Dystrophy (MD) ranges vastly in disease that affects 250,000 individuals in the United States and many more worldwide, ranges vastly in severity and time of onset within individuals affected by the same form of MD. Symptoms range from weak, but functional muscles to prenatal development of severe structural brain and eye abnormalities which may lead to miscarriage of the developing fetus. Dystroglycanopathic MD is characterized by improperly glycosylated dystrophin, the membrane protein responsible for MD. To better understand MD variability, a zebrafish was created with a mutated form of GDP-Mannose Pyrophosphorylase (gmppb), an enzyme that ensures proper dystrophin glycosylation. We hypothesize that variable phenotypes in MD are due to differences in gene regulation by a class of genes called long, non-coding RNAs (lncRNAs) which have yet to be investigated in this disease.

Materials & Methods
We have produced an RNA Sequencing data set of gmppb mutants with symptoms characterized as moderate or severe and we will analyze it to identify novel and previously discovered lncRNAs using bioinformatic methods. We will also determine the functions of protein coding genes adjacent to the lncRNAs since these genes could be targets of the novel lncRNAs. To validate the RNA expression of the lncRNAs and adjacent genes indicated by RNA Sequencing, a subset of 10 lncRNAs and their adjacent genes will be selected for quantitative Polymerase Chain Reaction (qPCR).

Results
Thus far, we have identified two novel lncRNAs that are differentially expressed in gmppb mutants. We will identify additional lncRNAs and then select the subset of 10 lncRNAs and adjacent genes for qPCR validation.

Conclusion
lncRNAs have yet to be investigated in this disease and will therefore provide completely novel understanding on the molecular mechanisms of MD. A better understanding of the role of regulatory genes in MD may help explain differences in MD severity and onset which could lead to more effective therapeutic treatments.
In vitro model of HBx-host interactions based on human stem cell-derived hepatocytes

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Introduction
Globally, around 240 million people are chronically infected with Hepatitis B virus (HBV). The HBx-cytokines interaction affects the proliferation, apoptosis of hepatocytes and ultimately causes the occurrence of hepatocellular carcinoma (HCC). Due to the lack of appropriate cell model for HBV study, HBx and host factors interaction remain unclear. Primary human hepatocytes (PHH) and hepatoma cell lines were limited in availability, variability from batch to batch or defects in signaling pathways. Recently, human embryonic stem cell derived hepatocytes (hESC-Heps) display stable hepatocyte function and have been demonstrated as a potential tool to deliver functional hepatocytes and used to support HBV infection. In this study, we aimed to develop an efficient, defined, and renewable in-vitro model for screening the HBx-interacted factors using hESCs.

Materials & Methods
We constructed a tetracycline antibiotic-induced HBx recombinant lentivirus. The pHBxE plasmid expressed HBx from the CMV promoter and co-expressed EGFP from an IRES site inserted between these two genes. HBx protein was labeled with a FLAG tag sequence at the amino terminus to facilitate protein detection. The lenti-LV-HBx-EGFP was produced and successfully used to transduce HBx into hESC. Finally, Immunofluorescence assay was used to verify hepatic markers expression in full matured hESC-Heps. Data were analyzed by Student's t-test. A P<0.05 was considered significant.

Results
A tetracycline antibiotic-induced HBx recombinant lentivirus plasmid was constructed and examined by the defined HBx-interacting factors such as DDB1, ID1, p53. A hESC linage integrated with HBx gene (hESC-HBx-EGFP) was successfully established and the monoclonal was selected. hESC-HBx-EGFP was completely differentiated into hepatocytes and stably expressed HBx-EGFP protein by adding DOX.

Conclusion
The novel screening model for HBx-interacted factors based on hESC-derived hepatocytes was developed. Moreover, it can be used for study the interaction between HBx and host cells infected with HBV.
The Role of DPCK in Drosophila Neurogenesis

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Introduction
Coenzyme A, a metabolite found in all living organisms, is involved in more than 100 metabolic reactions including Krebs Cycle and β-oxidation. Most organisms, including humans, synthesize it de novo from Vitamin-B5 through consecutive action of five enzymes. In Drosophila the last two steps of CoA synthesis are ensured by a bifunctional gene called PPAT-DPCK (Phosphopantetheine adenylyltransferase - Dephospho-CoA kinase, in humans also referred to as COASY). Mutations of the human gene cause a rare neurodegenerative disease with brain iron accumulation (NBIA) called CoPAN. Recently, a gene called DPCK (DCAKD in humans) was identified, that shows strong similarities to the DPCK part of COASY. However, evidence for a role in CoA synthesis or for other functions in Drosophila is so far lacking. The main goal of this study is to investigate the role of DPCK in Drosophila neuronal and glia development.

Materials & Methods
We silenced the expression of DPCK in different cell types using the previously described UAS-Gal4 system with tissue specific drivers (neuronal, glial, muscle) expressing a UAS-DPCK-RNAi. In these DPCK knock-down flies we assessed life span, brain morphology and behavioural traits like locomotion. To determine statistical significance (P<0,01) the standard one-way Anova or t-test were used.

Results
This study investigated the phenotype of DPCK silencing in different cell types. DPCK knock-down in neurons or glia cells lead to late pupal lethality, while knock-down in muscles resulted in late larval/early pupal lethality. Moreover, larvae with reduced DPCK expression moved significantly less than wildtype larvae. Confocal imaging of larval and pupal brains lacking DPCK revealed changes in brain morphology. This demonstrates that DPCK is a highly essential gene for Drosophila glia-neurogenesis.

Conclusion
Preliminary findings of this study point to a fundamental importance of DPCK in Drosophila glia-neurogenesis. Our findings suggest that DPCK affects cell viability and overall neuronal and glia development. Future research should focus on investigating the location of the DPCK protein within a cell in order to identify the cellular processes that DPCK might be involved in.
Endocrinology

Chair
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Wessel, H.K. (Hanna Karolina)
Yepes-Calderon, M. (Manuela)
The effect of yoga on lipid profile and C-reactive protein in women

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Introduction
Few scientific studies have been conducted about the effect of yoga on biochemical variables such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and C-reactive protein (CRP) to lay a scientific foundation regarding benefits of yoga, but its effect is not clearly detected yet. This study was conducted to assess the effect of yoga on lipid profile and CRP in women.

Materials & Methods
This research was designed as an interventional study. Inclusion criteria consisted of non pregnant women age 15–50 years willing to participate in the study, whereas exclusion criteria included the following: (1) irregular yoga practice or not cooperating during the intervention; (2) patients with an intervening disease or history of diseases or using medications in lipid profile and serum levels of CRP; (3) participants with CRP higher than 10 mg/L; and (4) significant change in diet and lifestyle during the intervention. Selected biochemical variables such as TG, TC, LDL C, HDL C, and CRP were measured for each participant. Hatha yoga instruction was done three times a week for 26 weeks by an experienced yoga instructor. After 26 weeks of yoga intervention, the above-mentioned dependent variables were assessed. SPSS Ver. 17 was used for data analysis and P<0.05 was considered significant.

Results
After a 26-week follow-up for participants, only 24 women had the necessary criteria to be included in the study. The mean TG was 157.33±68.416 mg/dL and 134.33±58.80 mg/dL before and after the intervention (P=0.108), respectively. The mean TC was 234.83±48.47 mg/dL and 183.33±55.09 mg/dL before and after the intervention (P=0.014), respectively. The mean HDL-C mwas 31.58±14.22 mg/dL and 38.25±13.5 mg/dL before and after the intervention (P=0.118), respectively. The mean LDL-C was 171.75±42.69 mg/dL and 142.91±36.4 mg/dL before and after the intervention (P=0.030), respectively. The mean CRP was 0.57±0.22 mg/L and 0.71±0.77 mg/L before and after the intervention (P=0.779), respectively.

Conclusion
The result showed that yoga reduced TC and LDL-C significantly, but had no significant effect on TG, HDL-C, and CRP. Complementary therapy like yoga is advised as a low cost and available method to reduce chemical medications and increase efficiency.
Perfluorooctane sulfonate exposure alters sexual behaviors and gene transcription in hypothalamic-pituitary-gonadal-liver axis of male zebrafish (Danio rerio)


Introduction
Perfluorooctane sulfonate (PFOS) is widely distributed and persistent in the environment and wildlife. It can disrupt the endocrine system activity. However, few studies have explored its effects on sexual behaviors and reproductive related genes systematically. This work was undertaken to evaluate the possible effects of PFOS exposure on the hypothalamic–pituitary–gonadal–liver axis (HPGL) and sexual behaviors in adult male zebrafish.

Materials & Methods
A total of 20 male zebrafish were exposed to 0, 2, 20, 200μg/L PFOS and 5μg/L estradiol (E2) for 21 days. After 21 days of exposure, all of the male zebrafish were sampled and total weight and length were recorded. Tissues from brain, liver and testis were preserved in TRIzol reagent for quantification of gene expressions. The sexual behaviors were evaluated via cameras and related gene expressions in HPGL axis were examined by real-time PCR.

Results
Exposure to PFOS significantly impaired the sexual standard behaviors such as ‘Nose-tail’ and ‘Tail-touching’. In brain, gonadotropin-releasing hormone (GnRH) gene and gonadotropin-releasing hormone receptor (GnRHR) gene were up-regulated in 200μg/L PFOS exposure group as compared with control group. In liver, the down-regulation of vitellogenin1 (VTG1) and estrogenic receptor β (ERβ) genes were observed in 5μg/L E2 group. In testis, follicle-stimulating hormone receptor (FSHR) and luteinizing hormone receptor (LHR) genes were significantly down-regulated after exposure to any concentrations group of PFOS and 5μg/L E2, while the expression of androgen receptor (Ar) gene was down-regulated in 2 and 200μg/L PFOS groups.

Conclusion
The present study demonstrated that PFOS may disturb zebrafish reproductive system through endocrine disrupted activity and the impairment of sexual behaviors.
Relationship between incidence of type 1 diabetes in children and their body-weight at disease onset in Poland (Lodz Province)

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Introduction
Incidence of type 1 diabetes is gradually increasing in most European centers, including Poland. This provokes a long-standing question about the environment-associated factors that may exacerbate B-cell destruction and promote T1D. One of the suggested culprits is excessive body weight, which is suspected to cause a long-term stimulation of B-cells and expedite already-ongoing autoimmune process. However, so far the evidence for “accelerator hypothesis” has been inconclusive and long-term observation of high-at-risk population such as Polish children might provide additional insight. The aim of the study was to investigate relationship between children’s BMI at T1DM onset and T1DM incidence rate in pediatric population 6-15 years old in years 1992-2016.

Materials & Methods
T1DM incidence for children aged 5 to 15 years was calculated using records retrieved from prospective register based on referential tertiary centers of pediatric diabetology in the Lodz Province and census data. Afterwards, for patients diagnosed in five three-year periods (1992-94, 1997-9, 2002-4, 2007-9, 2012-14) we retrospectively collected data concerning body weight and height from 1 to 6 months after diagnosis. For each child, body mass index (BMI) was calculated and expressed as z-score in reference to national growth charts.

Results
In the studied period T1DM incidence rate has increased from 7.58 (95%CI: 5.71 - 10.04) to 36.46 (95%CI: 29.52 to 45.00) per 100 000 children per year (annual percentage increase – 6.1%, p<0.001). We collected BMI data of 551 children which constitutes 69.2% of children diagnosed with T1DM in the studied periods. Mean BMI z-score for children diagnosed in each year showed increase in time (R=0.73, p=0.002) and correlated with T1DM incidence rate for a given year (R=0.71, p=0.003). However, there was no relation between each child’s age of T1DM onset and his BMI z-score (r=-0.04, p=0.324).

Conclusion
This 25–year-long observation demonstrates that T1DM incidence is rising, alongside the body mass index of children diagnosed with T1DM. However, lack of relationship between BMI and age at onset can suggest an incidental collinearity and can speak against “accelerator hypothesis”.
Muscle fiber composition in patients with metabolic syndrome measured with proton magnetic resonance spectroscopy

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Introduction
A low skeletal muscle mass and a high proportion of fast-twitch fibers (FT-II) in lower extremities are associated to a higher risk of developing metabolic diseases. Most information about that association has been gathered using muscle biopsies, something impractical when studying large populations. As an alternative, we standardized the method to measure intramuscular carnosine by proton nuclear magnetic resonance spectroscopy (1H-MRS) in patients with metabolic syndrome (MS) and age-matched controls in order to estimate their vastus lateralis muscle (VLM) composition.

Materials & Methods
A 3 Tesla Magnetom Skyra magnet and a flexible coil were used. A voxel of 35x10x35 mm was put into the most voluminous region of the right VLM, with the help of T1-weighted gradient echo sequences, in MS patients and controls. A point-resolved single voxel spectroscopy sequence was used, with and without water saturation. Signal processing was done in the jMRUI 5.1 software, using the intramuscular water peak as internal reference for carnosine quantification. Area occupied by FT-II was estimated according to Baguet, 2011. Statistical correlations were assessed by Pearson’s r and differences among subgroups by Student’s t-test for parametric variables using SPSS v23.0. Results are shown as mean±standard deviation and 95% confidence interval (CI) of the difference between means.

Results
65 subjects, 63% with MS, 34% men, were included in the analyses. MS patients and controls were comparable regarding age (51±6 vs 52±7 years old, P=0.32) and gender (39% vs 25% male, P=0.29). Patients with MS had higher values in body mass index (29.39±4.10 vs 25.93±3.81, P=0.002), carnosine [3.96±1.71 vs 3.02±1.63 mM, 95% CI (0.08-1.80), P=0.03] and FT-II [51.13±22.75 vs 38.58±21.71%, 95% CI (1.05-24.03), P=0.03] than controls.

Conclusion
We standardized a technique to quantify FT-II in VLM in patients with MS using 1H-MRS, a flexible coil and using internal water as reference. Our technique can be used in large population studies in a safety way. Carnosine and area occupied by FT-II were higher in patients with MS. This finding supports the hypothesis that this muscle fiber may be involved in the pathophysiological processes of MS.
Retinol binding protein 4 is associated with large VLDL and small LDL particles in subjects with and without Type 2 diabetes

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Introduction
Retinol binding protein 4 (RBP4), an adipokine which carries retinol in plasma, has been implicated in the pathogenesis of insulin resistance in mouse models but has been inconsistently reported to be elevated in type 2 diabetes mellitus (T2DM) and obesity. Plasma RBP4 may confer increased cardiovascular risk and correlates with total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides. Here we determined its relation with lipoprotein subfractions as determined by nuclear magnetic resonance spectroscopy.

Materials & Methods
Fasting plasma RBP4 (enzyme-linked immunosorbent assay) and retinol (reverse phase high performance liquid chromatography) were assayed in 41 T2DM subjects and 37 non-diabetic subjects. Lipoprotein subfractions (NMR spectroscopy) were measured in 36 T2DM subjects and 27 non-diabetic subjects.

Results
RBP4 and retinol were strongly correlated (r=0.881, P<0.001). RBP4, retinol and the RBP4/retinol ratio were not different between T2DM and non-diabetic subjects (all P>0.12), and were unrelated to body mass index. However, RBP4 and retinol were elevated in subjects classified with the metabolic syndrome (P<0.05), which was attributable to an association with elevated triglycerides (P=0.013). Large VLDL, LDL particle number and small LDL were increased in T2DM subjects (P=0.035 to 0.003). In all subjects together, RBP4 correlated with total cholesterol, non-high density lipoprotein cholesterol, LDL cholesterol, triglycerides and apolipoprotein B in univariate analysis (P<0.001 for each). Age-, sex- and diabetes status-adjusted multivariable linear regression analysis demonstrated that RBP4 was independently associated with large very low density lipoprotein (VLDL) particles (β=0.444, P=0.005) and with small LDL (β=0.539, P=0.001), and the association with large VLDL remained after further adjustment for retinol. The relationships of RBP4 with large VLDL and small LDL were not modified by diabetes status (both P>0.30).

Conclusion
RBP4 is associated with large VLDL and small LDL particles independent of the presence of T2DM. Higher RBP4 may make part of a proatherogenic plasma lipoprotein profile.
Circulating myokine musclin is not associated with insulin resistance or type two muscle fibers in adults with metabolic syndrome.

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Introduction
Skeletal muscle is a regulator of the body metabolism through the production and secretion of myokines. Musclin, a myokine mainly secreted by type II muscle fibers (FT-II), has been shown to reduce glucose uptake and glycogen synthesis in cellular and murine models. Then, it could be theorized that musclin could have a role in the pathophysiology of insulin resistance (IR) in humans. We aimed to evaluate the relationships between circulating musclin and IR, glucose, insulin, percentage of FT-II and waist circumference in adults with metabolic syndrome (MS).

Materials & Methods
Patients with MS were diagnosed according to the Joint intersocieties statement criteria (2009). Circulating musclin was quantified by enzyme-linked immunosorbent assay (ELISA) in fasting serum samples. Homeostatic model assessment (HOMA-IR), based on fasting insulin and glucose measurements, was used as indicator of IR. Waist circumference was assessed as usually. Percentage of FT-II were estimated in the right vastus lateralis muscle (VLM) by carnosine measurements with proton magnetic resonance spectroscopy. Statistical correlations were assessed by Spearman's ρ. For all analyses IBM SPSS software version 23.0 was used. Results are shown as median [interquartile range].

Results
In 29 subjects (52 [49-57] years old; 38% male; body mass index of 28.28 [26.17-30.67] kg/m2) the musclin concentration was 239.55 [145.12-609.11] pg/ml, HOMA-IR was 3.59 [2.96-5.02] and percentage of FT-II in VLM was 55.8 [39.4-65.6] %. Circulating musclin showed a trend to be correlated with plasma glucose concentration (ρ=0.368, P=0.05), but did not correlate with other variables associated with insulin resistance e.g. plasma insulin concentration (ρ=0.266, P=0.16), HOMA-IR (ρ=0.278, P=0.14) and waist circumference (ρ=0.060, P=0.76). No significant association was found either between circulating musclin and percentage of FT-II in VLM (ρ=0.018, P=0.93).

Conclusion
Plasma concentration of musclin was not correlated with IR-related variables nor with the percentage of FT-II fibers in patients with MS. These findings do not support the hypothesis that musclin is involved in the pathophysiological processes of IR and MS in humans.
Genetics

Chair
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Fabry disease: genotype-phenotype correlation in Brazil

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Introduction
Fabry disease (FD) is an inborn error of metabolism, linked to the X chromosome, with a progressive and inherited character, due to α-galactosidase A enzyme deficiency, responsible for globotriaosylceramide (Gb3) degradation. Its prevalence is estimated to range around 1:100.000. Patients with FD show progressive Gb3 storage in lysosomes of endothelium cells, especially in tissues such as kidneys, eyes, heart, brain. Acroparesthesia, angiokeratomas, cold and heat intolerance, hypohidrosis and proteinuria may be highlighted as symptoms with a common denominator. Each patient's phenotype might be determined by the type of mutation in the GLA gene. However, genotype-phenotype correlation is not well established yet.

Materials & Methods
In this study, held at UNIFESP, genomic DNA from 29 patients – five families – with previous clinical and biochemical diagnosis of Fabry disease was extracted from peripheral blood. Fragments containing all the seven exons and the exon/intron boundaries of the GLA gene were amplified by PCR and sequenced by Sanger sequencing. The Mainz Severity Score Index – MSSI – was the instrument taken to evaluate the disease phenotype by searching the information on medical records.

Results
DNA analyses led to the identification of four different mutations. P.N34D, c.59_72ins14pb, c.1129-1140ins were considered new variants, and each of these mutations was observed in a family with four patients. MSSI analyses revealed these news variants might lead to a high and severe score, as well to a classical phenotype of Fabry disease, with an early onset of symptoms, especially in male carriers. Patients carrying these new mutations also underwent renal transplantation. PR356W was a variant seen in two families, one consisting of nine, and the other of eight patients. MSSI results were shown to be equivalent to those reported in the literature, leading to a mild classical character.

Conclusion
Knowledge about GLA mutations is important to build a solid understanding on FD, and clinical correlations are essential to bring this molecular comprehension to medical conduct. Our study contributes to elucidate variants found in Brazilian patients, since new patients with these genotypes might present similar evolution of their phenotypes.
IL-1b and BDNF SNPs associated with the development of drug-resistant temporal epilepsy

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Introduction
Epilepsy is a chronic brain disorder affecting ~50 mln. people worldwide, characterized by enduring seizure predisposition, with its consequences often having a severe impact on the affected individual's life quality. Disease is currently incurable but can be effectively suppressed with antiepileptic drugs (AEDs). However, drug-resistance present in 20-40% of cases (according to different studies) calls for a research effort focused on finding the drug resistance risk factors, identification of which would allow for development of more effective therapeutic strategies. Our goal was to assess the potential role of SNPs rs16944, rs114363 in gene IL-1b and rs6265 in gene BDNF as risk factors for development of temporal epilepsy and their connection with the drug-resistant form of the disease.

Materials & Methods
Using TaqMan technology by quantitative RT-PCR, we identified carriers of the single nucleotide polymorphisms (SNPs) rs16944 and rs114363 in gene IL-1b and rs6265 in gene BDNF, from samples of 84 (28 males and 56 females, median age 33 [11; 74]) patients with temporal lobe epilepsy and 204 (54 males and 149 females, median age 23 [16; 74]) healthy volunteers of European descent.

Results
Homozygous allele C (IL-1b rs1143634) was associated with a higher tendency for the temporal lobe epilepsy development in our study population (OR = 2.01; 95% CI 1.31 – 3.08; p = 0.001). There was no significant difference in genotype distribution for SNPs rs16944 and rs6265 between two groups (p<0.05). Antibodies to phospholipids were predominantly detected in carriers (GA+AA) of the BDNF rs6265 (p<0.05) compared with carriers of the GG genotype. Drug resistant epilepsy occurs in 25% of patients (21/84). The carrier state frequency of the CT genotype IL-1b rs16944 is prevalent in patients with drug resistant epilepsy. The CT/CT haplotype carrier state of the IL-1b rs1143634 and rs16944 has a statistically significant role in the effectiveness of AED monotherapy.

Conclusion
Obtained results strongly suggest that IL-1b rs1143634 is associated with the tendency for the development of temporal lobe epilepsy. IL-1b rs16944 is associated with the drug-resistant form of the temporal epilepsy and can be viewed as a genetic risk factor which can later be utilized in the development of personalized therapeutic strategies.
Photocleavable guide RNAs for genome editing

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Introduction

The achievements of genome editing using CRISPR/Cas9 system demonstrate the possibilities of application of this system for therapeutic purposes. This system can become a basis for treatment of diseases caused by increased number of definite gene copies, for example Charcot-Marie-Tooth disease. The approaches for controllable gene editing, particularly for the decrease of copies number of multiplied gene, are nontrivial for the treatment of such diseases.

At the same time, one of the widespread ways for spatiotemporal control is the photocleavable oligonucleotide construction usage. Thereby, the main idea of this research is design and synthesis of photocleavable guide RNAs containing 1-(2-nitrophenyl)-1,2-ethandiol modification and their application for controllable gene editing using CRISPR/Cas9 system.

Materials & Methods

All oligoribonucleotides were synthesized by the standard solid phase phosphoramidite method. The newly designed photosensitive RNAs were obtained using specially prepared photoactive phosphoramidite. Recombinant endonuclease Cas9 was obtained according to the standard protocol. Photocleavable RNAs were inactivated by UV-irradiation 365 nm wavelength. 3’- Fluorescein modified photocleavable RNAs was used for the investigation of UV-induced cleavage. Analysis of dsDNA cleavage efficiency was carried out using pBluescript II SK(−) vector with the insertion of protospacer sequence and PAM (Protospacer Adjacent Motif).

Results

sgRNA, crRNA/tracrRNA and their analogues containing one or two photocleavable sites both in the region of targeted DNA binding and in the region of Cas9 protein interaction were synthesized. Kinetic cleavage assays of photocleavable RNAs demonstrated 75% cleavage degree after 10 minutes of UV-irradiation. The possibility of DNA cleavage in vitro by CRISPR/Cas9 system in the presence of all synthesized guide RNAs was demonstrated. The system containing photocleavable crRNA was more effective among all modified guide RNAs. This system permits to reach 80% cleavage degree of DNA during 20 minutes. The UV-irradiation provoked the modified RNAs cleavage and inhibited the gene editing. The conditions of reaction mixture UV-treatment were optimized to obtain the 50% cleavage degree.

Conclusion

The possibility of controllable switching off the gene editing system using photocleavable oligoribonucleotide constructions was demonstrated. Suggested strategy can become the basis for the development of unique approach for deleting «unnecessary» gene copies from genome.
Irradiation-induced mortality-predictive model combining circulating microRNA and citrulline

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Introduction
Currently available biodosimetry methods, given their limitations, such as low availability and time burden, would be ineffective in mass casualty radiation exposure incident and therefore new markers need to be found. Our recent study evaluating ability of serum microRNAs to predict impact of radiation on macaques showed promising results of application of miR-30a, miR-126 as potential prognostic biomarkers of mortality. Aim of this work is to investigate, whether a combination of miRNAs with additional blood biomarkers would be more effective in predicting death due to ARS than a model reliant on miRNA alone.

Materials & Methods
Levels of IL-6, IL-8, IL-10, IL-1B, TNF-a, G-CSF, GM-CSF, citrulline, CRP and microRNA were measured in serum once before and in following 16 timepoints (or until animal died) after irradiation of 24 healthy Non-Human Primates (NHPs) – Macaca mulatta. The data originate from our earlier described cohort of macaques exposed to LF30/60D-LD70/60D doses of ionizing radiation. Logistic regression models based on miR-30a, miR-126 (as in reference classifier), sex and additional blood biomarkers predicting death within 60 days after irradiation were created, evaluated and compared.

Results
The reference model consisting of miR-30a, miR-126, sex showed an area under the ROC curve (AUC) = 0.80 (95% CI: 0.60–1.00) and sensitivity and specificity of 75.00% and 86.67% respectively. From 9 investigated additional blood biomarkers, only citrulline improved the fit of initial model – combination with difference between citrulline levels in 1st and 2nd day after irradiation showed AUC = 0.87 (95% CI: 0.69–1.00) with sensitivity of 87.50% and specificity of 93.33%. Serum levels of this amino acid, released to blood mainly by enterocytes, decreased within 4 hours after radiation injury. Animals who died before 60 days showed a decrease between the 1st and 2nd day after irradiation – this trend was reversed among survivors in whom a steady increase of citrulline levels was noted (p = 0.0362).

Conclusion
Incorporation of citrulline into a prognostic model of radiation-induced mortality improves its accuracy.
Differential methylation in the D-loop region of mitochondrial DNA is associated with mitochondrial myopathy

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Introduction
Mitochondria play a key role in ATP production, which is essential for driving energy dependent metabolic processes within the cell. Mutations in nuclear or mitochondrial DNA, can give rise to metabolic disorders such as mitochondrial myopathy. In myopathy, dysfunctional mitochondria is observed and these patients suffer from chronic fatigue amongst other complaints. Interestingly, there are cases where patients do not harbour any mutations in their nuclear nor mitochondrial genomes, yet they develop mitochondrial myopathy. In muscle biopsy the ATP generating capacity is decreased compared to reference values. Epigenetics could explain the observed phenotypic differences that could not be explained by the genotype. Although controversial and still under debate, mitochondrial DNA (mtDNA) can be methylated and it has been suggested that this methylation might be a form of epigenetic regulation. In the mtDNA a non-coding regulatory region is present termed the D-loop. Its functions consist of mtDNA replication and transcription of mitochondrial genes. We hypothesized that methylation within the D-loop may affect gene expression and consequently the overall functioning of mitochondria.

Materials & Methods
Muscle biopsies and skin fibroblasts were obtained from healthy controls (n=4) and myopathy patients (n=16) whose DNA was negative for mitochondrial and nuclear DNA mutations. The mtDNA was isolated and pyrosequencing was conducted to determine levels of methylation within the D-loop, specifically. qRT-PCR was used to measure mitochondrial gene expression and mitochondrial copy number, which is a measure of the mitochondrial content.

Results
Our preliminary data showed an increase in mtDNA methylation in a specific D-loop region in both muscle biopsies and cultured skin fibroblasts from the patients, compared to control individuals. In fibroblasts, the ratio between the expression of a mitochondrial gene and a nuclear gene as measure for mitochondrial copy number was significant higher in patients compared to control.

Conclusion
The observed differential methylation in the D-loop of myopathy patients compared to healthy controls suggests a potential marker for myopathy which may be used as a diagnostic tool in the future. More research needs to be done to understand how mtDNA gene expression is regulated and how certain epigenetic changes may be reversed to alleviate the progression of mitochondrial myopathy.
Functional analysis of mutations in the gene encoding the CMP-sialic acid transporter leading to congenital disorders of glycosylation

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Introduction
Congenital disorders of glycosylation (CDG) are a group of rare genetic and metabolic diseases caused by alterations in glycosylation pathways. Four cases of CDG, resulting from a mutation in the SLC35A1 gene encoding the CMP-sialic acid transporter (CST) are known until now. This protein delivers CMP-sialic acid into the Golgi lumen and is, therefore, responsible for providing substrate in late glycosylation reactions. In this study we determined how specific mutations affected the function of the CST in two previously described CDG cases: one caused by a substitution p.Q101H, and another, involving a double mutation (p.T156R + p.E196K).

Materials & Methods
We tested the ability of mutant CST variants to restore the proper sialylation in CHO-Lec2 cells, which are defective in the CMP-sialic acid transport into the Golgi apparatus. Mutant SLC35A1 sequences were generated through site-directed mutagenesis and stably overexpressed in CHO-Lec2 cells. We assessed the changes in the cell phenotype using immunofluorescence staining and tested lectin reactivity with cell lysate glycoproteins. Additionally, the subcellular localization of mutant CSTs was determined using immunofluorescence microscopy.

Results
We observed that CDG-causing mutations did not alter the localization of the CMP-sialic acid transporter in tested cells, but caused an overall reduction in sialylation. The negative effect of the double mutation on the protein function was more prominent than in the case of the p.Q101H substitution. Moreover, a glycosylation defect occurred only when both p.T156R and p.E196K mutations were present as CST variants containing one of these mutations fully restored sialylation in CHO-Lec2 cells.

Conclusion
This study contributes to our understanding of the molecular basis of specific congenital disorders of glycosylation. Furthermore, the analysis of separate mutations as well as their cumulative effect on the CMP-sialic acid transporter provides new insights into the relationship between the structure and function of this protein.
Infectious disease

Chair
Douwe F. Postma MD PhD

Presenters
Bieńkowski, C. B. (Carlo)
Cabalín, C.
Gebreyohannes, E.A.G. (Eyob)
Kardani, K (Kimia)
Nwozor, K.O.
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The clinical course of *Listeria monocytogenes* meningitis compared to other community-acquired bacterial meningitis

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**Introduction**

Bacterial meningitis (BM) is a life-threatening infectious disease. *Listeria monocytogenes* is a gram-positive bacillus principally spread by contaminated food. The main risk factor for *Listeria* meningitis (LM) is age and immunodeficiency. Due to the resistance of *L.*monocytogenes to third generation cephalosporins (empiric treatment of BM), it is important to distinguish a group of patients with an increased risk of *Listeria* meningitis where the drug of choice is ampicillin.

**Materials & Methods**

Medical charts of all patients with BM diagnosed in Department of Infectious Diseases for Adults between 2010 and 2017 were analyzed. There were 337 patients with BM divided into two groups of LM (Group A; n=24) and non-Listeria bacterial meningitis (NLBM) (Group B; n=313). The diagnosis was based on the clinical manifestation, CSF tests, positive cultures or positive direct microscopy. All cases of LM were confirmed microbiologically. Symptoms and signs, incidence of comorbidities, deviations in blood and CSF laboratory tests, treatment results were studied in both groups.

**Results**

The age range was 17-93 years. Patients from group A were older compared to group B (62 years vs. 57 years, \(p=0.039\)). The analysis showed no significant differences in symptoms and signs. Patients with LM were more likely to have tumors (29.17\% vs. 8.59\%, \(p=0.002\)) and more often had any immunodeficiency (45.93\% vs. 10.58\%, \(p<0.05\)). Laboratory tests showed a lower WBC level in blood (10.7 cells/mm\(^3\) vs 15.5 cells/mm\(^3\), \(p=0.0036\)), lower granulocytes\% (62\% vs. 90\%, \(p=0.002\)) and lower CRP level (150 mg/L vs 230 mg/L, \(p=0.02\)) in group A. The CSF tests showed a lower cell count (531.5 cells/mL vs. 1230 cells/mL, \(p=0.01\)) and a lower chloride level (113 mmol/L vs. 117 mmol/L, \(p=0.009\)) in Group A.

**Conclusion**

LM is a disease that occurs more often among immunocompromised and elderly individuals. Symptoms and signs are similar in both groups. Patients with LM have a lower cytosis in CSF and a lower WBC level in peripheral blood morphology.
Effect of Staphylococcus aureus and Staphylococcus epidermidis in human keratinocyte immune defense

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Introduction
Atopic dermatitis (AD) is a chronic inflammatory skin disease with multifactorial causes. AD is associated with skin immune defense alterations characterized by i) a deficiency in wound repair due to decreased proliferation and differentiation of keratinocytes, ii) a deficiency in the secretion of cutaneous antimicrobial peptides (AMPs, molecular mediators of innate immunity against microbial pathogens) and, iii) a dysbiosis characterized by increased colonization by Staphylococcus aureus and decreased colonization by Staphylococcus epidermidis, pathogenic and commensal bacterium on the skin, respectively. Skin dysbiosis correlates with AD exacerbation, and recent studies suggest that restoration of commensal bacteria might decrease disease progression and severity. Also, an increase of oxidative stress is associated with several inflammatory diseases and the exacerbation of AD. However, how S. epidermidis might improve host immune defenses against S. aureus infection in the skin is unclear yet.

Aim: To evaluate the change in the immune defense of human keratinocytes in response to S. Aureus and S. epidermidis.

Materials & Methods
Keratinocytes (HaCaT cells) were stimulated for up to 24h with heat-inactivated S. Aureus (ATCC 25923) and heat-inactivated S. epidermidis (ATCC 12228) (Multiplicity of infection=100). An MTT assay and Ki-67 immunofluorescence were performed to assess cell viability and cell proliferation, respectively. The mRNA expression of AMPs (CAMP, S100A7, RNAse7, and HBD3) was quantified by real time-PCR. Finally, oxidative stress of HaCat was measured by the Griess test.

Results
S. aureus stimuli induce loss of HaCaT viability at 30 minutes and 6h (p&lt;0.05) compared with S. epidermidis stimuli. Also, preliminary results show that S. Aureus change HaCaT proliferation starting at 12h while S. epidermidis increase proliferation during 24h. S. aureus and S. epidermidis increase expression of CAMP, S100A7, RNAse7 and HBD3. However, S. epidermidis stimuli show a higher expression of AMPs. S. aureus incubation increases oxidative stress at 30 minutes (p&lt;0.001) while S. epidermidis did not.

Conclusion
S. epidermidis might improve host immune defense against S. aureus infection in skin maintaining keratinocyte viability, increasing cell proliferation, and inducing higher levels of AMP expression. More studies are needed to establish the potential beneficial effects of S. epidermidis against S. aureus infection in human keratinocyte immune defense.
The effectiveness of pictogram intervention in the identification and reporting of adverse drug reactions in naïve HIV patients in Ethiopia: a cross-sectional study

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Introduction
In health communication, pictogram has a comprehensive place to aid attention, memory recall and promote adherence. This study was conducted to assess whether pictorial intervention would help to identify and improve adverse drug reactions (ADR) reporting in an antiretroviral therapy (ART) clinic in Northwest Ethiopia.

Materials & Methods
A cross-sectional study on ART-naïve HIV-positive patients was conducted from July 2015 to January 2016. The patients were randomly categorized into two groups. Group A was subjected to receive pictorial medication information and a pictograms-enhanced tool to identify and report ADRs, while group B did not receive any pictogram-enhanced tool.

Results
A total of 207 ART-naïve HIV-positive patients who were registered for the ART treatment attending Gondar University Hospital ART clinic were included. Bivariate analysis showed that sociodemographic characteristics such as age, sex, education, employment, and marital status were the main predictors of identifying and reporting ADRs. Males were twice more likely to identify ADRs than females. Univariate analysis revealed that the intervention group showed a significant association with the ability to identify ART medications using pictograms. Intervention group patients were more likely to identify lamivudine [OR (95% CI) =7.536 (4.042-14.021), P≤0.001], tenofovir [(OR (95% CI) =6.250 (2.855-13.682), P≤0.001)], nevirapine [(OR (95% CI)=5.320 (1.954-14.484), P=0.001)], efavirenz [(OR (95% CI) =3.929 (1.876-8.228), p≤0.001)], and zidovudine [(OR (95% CI) =3.570 (1.602-7.960), P=0.002] using pictograms. Patients in group A showed 4.3 times more likely to identify diarrhea as an ADR using pictogram comparing to group B.

Conclusion
This study found that the use of pictogram-based intervention for ART medications resulted in increased identification of ADRs and improved ADR reporting among ART-naïve HIV-positive patients with limited literacy in Northwest Ethiopia. This intervention provided promising innovation with the potential implications to improve ADR reporting and promote patients safety, particularly for HIV-positive patients with limited educational levels.
B- and T-cell epitope prediction of HIV-1 NEF and VPU proteins

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Introduction
There is a huge need of vaccine against HIV-1 infection. The epitope-driven vaccines against variable pathogens represented good results. Thus, to overcome this hyper-variable virus, we designed the most conserved and immunodominant peptide epitopes. The HIV-1 nef and vpu accessory genes were selected to design peptide-based vaccines.

Materials & Methods
At first, we determined potentially immunostimulatory B cell epitopes using IEDB B cell epitope prediction tool. Three servers were used to predict peptide-MHC-I binding affinity including NetMHCpan4.0, syfpeithi, and IEDB MHC-I binding prediction tool servers. The NetMHCIIpan3.2 server was used for MHC-II binding affinity. We evaluated immunogenicity scores by the IEDB immunogenicity predictor. The allergenicity of epitopes were calculated with PA3P using ADFS-motif-based and Allergen online (8aa and 80wordmatch). The IEDB population coverage tool was utilized to estimate population coverage of both selected epitopes in Iran, Europe and South Africa Black. The investigation of MHC-peptide complex was done by GalexyPepDock peptide-protein flexible docking server.

Results
The potentially immunostimulatory B-cell epitopes were NEF148-162 (VEPDKIEEANKGENT) and VPU48-59 (RAEDSGNESEGE). Our data showed that NEF105-113 (QEILDLWVY), VPU66-74 (ALVEMGHHV) sequences have the greatest binding affinities to MHC-I and NEF176-193 (PEREVLVWKFDSRLAFHH) and VPU28-42 (EYRKILRQRKIDRLI) sequences have the highest binding affinities to MHC-II. The immunogenicity rates of NEF105-113 and VPU66-74 were 0.25 and 0.34, respectively. None of selected epitopes were allergen. The interaction scores obtained from MHC-peptide complex docking for NEF105-113 and HLA-B18-01, and for VPU66-74 and HLA-A-24-02 were 193.0 and 201.0, respectively.

Conclusion
To design an effective peptide-based vaccine against hypervariable HIV-1, we should concentrate on stimulating both humoral and cellular immune responses. Herein, we used epitope mapping as a critical step for selection of the most conserved and immunodominant epitopes. The chosen epitopes must be employed in the next experimental studies to determine the correlation between immunobioinformatics and in vitro/invivo studies.
Micro RNA expression profile in whole blood may be altered by invasive aspergillosis

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Introduction
MicroRNAs (miRNAs) are small 19- to 23- nucleotide long, noncoding single stranded RNA molecules. They are key regulators of various physiological and pathophysiological processes. Altered expression levels of miRNAs have been associated with many diseases. Increasing number of evidence demonstrates that specific miRNAs can be a great promise as novel biomarkers for clinical diagnosis of many types of diseases. Invasive aspergillosis (IA) is a life-threatening infection caused by Aspergillus especially in immunocompromised patients. Regrettably, the gold-standard diagnostic setups for this condition take days to produce a reliable result. We aimed to measure the expression profiles of 15 selected miRNAs in patients with fevered neutropenia (FN) and in further non neutropenic volunteers. We hypothesized that IA could change the miRNA profiles in whole blood (WB) of patients with FN, making the miRNAs possible diagnostic markers.

Materials & Methods
We obtained WB samples from 16 patients with neutropenic fever and from 5 healthy volunteers with no fever. Total RNA was isolated from the whole blood using the MagMaxTM mirVanaTM Total RNA Isolation Kit. MiRNAs were reverse transcribed to cDNA with TaqMan® Advanced miRNA cDNA Synthesis Kit. TaqMan® quantitative real-time PCR (miRNA assay) was used for detecting miRNA expression profiles. Relative mRNA expressions were calculated with the ΔΔCt method using miR-191 for normalization. P-values were calculated on Microsoft Excel program using two-tailed Student’s t-test for samples of unequal variance. P<0.05 was considered significant.

Results
We found that 7 out of the 15 miRNAs showed significant upregulation in the expression levels at p<0.05. Increased expression levels were also observed in 7 other miRNAs from the patients but these differences proved not to be statistically significant.

Conclusion
Based on the result of this pilot study, 7 miRNAs with significant different expression levels between the test group and the control may be effective biomarker targets when monitoring patients with FN to support the diagnosis of IA. Further and more in-depth research is needed to determine the functional consequences of the differential miRNA expression induced by the IA.
Development of Cas13-based detection systems for West Nile Virus and Crimean-Congo hemorrhagic fever virus

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Introduction
Modern infectious diseases, faced by doctors, require urgent medical intervention to improve the patient's condition. In the last decade, plenty of molecular methods with high sensitivity and specificity have been adopted for diagnostics but they have several disadvantages. Programmable endonucleases Cas13 provide new instruments in the field of Point-of-care testing. The nuclease activity of Cas13 proteins allows to specifically detect the presence of target viral nucleic acids. Previously J.S. Gootenberg and O. Abudayyeh adopted this technology for Zika virus and Dengue virus detection. Here we aimed to develop two systems for detection of actual arbovirus infections - West Nile Virus (WNV) and Crimean-Congo hemorrhagic fever virus (CCHFV).

Materials & Methods
To achieve this goal the programmable endonucleases Cas13 from Leptotrichia wadei and Leptotrichia bucallis fused with His-Tag sequence were overexpressed in E.coli. The following purification of the proteins was carried out using the affinity chromatography. For detection the mix of target viral fragments, Cas13 protein (LwaCas13 or LbuCas13), short guide crRNAs and non-specific fluorescently labeled reporter RNA was used. The change of fluorescent signal was estimated for 120 minutes.

Results
SDS-PAGE electrophoresis showed that eluted fractions after NINTA affinity chromatography contained monomer individual proteins with apparent molecular mass of 180 kDa and 150 kDa for LbuCas13 and LwaCas13 respectively. Two targets were chosen for specificity evaluation of Cas13 proteins: nucleoprotein of CCHFV and RNA-depended RNA polymerase NS5 of WNV. LbuCas13 showed activation of the lateral nuclease activity upon adding a guide crRNA, however the activity was observed regardless of the target presence in the mixture revealing non-specificity of the protein action. For LwaCas13 no nuclease activity was shown. We relate this to the peculiarities of the expression construction, where several additional fragments take place.

Conclusion
Based on the data obtained, the further optimization of LbuCas13 and LwaCas13-based diagnostic platforms is necessary. Changing the expression protocol for LwaCas13 and selection of alternative crRNAs are the first steps towards development.
Neurology I

Chair
Prof. H.P.H. (Berry) Kremer MD PhD

Presenters
Fedotova, A. (Anna)
Jorna, L.S. (Lieke) MSc
Landa-Navarro, L (Lucia)
Purevdorj, N (Narangerel)
Skinningsrud, B. S. (Bendik)
Zdanowski, S.M. (Szymon)
First-episode schizophrenia patients demonstrate disturbances in sensory perception, attention and inhibition in a “Go/No go delay” saccadic task

Fedotova, A. (Anna); Slavutskaya, M (Maria) D.Sc. in Biology

Introduction
Schizophrenia is a severe brain disorder. Cognitive control dysfunction is a central feature of this disease. Saccades (quick ballistic movements of both eyes that abruptly change the point of fixation) are a perspective model for studying cognitive control of motor responses. The aim of the study was to investigate whether saccadic impairments in “Go/No go delay” paradigm could be a marker of schizophrenia.

Materials & Methods
The data of 10 first-episode schizophrenia patients (code F20 according to ICD-10, age 21.8±1.8) and 21 healthy subjects (age 21.3±0.4) were included in the analysis. Written informed consent for the investigation was obtained from all subjects. Each subject participated in a “Go/No go delay” saccadic task. This paradigm is characterized by increased spatial attention, motor preparation and voluntary inhibition. It contained two types of visual target stimuli: “go” - a signal to make a saccade, and “no go” - a signal to inhibit the response. Visual stimuli were demonstrated on the PC-screen in front of the subject. Electrooculography technique (EOG) was used for recording saccades. The number of erroneous reactions and the latency of saccades were analyzed. Because distributions were non-normal, Mann-Whitney U test was used for the analysis.

Results
First-episode schizophrenia patients produced 3.6 times more erroneous saccades in response to “no go” stimuli (p<0.001) and missed 5.6 times more “go” stimuli (p<0.01) than healthy subjects. This is probably due to attenuation of inhibitory control because of the right frontal cortex dysfunction in schizophrenia. Patients demonstrated significantly increased latency of correct saccades (by 30 ms, p<0.0001) and significantly shorter latency of erroneous saccades (by 54 ms, p<0.0001) as compared to healthy controls. These data indicate disturbances in sensory perception and attention processes in patients with schizophrenia and reveal inhibitory control deficit.

Conclusion
The obtained results suggested that first-episode schizophrenia patient have difficulty in inhibiting eye movements and demonstrate problems with visual perception and attention. The main limitation of the study is that the group of patient was relatively small so we continue to collect data. We expect the “Go/No go delay” saccadic paradigm can be used together with other tests in clinical diagnostics.
Care for Cognition: The Role of Neuroinflammation in Postoperative Cognitive Decline

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Introduction
A decline in cognitive function, also known as postoperative cognitive decline (POCD), is a common complication after surgery (Rasmussen, 2006). POCD includes subtle impairments in different domains, including memory, attention, learning, information processing and executive functions (Hovens et al., 2012). There is an increasing amount of evidence for a key role of neuroinflammation in POCD (Krenk et al., 2010). Drugs with anti-inflammatory effects may slow down or stop microglial activation and consequently prevent or improve cognitive deterioration. The aim of the current study is to better understand the role of neuroinflammation in patients with cognitive deficits after surgery.

Materials & Methods
A meta-analysis was performed to investigate the effects of anti-inflammatory medication on post-operative cognition. Results from nineteen studies, including ten different agents with anti-inflammatory properties and a total of 3394 patients, were included.

Results
For the effect of the anti-inflammatory agents on POCD an odds ratio of 0.517 was found, indicating a significant effect of anti-inflammatory agents on the incidence of POCD (Z = -3.934, p = 0.000). Heterogeneity was substantial to high (I² = 79.8%). Erythromycin and erythropoietin seem to be the most promising agents for the treatment of POCD.

Conclusion
The administration of anti-inflammatory agents was found to reduce the incidence of POCD in patients. Erythromycin and erythropoietin seem to be the most promising agents for the treatment of POCD. However, more research into the administration of ketamine, parecoxib, dexamethasone, dexmedetomidine and lidocaine is needed to draw conclusions on these substances.
Intrahippocampal administration of Amyloid beta 42 diminishes catecholaminergic axons and disrupts spatial contextual memory

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Introduction
Alzheimer’s disease (AD) is the most prevalent type of dementia in the elderly. Its major characteristics are amyloid-beta (Aβ) aggregates, neurofibrillary tangles of hyperphosphorylated tau, synaptic failure and neuritic dystrophy that lead to cognitive impairment and memory loss.

It has been reported that increased Aβ deposition or its exogenous administration reduces catecholaminergic neurotransmission, impairs recognition memory and converts long-term potentiation in long-term depression in the cerebral cortex and dorsal hippocampus. Recent evidence from our laboratory has shown that Aβ pathologic alterations, in a transgenic mouse model for AD, coincide with catecholaminergic neurotransmission disruption and recognition memory impairment. Moreover, recently we have shown data that links catecholaminergic input into the hippocampus with the encoding of novel contextual information. In this paper, we aim to evaluate the effects of exogenous Aβ administration on long-term spatial and contextual memory evocation and the induced changes in the catecholaminergic system.

Materials & Methods
In a Morris Water Maze (MWM) task, we measured the number of crosses with one-way ANOVA Fisher LSD. Also, in a location memory task (OLM) we measured the preference of a novel object location with a two tailed Student’s t test. To evaluate the length of tyrosine hydroxylase (TH +) and microtubule-associated protein 2 (MAP2), stereology analyses were evaluated using two-way Fisher LSD ANOVA.

Results
We found that the intrahippocampal administration of Aβ after memory acquisition and before evocation impairs spatial memory (F4,39 = 6,256, P = 0.0005), codification of novel contextual information (t9= 1.446, p= 1.822) and decreases TH + axons after 24 h, but not after five days (F2.21 = 10.58, P = 0.0007). While no differences were found when analyzing the MAP2 + axons (F2,8 = 1,351, P = 0.3123).

Conclusion
Catecholaminergic neurotransmission spatial and contextual memory evocation are disrupted by intrahippocampal Aβ administration. These findings suggest the importance of the catecholaminergic system in AD that is relevant for the development of new therapeutic targets.
To investigate the pathological amyloidosis components in the serum of patients with Alzheimer's disease

Purevdorj, N (Narangerel)

Introduction
Alzheimer's disease (AD) is a common central nervous system degenerative disease. Currently, approximately 15 million people worldwide suffer from Alzheimer's disease. With the increase of age, the incidence of AD is also on the rise. To explore the formation process of Aβ amyloidosis in the brain tissue of patients with AD, which is helpful to analyze the pathogenesis of AD disease.

Materials & Methods
This paper selected 260 healthy volunteers and 60 patients with AD (The CR staining method stains amyloidosis in tissues to determine amyloidogenic components in tissues. The presence and presence of pathological amyloidosis in serum were analyzed by ThT PAGE gel staining, ThT quantitative detection of pathological amyloid fibrils and WB hybridization test.

Results
CR staining of AD patients' tissues showed that CR stained red in heatstroke nerve tissue. After binding to polarized light microscopy, it was found to have green fluorescence, indicating the presence of amyloid deposition in organ tissues. The serogroups of the subjects and the amyloid-fluorescence intensity levels in PBS buffer were compared, and the results showed that the amyloid-fluorescent intensity in the serum was significantly higher than that in the PBS buffer, indicating the presence of amyloid components in the serum. Further, using SDS-PAGE electrophoresis analysis, the amyloid fibril staining zone was also found, and the experimental results also supported the presence of pathological amyloid components in the serum. Statistical analysis of pathological amyloidosis levels in AD patients and healthy volunteers, the level of amyloidosis in the serum of AD patients was significantly higher than the control group, with clinical significance.

Conclusion
(1) Using the ThT staining SDS-PAGE electrophoresis amyloid fiber assay and amyloid fibrosis quantitative experiments, the pathological amyloid components in the blood of healthy volunteers and AD patients were confirmed.

(2) The amyloid component video in the serum of AD patients was significantly higher than that in the control group, suggesting that there is an increase in the level of amyloidosis in the serum of AD patients.
Prevalence of ponticulus posticus and its association with headaches and migraines: a meta-analysis


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Introduction

Ponticulus posticus (PP) is an osseous bridge located over the vertebral artery on the posterior arch of the atlas. Its presence has been associated with compression of the intraforaminal part of vertebral artery leading to a range of symptoms including headaches and migraines. Significant improvement in symptoms have been reported after surgical dissection of the PP. It can also pose a risk when viewed dorsally during C1 lateral mass screw insertion by providing a false impression of a broader posterior arch. The aim of this study was to determine the true prevalence and anatomical characteristics of the PP and determine its role in headaches and migraines through an evidence-based approach.

Materials & Methods

An extensive search of the major electronic databases was performed to identify all studies reporting relevant data on the PP and the prevalence of headaches or migraines in each group. Data regarding prevalence, type (complete and incomplete), laterality, and association with headaches or migraines were extracted and pooled into a meta-analysis.

Results

A total of 127 studies (n=55,985 subjects) were included into the meta-analysis. The prevalence of a complete PP was 9.1% (95%CI:8.2-10.1) and the prevalence of an incomplete PP was 13.6% (95%CI:11.2-16.2). Moreover, 168/412 (40.8%) patients in the PP group reported headaches compared to 368/1691 (21.8%) patients in the non-PP group (OR 4.68; p=0.002). The proportion of headaches in patients with a complete PP was 73/125 (58.4%) compared to 80/413 (19.4%) in patients with an incomplete PP (OR 5.04; p=0.04). A significant difference was observed between patients with an incomplete PP 36/85 (42.3%) and patients without a PP 65/560 (11.6%) (OR 6.13; p=0.009).

Conclusion

This meta-analysis reported a relatively high prevalence of PP in the population and a significant association between PP and headaches. We recommend screening for the presence of a complete PP in cases where neurological symptoms suggests compression of the vertebral artery without another cause.
Feasibility of 9-Hole Peg Test in the assessment of manual dexterity in Huntington’s disease.

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Introduction
Huntington’s disease (HD) has complex motor symptomatology, from early oculomotor dysfunction and most prominent choreic movements to dystonia, bradykinesia and rigidity. The 9-Hole Peg test (9-HPT) is a simple manual dexterity and eye-hand coordination test which is routinely used in a variety of clinical settings, e.g. in the upper extremity assessment in post-stroke rehabilitation or multiple sclerosis. This study aims to further assess the applicability of 9-HPT in HD and the association of its results with HD-specific motor, cognitive and functional measures.

Materials & Methods
Twenty symptomatic HD patients (aged 60.1±8.72, UHDRS-TFC 8.1±2.4, stages I-III) performed 9-HPT along with a battery of other tests during their routine follow-up visit within Enroll-HD project. The task requires to singlehandedly place nine pegs into nine holes and then remove them. Two measures for dominant (DH) and non-dominant hand (NDH) were recorded – insertion and completion time (DH-C, NDH-C). Comparison with appropriate completion time norms for healthy subjects and correlation analyses with other clinical measures (Unified Huntington’s Disease Rating Scale - UHDRS, MMSE, Symbol Digit Modalities Test - SDMT, Stroop test) were performed. Using Statistica 13.0 software, Shapiro-Wilk W statistic was used to test for normality of distribution and Spearman’s rank correlation analysis was performed to test the association of the results with other measures. P<.05 was considered statistically significant.

Results
The z-scores of the completion time for the dominant and the non-dominant hand were 2.22±2.7 and 2.21±1.9 respectively. DH-C and NDH-C correlated significantly with UHDRS total motor score (rho=.85; rho=.81), oculomotor subscore (rho=.82;rho=.76), and Total Functional Capacity score (rho=-.83;rho=-.70), SDMT (rho=-.72;rho=-.60), and Stroop test subscores: colour naming (rho=-.82;-.77) and interference (rho=-.71;rho=-.72). The correlation of MMSE with DH-C and NDH-C was only moderate (rho= -.59;rho=-.68).

Conclusion
The 9-HPT can be administered to HD patients in stages I-III and its results are closely related to the patients’ daily function. The 9-HPT scores are highly associated with both motor and cognitive measures commonly used in HD. As 9-HPT scores are so closely related to the patient’s functional status they may be helpful in establishing the patient’s functional ability during follow-up in case of reduced insight and lack of informant.
Nuclear medicine and Imaging Techniques

Chair
Hendrikus H. Boersma PhD

Presenters
Abdelwahab, M. (Mostafa)
Babaei, M.B. (Mahsa)
Lopareva, A. (Aleksandra)
Santa-Maria, A. R. S. M. (Ana R.)
Scandiuzzi Maciel, E. (Elisa)
Yang, Y. (Yufan)
Non-Invasive Extremely Low Frequency Electro-Magnetic waves (ELF-EM) for effective accelerated healing of skin infections

Elnakib, M. (Mostafa) Dr. 1,2, Abdelwahab, M. (Mostafa) 2, Rashwan, M. (Mohamed) 2, Wahba, S. (Saif) 2, Abdelkader, A. (Amr) 2, Galal, A. (Ahmad) 2, Abdelzaher, H. (Hana) Dr. 3,2, Elmenofy, T. (Tarek) Dr. 4, Hegazy, M. (Mohamed) Dr. 5,2

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Introduction
The skin provides primary protection against infection by acting as a physical barrier. When this barrier is damaged, pathogens directly infiltrate the body, resulting in infection. We aimed to demonstrate a new method for the control of bacterial growth by evaluating the efficacy of Non-Invasive Metabolic Bio-Magnetic Resonance Technique (NIMBMRT) in the treatment of patients with bacterial-infected skin conditions (infected ulcers, burns and diabetic foot).

Materials & Methods
The study included 100 patients, they were diagnosed as infected wounds depending on clinical, laboratory and radiological investigations. Patients received a session of treatment by Extremely Low Frequency Electromagnetic (ELF-EM) fields every other day till complete eradication of causative pathogen of the infection. Direct current power supply (400 V) through an electronic switching device was maintained to produce ELF-EM designed square pulses with different frequencies. The output was connected to two parallel electric conducting capacitance electrodes, and the patients, under treatment, sat between the two electrodes in a field of strength 0.3 – 0.8 KV/m according to isolated organisms. The electrodes were insulated so that no direct contact of the patient with the electrodes would occur and exposure was targeted to the affected area. Transmission electron microscopy (TEM) and DNA damage assay were performed on bacterial cultures both prior to and post exposure. Paired t-test repeated measure ANOVA test were used to estimate the changes in numerical variables throughout the study visits.

Results
TEM imaging showed intact bacterial cell wall and bacterial content before exposure to ELF-EM impulses. After exposure it revealed evacuation of bacterial contents, disfiguration and bacterial cellular adhesion. DNA damage assay showed a significant reduction in bacterial DNA concentration post-exposure (p<0.05).

Conclusion
The ELF-EM application is a promising method for the treatment of infected skin. ELF-EM resulted in a decrease in bacterial growth and its morphological alternations triggered by changes in metabolic activity or electrostatic properties of cell surface or both.
Introducing a Novel Fluorescent-Based Biosensor for Detection of Antibiotic Oxytetracycline in Dairy Products

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Introduction

Oxytetracycline (OTC) is one of the most used antibiotics in veterinary medicine. There is a huge concern about developing antibiotic resistance in humans as a result of the consumption of products contaminated with OTC, so a fast detection technique for an on-field screening test is in demand. Here we introduced a novel DNA based biosensor (Aptasensor), based on a triple helix molecular switch (THMS) complex formation.

Materials & Methods

Three DNA strands according to previous studies, with varying arm segments (Apt1, Apt2, and Apt3) were synthesized. An oligonucleotide sequence as fluorescent signal transduction probe (STP), was provided by MicroSynth (Switzerland). For the preparation of THMS, each aptamer and STP were prepared in the probe buffer. Then, fluorescence emission was measured by Multi-Mode Microplate Reader. First, fluorescence emission intensities (FEIs) were regularly recorded. Then, after the intensity reached a plateau, OTC was added to the solution and the fluorescent intensity was measured again. The designed aptasensor consists of two parts: An aptamer with two arm segments at each end, for binding to the target, and STP which is a hairpin shaped single stranded DNA (ssDNA) attached to a quencher and a fluorophore group at each end. In the absence of a target, the aptamer and STP form a THMS structure. Here, fluorescence is on as the quencher is far from the fluorophore. In the presence of OTC, the THMS structure is disassembled and the STP forms a hairpin structure, bringing the quencher and fluorophore close together. Therefore, fluorescence is efficiently quenched by fluorescence resonance energy transfer (FRET).

Results

Addition of Apt1 could not change the fluorescence intensity, confirming that the hairpin structure of STP is more stable than THMS. Apt2 showed a higher FEI than that of Apt1, but it was not as noticeable as Apt3. Addition of OTC to Apt3-STP complex could decrease the fluorescence intensity of the STP within several minutes, therefore it was chosen.

Conclusion

In this study, a simple and rapid aptamer-based assay for detection of OTC was developed. We showed that a THMS-based sensor was a reliable method for screening of OTC in dairy products.
Modifications of electrodes in electrochemical biosensors open perspectives for non-immune detection of apoptosis

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Introduction
The release of proteins, such as cytochrome c (cyt c), from mitochondria into the cytosol is a critical event in the activation of intracellular signaling when mitochondria are damaged under pathological conditions or drug treatment. Cytochrome c is a hemeprotein with the main function of carrying electron in mitochondrial respiratory chain. It’s also known for many functions, but we focused on its ability to participate in the activation of a programmed cell death cascade. The foundation of an electrochemical measurement is the reaction on an electrode surface. Cyt c is a good object for detection by electrochemical biosensors due to its redox reaction with electrodes. There are few electrochemical techniques for apoptosis detection using cyt c as a marker, but almost all of them based on immune-detection. In our experiment we tried to evaluate cyt c in cell lines without specific antibodies.

Materials & Methods
Based on series of screen-printed electrodes (SPEs) modifications with cyt c from horse heart as a model the best modification was chosen. Modification was prepared using multi-walled carbon nanotubes (MWNT) dispersed in zwitter-ion synthetic polymer (PS37-b-PDha46) and DNA as natural polycation polymer. This modification was used for electrochemical analysis of cancer cell lines MCF-7 and K562 before and after doxorubicin treatment during 24 and 48 hours. Electrochemical measurements were performed using a potentiostat/galvanostat Autolab «PGSTAT 312 Autolab» (Metrohm Autolab, The Netherlands) running by the NOVA software (version 2.0).

Results
Our preliminary results demonstrated that comparative voltammetric analysis using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) of MCF-7 cells, demonstrated a clear reductive peak in the potential area typical for cyt c for cell samples processed by doxorubicin.

Conclusion
CV and DPV technique revealed the opportunity to detect apoptosis using cyt c as a apoptotic marker. Nanostructured electrodes as sensing elements for electrochemical biosensors might be effective substitution for immune analysis. Hence, further study is required for better understanding of this approach.
A novel reusable, versatile, microelectric organ-on-a-chip device
to study blood-brain barrier functions

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Introduction

Biological barriers-on-a-chip models are cutting edge microengineered devices, but only a few combine the crucial parameters to study transport mechanisms, drug delivery and pathologies. Our laboratory developed a microelectric device (Walter et al, 2016), which enables visual observation, transendothelial electrical resistance (TEER) and permeability measurements on several biological barriers. The objective of our study was to further improve the device to make it more user-friendly and add novel functions.

Materials & Methods

The device was built up from a porous cell culture membrane sandwiched between two layers of PDMS and a top and bottom plastic slide coated with gold electrodes. After an automatic feeding period when the cells became confluent, a peristaltic pump was used to circulate the cell culture medium to mimic the blood flow. To verify the integrity, TEER was assessed with custom electrodes connected to an EVOM2 device. The endothelial surface charge was measured using silver electrodes connected to the outlets of the device. To validate our biochip we cultured the hCMEC/D3 human brain endothelial cell line and the stem cell derived CD34+ human endothelial cells in co-culture with bovine pericytes.

Results

We improved and optimized the biochip by (i) redesigning the shape of the electrodes, (ii) using universal luer-outlets, (iii) introducing small screws around the edges of the biochip we eliminated the use of the adhesive glue and (iv) could disassemble and reuse the device. The resistance was measured in real time using a custom made application compatible with cell phones. In the biochip under flow conditions the TEER elevated significantly in both BBB models which was also confirmed by ZO-1 and β-catenin immunostainings. A gene expression study was performed to investigate the differences between static and dynamic conditions on brain endothelial cells. Moreover a novel measurement of surface potential was also introduced.

Conclusion

This novel in vitro device for BBB culture models provides users with a standardized, reliable and reusable platform to perform pathology and pharmacology experiments. With advancement of the electrode layout, TEER automation and surface potential measurement our device is a cutting edge invention in the barrier-chip field.
SINGLE-DOSE WHOLE BRAIN IRRADIATION CAUSES GLIAL ACTIVATION AND INCREASED CEREBRAL BLOOD FLOW IN RATS: A LONGITUDINAL PET/SPECT IMAGING STUDY

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Introduction
Whole brain irradiation, despite being an important therapy for brain tumor patients, can lead to cognitive impairment. The specific mechanisms involved in this damage are not yet fully understood, but seem to be related to a neuroinflammatory response to irradiation. Through Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), our study aimed to investigate the effects of irradiation in normal rat brain, particularly regarding microglial activation and cerebral blood flow – both parameters related to neuroinflammation.

Materials & Methods
Male Wistar rats (n=8 per group) subjected to 25 Gy X-ray radiation and controls were submitted to [11C]-PK1195 PET imaging to assess microglial activation (at baseline and 1, 3, 5, 9, 12, 59 and 88 days after irradiation) or [99mTc]-HMPAO SPECT imaging to assess cerebral blood flow (at baseline and 1, 3, 5, 9, 60 and 90 days after irradiation). The Generalized Estimating Equations model was used for statistical analysis of the data.

Results
Irradiated animals showed a significant increase in [11C]-PK1195 uptake in all brain regions and in the whole brain (36%, p<0.001) on day 12. The percentage increase at this timepoint was significantly higher in non-cortical than in cortical regions (39-64% vs 26-30%; p<0.001). The increase did not persist, and uptake had normalized to baseline values on days 59 and 88. In addition, irradiated animals showed gradual increase in [99mTc]-HMPAO uptake, which was significantly higher than baseline from day 5 onwards in most brain regions and in the whole brain (42%, p=0.003). In later timepoints, the uptake kept on increasing, being the highest on day 90 amongst the analyzed timepoints (87%, p<0.001).

Conclusion
Whole brain irradiation induced an acute and transient increase in microglial activation in rats, more expressive in non-cortical brain regions. In addition, the whole brain irradiation also induced a progressive increase in cerebral blood flow, which was already significant in the acute phase but even higher in later timepoints. Our study therefore supports the hypothesis that neuroinflammation is involved in impairment following brain irradiation.
Rational Design of Nanoparticle Morphology and Surface Charge for Targeted Cellular Delivery

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Introduction
An unsolved obstacle for targeted cellular drug delivery via nanoparticles (NPs) is nonspecific circulatory clearance by the body’s mononuclear-phagocytic system (MPS), which is comprised of various phagocytic cells. Recently, it has been discovered that preferential uptake of NPs, composed of poly (ethylene glycol)-block-poly (propylene sulfide) (PEG-b-PPS), by antigen presenting cells (APCs) can be achieved solely by modifying the NP morphology. Additionally, APCs—a subset of MPS cells—can also have their uptake specificity altered by the NP surface charge. Uptake by certain APCs called dendritic cells (DCs) can avoid nonspecific circulatory clearance and prime distinct immune responses useful in immunotherapy. We have previously demonstrated that PEG-b-PPS micelles, filomicelles, and polymersomes have significantly different biodistributions within the MPS. Herein, we assess how the combined influence of NP morphology and surface charge can further specify uptake of these three PEG-b-PPS nanostructures by relevant APC populations.

Materials & Methods
Derivatives of PEG-b-PPS exhibiting either hydroxyl, phosphate, or methoxy terminal groups were prepared. Block copolymers (BCPs) were characterized via ¹H NMR, GPC, and FT-IR. NPs were formed through either thin film hydration or flash nanoprecipitation and were characterized via Cryo-TEM and SAXS. NP cytotoxicity was assessed through the MTT assay and biodistribution studies were conducted in C57BL6 mice.

Results
Cryo-TEM confirmed that the PEG-b-PPS BCPs formed micelles (~15nm diameter), filomicelles (~1500nm lengthwise), and polymersomes (~80nm diameter). The NPs exhibited zeta potentials ranging from ~40 mV to +2mV. Biodistribution studies suggest that the presence of a negative surface charge enhances morphology-dependent targeting effects with regards to NP uptake in lymph node DCs and macrophages following subcutaneous (SC) administration. In particular, anionic FMs demonstrated much greater DC uptake preference than neutrally-charged FMs.

Conclusion
Previously unreported derivatives of PEG-b-PPS BCPs exhibiting hydroxyl, phosphate, and methoxy terminal groups have been characterized. These BCPs are capable of forming micellar, filamentous, and vesicular NPs that exhibit a wide array of zeta potentials. The combined differences in NP morphology and surface charge displayed greater variations in DC uptake than NP morphology differences alone, following SC injection in mice. Future studies will assess the inherent immunogenicity and cellular uptake of these NPs within APCs from human blood samples.
Oncology I

Chair
Prof. Frank A.E. Kruyt MD PhD

Presenters
Fang, C (Canbin)
Fu, H. (Hangwei)
Liu, J.F.L (Juanfang)
Suárez-Barrera, M.O.S.B. (Miguel Orlando)
Ullah, S. (Saif)
Wang, J.C. (Jingchun)
Whole Genome Sequencing Identifies Genes in Fanconi Anemia Pathway as the Candidate Breast Cancer Susceptibility Gene of Chaoshan Area

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Introduction
Up to 15% of cases of breast cancer are familial, but so far, the two most prevalent susceptibility genes, BRCA1 and BRCA2, together with other high, moderate and low penetrance genes, such as TP53, PALB2 and ATM, only account for 35% of the familial cases. To this regard, we aimed to identify new candidate genes predisposed to familiar breast cancer without pathogenic BRCA1/2 variants.

Materials & Methods
In the present study, Whole Genome Sequencing was performed for 21 BRCA1/2 negative familiar breast cancer index cases from Chaoshan Area. All the variants were filtered and prioritized by bioinformatic analysis followed by Sanger Sequencing and co-segregation validation.

Results
A total of 9836403 variants were detected after quality control, including 8930532 SNPs and 905871 INDELs. 160 rare variants were predicted to be pathogenic in Silico and located in the genes involved in the DNA repair pathways, of which Fanconi Anemia pathway is the most significant one in all the mutational genes. Among all the 15 mutated FA genes, FANCI carried 6 variants, with an overall mutation prevalence up to 28.6%. The FANCI p.E868D and p.H1218Y co-segregated in one family respectively, which conferred to a likely strong predisposition for FBC. The p.Y458H in FANCD2 and p.S186Y in FAN1 also represented to be pathogenic as both of them are located in the conserved loci by the MSA analysis and predicted to be damaging by SIFT and PolyPhen-2. All the variants in FA pathway were validated by Sanger Sequencing. In addition, we’ve also identified 26 variants in 13 known breast cancer susceptibility genes including ATM, CHEK2 and TP53, which further corroborated this study.

Conclusion
Mutations in Fanconi Anemia Pathway are of great significance to familial breast cancer. FANCI, FANCD2 and FAN1 are the candidate breast cancer susceptibility genes of Chaoshan Area. Further functional assay and a larger scale of case-control study are in progress to validate the pathogenicity and predisposition to breast cancer.
A novel protein-binding circular RNA circ-CET promotes hepatocellular carcinoma metastasis.

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Introduction
Circular RNAs (circRNAs), a subclass of noncoding RNA characterized by covalently closed continuous loops, have been shown to play emerging regulatory roles in cancer biology in recent years. However, the contributions of circRNAs to hepatocellular carcinoma (HCC) remain largely unknown. Here, we screened one exonic circRNA circ-CET from circRNA sequencing data and identify it as a novel driver of HCC progression.

Materials & Methods
A novel circRNA circ-CET was screened from circBase and validated by quantitative reverse transcription PCR (RT-qPCR). Next we evaluated circ-CET levels in HCC and normal hepatocyte cell lines by RT-qPCR, and performed in situ hybridization on tissue microarray containing HCC and adjacent liver tissues with digoxin-labeled circ-CET probe. The role of circ-CET in HCC progression was assessed both in vitro and in vivo. In addition, gene microarray, RNA immunoprecipitation (RIP) assay, biotin-labeled circRNA pull-down, mass spectrometry assay and luciferase reporter assay were conducted to explore the possible molecular mechanisms of circ-CET in HCC metastasis.

Results
Circ-CET was predominantly expressed in the nucleus, upregulated in HCC tissues and HCC cell lines, and associated with unfavorable outcomes in HCC patients. In vitro loss and gain-of-function assays revealed that circ-CET promotes the epithelial-to-mesenchymal transition (EMT) and migration of HCC cells. In vivo xenograft experiments in nude mice confirmed that overexpression of circ-CET increased the intrahepatic metastasis of HCC cells compared to the negative control HCC cells. Mechanically, gene microarray and Ingenuity pathway analysis showed that circ-CET is a cell adhesion-associated molecule and regulates the expression of several EMT-related genes. RIP assay with Ago2 antibody revealed that unlike most of the currently reported circRNAs, circ-CET may not serve as a miRNA sponge. Instead, circ-CET binds to an EMT-associated transcription factor Snail and augments its function, which inhibits the gene expression of tight junction protein occludin.

Conclusion
A novel protein-binding circular RNA, circ-CET, binds to Snail to mediate HCC metastasis. These findings provide a fresh perspective on circRNAs in HCC progression, and a potential target for HCC therapy.
Comparison of efficacy between TACE combined with apatinib and TACE alone in the treatment of huge hepatocellular carcinoma

Liu, J.F.L (Juanfang)

Introduction
Patients with huge HCC are generally at the advanced or late stage of the disease, with a poor prognosis, and the survival time is considerably shorter than that of patients with smaller HCC. In the present study, we conducted a retrospective evaluation of the therapeutic effect of TACE combined with apatinib on patients with huge HCC.

Materials & Methods
From July 2016 to December 2017, a total of 45 patients with huge HCC were consecutively enrolled. 23 underwent the combined treatment of TACE plus apatinib and 22 underwent TACE alone. The objective response rate (ORR) was assessed at first month after TACE therapy and survival rate at median follow-up time was also compared between the two groups; Furthermore, progression free survival (PFS), overall survival (OS) and treatment-related complications were also recorded and compared.

Results
ORR at first month after treatment in TACE plus apatinib group and TACE alone group were 56.5% and 40.9% respectively. And the differences between these two groups were not statistically significant (P>0.05). While, during a median follow-up period of 190 days, 69.6% (16/23) patients were still alive in TACE + apatinib group compared with that of 27.3% (6/22) patients in TACE group, and the difference was statistically significant (P<0.05). Median OS as well as median PFS were longer in TACE plus apatinib group compared with TACE alone group (250 vs 175 days, P=0.002; 100 vs 70 days, P=0.014; respectively). The incidences of complications were related to apatinib, such as hypertension, hand-foot syndrome and proteinuria, were higher in TACE plus apatinib group than in TACE alone group, and the differences were statistically significant (P<0.05). However, all the adverse events could be clinically managed by symptomatic treatment.

Conclusion
TACE combined with apatinib can obviously prolong the median OS as well as median PFS of patients with huge HCC, with a relative safety. It thus appears to be a feasible and promising approach to the treatment of huge HCC.
Bioinformatics approaches to obtain parasporins with improved antitumor activity, as potential agents for colorectal cancer treatment

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Introduction
According to the World Health Organization (WHO), 9.6 million deaths were produced by cancer in 2018. Colorectal cancer alone accounted for 1.8 million cases and 862,000 demises. Parasporins, the toxins of Bacillus thuringiensis, have been shown to have anti-proliferative activity in human cancer cells, in particular in the Caco-2 and HCT-116 cell lines. In this work, we used a bioinformatics approach with the aim to design new parasporin mutants with improved binding to the aminopeptidase N (h-APN) human membrane receptor.

Materials & Methods
Local alignments were performed to detect similar regions between parasporin PS2Aa1 and regions of the receptor-binding domain (RBD) of the human alpha-coronavirus HcoV-229E, which has been shown to interact with h-APN. Our own MutProt program was developed using Python 2.7, the PS2Aa1 sequence and the maximum number of changes/deletions in the desired regions were received as input. We selected several of these mutants, based on calculated parameters such as charge, isoelectric point and hydrophobicity, to perform molecular docking simulations.

Results
Three similar regions were identified between PS2Aa1 and RBD-HCoV-229E (loop 1 97NAVKPP102, loop 3 82GTNPD86, loop 8 254GPGG257), as the delimited regions by local alignment. 500 mutants were obtained as output, whose structures closer to the native were selected for molecular docking and dynamic analysis.

Conclusion
The shared regions between PS2Aa1 and RBD-HCoV-229E, are key information to design mutants and/or chimeric proteins, because the latter form important interactions such as hydrogen bonds and salt bridges with h-APN. MutProt could save resources, time and budget; it has the potential to become a new site-directed evolution tool to design e.g. anti-cancer toxins. In perspective, this work is on the first phase in a multinational program directed to prevent and treat colorectal cancer, known as Nano-Biocancer.
Mucosal transplantation from stomach into esophagus for the management of post-circumferential endoscopic submucosal dissection stricture of early esophageal cancer

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Introduction
Endoscopic submucosal dissection (ESD) of high grade dysplasia and early esophageal cancer has gained acceptance in the last decade as an effective therapeutic option. Although the short term results of ESD are promising, a high risk of procedure related complications, including post-procedural stricture remains unresolved. The aim of this study were to assess the effectiveness and safety of mucosal transplantation into esophagus from the stomach in preventing stricture formation after ESD in early esophageal cancer.

Materials & Methods
Six patients who underwent circumferential ESD for early esophageal cancer were enrolled. After the patients underwent ESD, the mucosal patches taken from the posterior wall of the middle part of the gastric body by the ESD were placed to the ulcer site of esophagus. The guide wire was then inserted into the gastric cavity via flexible endoscopic channel to fix the patches with the stent at the ulcer site. The stent was removed after the performance with media of 7.83 days (range 7-9). All of the patients were followed up with endoscopy.

Results
The graft survival rate was 83.3% with strictures occurred at a mean of 33.67 days (range 20-56) after the procedure. The median number of endoscopic balloon dilatation sessions was 5.67 (range 4–7).

Conclusion
Gastroesophageal mucosal transplantation for stricture prevention after circumferential submucosal dissection for early esophageal cancer and or high grade dysplasia seems feasible with excellent outcome. This study opens new perspective in this field.
RIPK3 orchestrates fatty acid metabolism in tumor-associated macrophages and hepatocarcinogenesis.

Wang, J.C. (Jingchun)

Introduction
Hepatocellular carcinoma (HCC) is one of the most lethal human malignancies worldwide. It is a typical inflammation-associated tumor, and tumor associated macrophages (TAMs) are one of the most prominent components of infiltrating immune cells which play crucial roles in the initiation and development of HCC. The majority of TAMs polarizes towards an M2 state and promotes HCC progression by suppressing the activation of tumor infiltrating T cells. Accumulating evidence suggests that macrophage polarization and functions are associated with metabolic reprogramming, especially fatty acid oxidation (FAO). However, the molecular mechanisms reprogramming lipid metabolism of TAMs is unclear. Receptor-interacting protein kinase 3 (RIPK3) is a center factor in necroptosis, but its impact on lipid metabolism and tumor immunity remains largely unknown. This study aims to explore the role of RIPK3 in regulating fatty acid metabolism and anti-tumor immunity of TAMs.

Materials & Methods
Human HCC and adjacent tissues samples were collected from Department of Hepatobiliary Surgery of Xinqiao Hospital, Army Medical University, Chongqing, China. Mouse HCC models were established with diethylnitrosoamine (DEN) i.p. and choline deficient amino acid defined (CDAA) diet. Flow cytometry (FCM), immunofluorescence, qPCR, western blotting, and metabolic flux assay were applied to determine indicated genes or proteins.

Results
RIPK3 was downregulated in HCC-associated macrophages. RIPK3 KO mice showed a promoted hepatocarcinogenesis with increased infiltration and M2 polarization of TAMs. Mechanistically, RIPK3 deficiency induced fatty acid oxidation (FAO) and M2 activation of macrophages via ROS-caspase1-PPAR pathway. Inhibition of FAO significantly reversed the immunosuppressive activity of TAMs and dampened HCC tumorigenesis. Treatment of macrophages with hypomethylating agent decitabine increased RIPK3 expression and inhibited FAO and suppressed hepatocarcinogenesis.

Conclusion
Our findings provided molecular basis for RIPK3 regulating fatty acid metabolic reprogramming of TAMs and highlighted a potential strategy for targeting ROS-caspase1-PPAR pathway in the immunotherapy of HCC.
Pharmacology I

Chair
Prof. Rob H. Henning PhD

Presenters
Abdelbaset Othman, A. (Ahmed)
Goswami, K.S. (Kavisha)
Masoud, F.M (Farid)
Rahimi, N (Nastaran)
Shah, M (Mandar)
Vos, B.O. (Björn)
TOLERABILITY AND EFFICACY OF A FIXED COMBINATION OF CINNARIZINE AND DIMENHYDRINATE VERSUS BETAHISTINE IN THE TREATMENT OF VERTIGO: A META-ANALYSIS

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Introduction
A fixed combination of cinnarizine and dimenhydrinate (Arlevert, [ARL]) is a remarkable bimodal antivertiginous drug; cinnarizine as a calcium channel antagonist and dimenhydrinate as an antihistaminic. It demonstrated high efficacy, compared to placebo in the treatment of vertigo of various origins. We aimed at synthesizing evidence from published randomized controlled trials (RCTs) about the tolerability and efficacy of ARL versus Betahistine in symptomatic treatment of vertigo.

Materials & Methods
We searched nine databases for relevant RCTs. Citations were screened for eligibility and data were extracted and analyzed using RevMan. Changes in mean vertigo score (MVS) and mean score of vegetative symptoms (MSVS) were pooled as mean difference (MD). Spontaneous nystagmus and tolerability were pooled as odds ratios (ORs) in a meta-analysis model. Heterogeneity was assessed by Chi-square and I-square tests.

Results
Five low risk of bias RCTs with 292 patients (ARL n= 144, and Betahistine n=148) were included. ARL was marginally superior to Betahistine in reducing MVS after one week. However, there was no significant difference at the end of follow up (MD = -0.14, 95% CI [-0.29 to -0.001], p = 0.05), (MD = -0.08, 95% CI [-0.49 to 0.34], respectively). ARL was superior to Betahistine regarding MSVS after one week and at the end of follow up (MD = -0.34, 95% CI [-0.60 to -0.08]), p = 0.01, MD = -0.30, 95% CI [-0.48 to -0.13], p = 0.0009, respectively). For MSVS, no significant heterogeneity was found (Chi-square p > 0.1 and I² = 0%). At the end of follow up, no significant difference was found regarding spontaneous nystagmus or tolerability.

Conclusion
Except for spontaneous nystagmus and patients' tolerability, the ARL achieved significant improvement in MSVS and a slight improvement in MVS. Therefore, larger RCTs are Recommended to guarantee the difference.
Study Of Enalapril And Its Concomitant Treatment With Diclofenac Sodium In Osteoarthritic Hypertensive Patients.

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Introduction
The present study was designed as an open label, multiple-dose, randomized, parallel clinical trial to evaluate the pharmacodynamic drug-drug interaction between enalapril and concomitantly administered diclofenac sodium in osteoarthritic hypertensive (with or without type 2 diabetes mellitus (T2DM)) patients based on evaluation of blood pressure (BP), insulin sensitivity, renal function and serum electrolytes levels.

Materials & Methods
Post-screening and on inclusion, 67 patients were randomized to either only enalapril 10 mg or concomitant treatment of enalapril 10 mg and diclofenac sodium 100 mg for 8-12 weeks in diseased states of hypertension and osteoarthritis with or without T2DM. Patients were evaluated and analyzed for systolic BP (SBP), diastolic BP (DBP), insulin sensitivity, urinary albumin excretion rate (UAER), serum sodium (S. Na+), serum potassium (S. K+), serum creatinine (Scr), creatinine clearance (CLCR) and blood urea nitrogen (BUN).

Results
Baseline demographics and characteristics of the patients were comparable amongst all the groups. Adequately controlled antihypertensive effect of enalapril was significantly attenuated by diclofenac sodium when concomitantly administered with enalapril among diabetic (SBP: p=0.004; DBP: p=0.007) and non-diabetic (SBP: p=0.007; DBP: p=0.00006) pool of the patients. Insulin sensitivity was improved (p=0.001) and UAER (p=0.04) was better controlled among enalapril treated diabetic patients, while these effects were attenuated in diabetic patients receiving enalapril and diclofenac sodium concomitantly. S. Na+ and K+ levels were reduced and raised significantly in diabetic as well as and non-diabetic patients, respectively, receiving concomitant treatment of enalapril and diclofenac sodium concomitantly. Scr, CLCR and BUN were significantly increased (p=0.002), lowered (p<0.000001) and raised (p=0.006), respectively, with enalapril and diclofenac sodium concomitant treatment as compared to enalapril treatment. BUN was significantly increased (p=0.014) in enalapril and diclofenac sodium concomitantly treated patients when compared to enalapril treatment among diabetic pool.

Conclusion
Chronic concomitant treatment of oral diclofenac sodium with enalapril led to deterioration of insulin sensitivity (T2DM patients), serum electrolytes and renal function in osteoarthritic hypertensive patients (with/without T2DM). Thus, the concomitant treatment of oral diclofenac sodium with enalapril should be considered with due monitoring of the described parameters at appropriate time intervals in above group of patients.
Evaluating the Efficacy of Topical Herbal Solution on the Treatment of Androgenetic Alopecia and Comparison with Minoxidil 5%: A Double-Blind, Randomized, Clinical Trial Study

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Introduction
Androgenetic alopecia (AGA) is caused by miniaturization of androgen-sensitive hair follicles and common form of scalp hair loss. Finasteride and Minoxidil have been approved by the American Food and Drug Administration (FDA) for the treatment of AGA. But these have a lot of side effects. Herbal extracts have more mechanism for treating AGA, fewer side effects and patient satisfaction.

The aim of this study was to examine the efficacy and safety of topical herbal solution in males with AGA.

Materials & Methods
We conducted a randomized, double-blind, parallel-group clinical trial at the dermatology department in Sina hospital. Male volunteers aged between 18 and 50 years with mild to moderate AGA were randomly assigned (1:1), via computer-generated randomization, to receive either herbal or Minoxidil 5% topical solution. The first group received herbal solution every evening + Minoxidil 5% every morning for 12 to 24 weeks, while the second group received only Minoxidil 5% for the same period. After a baseline visit, patients were evaluated by clinical examination, photographic documentation, a self-assessment test, and measuring hair diameter every month. Written informed consent was obtained from all participants prior to entry.

Results
Analysis of the two groups showed significant differences and highly positive response to treatment in the first group compared to the second group. In the first group, hair diameter increased compared to the baseline visit. Specifically, after a few weeks, hair loss was stopped only in the first group. The patients were satisfied with the herbal solution and during this period, no significant adverse events were reported.

Conclusion
These results suggest that the new herbal solution is responsible for a significant improvement of AGA and could be an alternative treatment in patients who didn’t have an efficiency of standard medications or cannot tolerate those side-effects. To our knowledge, this herbal solution for the first time covers all three major causes of AGA, including the 5α-reductase enzyme, androgen receptors, and paracrine agents that affecting dermal papilla. Therefore it acts with the triple mechanism, different from the already existing therapies.
Involvements of nitrergic and opioidergic systems on experimental colitis in cirrhotic rats

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Introduction
Colitis, a colonic inflammatory condition, showed a linkage with hepatobiliary disorders such as cirrhosis. It has been reported that both endogenous opioids and nitric oxide (NO) play critical roles in colitis pathogenesis. Moreover, opioid and NO levels showed elevation in patients with cirrhosis. The aim of this study was to evaluate the effect of cirrhosis on the experimental model of colitis and the possible involvement of opioidergic/nitrergic systems in rats.

Materials & Methods
To induction of cirrhosis, rats were anesthetized with a single intraperitoneal injection of ketamine HCl (80 mg/kg) and xylazine HCl (10 mg/kg). Following a midline, laparotomy ligation was performed at two different locations on bile duct with absorbable surgical threads. Colitis was induced by intrarectal administration of acetic acid (4%) 28 days after bile duct ligation (BDL). L-NAME, as an inhibitor of nitric oxide synthase and naltrexone, as an antagonist of opioid receptors were administered to animals during 3 days after that. Macroscopic colitis lesion area, inflammatory mediators change, NO metabolite levels, and colon microscopic injuries were assessed 3 days after induction.

The data were expressed as means ± S.E.M. for 8 observations in each group. All data were analyzed with SPSS statistical software package (version 22). Analysis of variance (ANOVA) followed by Tukey's post-hoc test was used for statistical significance. P-value less than 0.05 was considered as statistically significant in all comparisons.

Results
Cirrhosis significantly reduced the macroscopic and microscopic scores of damages to the colon (P < 0.001). Administration of L-NAME (10 mg/kg; (P < 0.001)), naltrexone (10 mg/kg; (P < 0.001)) and co-administration of L-NAME (1 mg/kg) and naltrexone (5 mg/kg) significantly reduced the protective effect of BDL on colitis. Nitrite elevated levels in BDL rats were significantly diminished in L-NAME- and naltrexone-treated animals. Histopathology parameters and cytokines level alterations in the colon of acetic acid-treated animals after BDL was reversed after injection of L-NAME, naltrexone, and co-administration of L-NAME (1 mg/kg) + naltrexone (5 mg/kg).

Conclusion
The opioidergic and nitrergic systems may mediate the protective actions of cirrhosis on the experimental model of inflammatory bowel disease induced by acetic acid in rat.

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Introduction
The term PONV is typically used to describe nausea and/or vomiting or retching in the post-anesthesia care unit (PACU) and in the immediate 24 postoperative hours. Ondansetron is a serotonin 5 –HT3 receptor antagonist used for prevention of postoperative nausea vomiting. Another drug is Metoclopramide, a prokinetic drug is also used for treatment of the same. There is lack of systematic review to suggest which Antiemetic drug is superior over other.

Materials & Methods
All randomised control trials which follows PRISMA guidelines 2009 and in which Ondansetron and Metoclopramide were first compared with placebo for the prevention of postoperative nausea vomiting. Clinical trial registries, MEDLINE,SCOPUS,EMBASE database were searched for MeSH terms Ondansetron, Metoclopramide, Placebo which resulted in prevention of postoperative nausea vomiting in Early(0-6hr) and Late(6-48hr) phases. Observational studies, Unpublished studies, RCTs not following PRISMA guidelines were excluded. Data was analyzed using RevMan version® and Odd’s Ratio was calculated to determine the difference in Early and late phases. Both Fixed and Random effect model was utilized to calculate the difference. P value less than 0.05 was considered as statistically significant. The I2 will be used to measure the heterogeneity between studies and a value &gt;30.0 will be considered to reflect heterogeneity.

Results
A total of 21 studies were included. A total of 10,175 patients were recruited in all RCTs. Ondansetron was effective than placebo to prevent early vomiting.(Odd’s ratio=2.255,CI=1.826 to 2.786, p value less than 0.01). Metoclopramide was also effective when compared to placebo to prevent early vomiting. (Odd’s ratio=1.978, CI=1.060 to 3.692, p=0.032). When ondansetron was compared indirectly with Metoclopramide no statistically significant difference was seen (P=0.1136). Ondansetron was effective than placebo to prevent late vomiting(Odd’s ratio=1.880,CI=1.626 to 2.174, p value less than 0.01). Metoclopramide was also effective when compared to placebo to prevent early vomiting. (Odd’s ratio=1.595, CI=1.261 to 2.016, p value less than 0.01). When ondansetron was compared indirectly with Metoclopramide statistically significant difference was seen. (P=0.0058).

Conclusion
Both Ondansetron and Metoclopramide are effective to treat Postoperative nausea and vomiting when compared to placebo. Ondansetron is more effective than Metoclopramide to prevent Late Postoperative vomiting.
Adverse events associated with pediatric usage of complementary and alternative medicine (CAM) in the Netherlands: a National Surveillance Study

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Introduction
Paediatric usage of complementary and alternative medicine (CAM) is common. This usage however is not commonly discussed between doctors and parents. Worryingly, research in various countries has shown that adverse events have been associated with paediatric CAM usage. The motto "If it doesn't cure, it doesn't harm" therefore does not hold up. The objective of this study was to investigate the adverse events associated with paediatric CAM usage in the Netherlands.

Materials & Methods
A three-year survey was started at the national Dutch Pediatric Surveillance Unit (DPSU). Pediatricians were asked to register all cases of adverse events associated with pediatric CAM usage. In the last three months of the study period a random selection of 9 pediatric units was directly approached and more publicity for the study was generated.

Results
In three years, a total of 32 cases of unique and valid adverse events was registered at the DPSU. 19 of these adverse events were mild to moderate, 8 were severe and 5 very severe. Dietary supplements/vitamins, orthomolecular therapy and homeopathy were the most prevalent therapies in the registered adverse events. About 1/3 of all adverse events were direct adverse events related to the specific CAM therapy used while the other events were due to indirect effects such as delaying a regular diagnosis, delaying/changing/stopping of a regular treatment or starting a deficient or restrictive diet. Half of the adverse events was gathered in the last three months of the study.

Conclusion
Relatively few cases of adverse events due to paediatric CAM usage were found but vast underreporting is suspected. In most cases the adverse event was not directly caused by the specific CAM treatment but rather indirectly due to delaying, stopping or changing a conventional diagnosis or treatment or because of a deficient diet. Since a myriad of different therapies was involved, this suggests that indirect adverse events are a risk inherent to any CAM treatment. Supplements, vitamins, (Chinese) herbs and manipulation of the head and neck were involved in direct adverse events and can cause serious harm in children. Parents and paediatricians should be vigilant for adverse events when CAM therapies are being used.
Pulmonary Medicine

Chair
Prof. Huib A.M. Kerstjens MD PhD

Presenters
Arias, P.V. (Pamela)
Baez-Navarro, X. (Ximena)
Barbosa, V.B. (Violina)
Felzen, A.
Singh, A (Ashwini)
Zulu, C (Ananias)
Effects of a melatonin prenatal treatment in pulmonary vascular function and histomorphology in newborn lambs gestated and born in hypobaric hypoxia

Arias, P.V. (Pamela) Medical student, González-Candia, A. (Alejandro) MSc PhD(c), Reyes, R.V (Roberto) PhD, Ebensperger, G (German) PhD, Llanos, A.J. (Aníbal) MC, Herrera, E.A. (Emilio) MV PhD, 1 Faculty of Medicine, University of Chile, Pathophysiology Program, ICBM, Santiago, Chile, 2 University of Chile, International Center for Andean Studies (INCAS), Putre, Chile

Introduction
Perinatal hypoxia is a relevant cause of neonatal morbimortality, triggering pulmonary pathologies that affects up to 10% of newborns at high altitudes. Hypoxia-induced oxidative stress determines pulmonary vascular dysfunction and remodeling. Melatonin is a neurohormone with antioxidant, anti-remodeling and vasodilator actions. This study proposes to determine the effect of prenatal treatment with melatonin on the vascular function and structure of small pulmonary arteries from lambs gestated and born in hypobaric hypoxia.

Materials & Methods
Ten pregnant ewes and their lambs were gestated and studied at 3,600 m. Five received oral melatonin during the last third of gestation (MM, 10mg*kg-1*d, oral) and five received the vehicle as control group (CM, 5ml*kg-1*d1, oral). Ewes delivered and at 12 postnatal days, lambs were euthanized and small pulmonary arteries were obtained to evaluate the vascular reactivity by wire myography and pulmonary tissue to evaluate histomorphology, prostanoids and nitric oxide pathway proteins expression, proliferative and oxidative stress markers. All data were expressed as mean ± SEM and analyzed by unpaired t-test in GraphPad Prism. All procedures were approved by the Bioethics Committee (CBA#0761 FMUCH).

Results
Melatonin significantly decreased contractile capacity in response to potassium and thromboxane and improved vasoconstriction to serotonin. In addition, MM showed an improved vasodilation to endothelium dependent and independent mechanisms. Furthermore, melatonin increased the protein expression of eNOS, COX-1, COX-2, PGI2s and TXs relative to CM. No changes were observed in GCs, PDE-5, PKG-1, TP and Ip expression between groups. Finally, melatonin increased adventitia thickness, without changes in media and luminal area/wall area ratio in small pulmonary arteries. Moreover, MM showed decreased levels of the proliferative markers +Ki67 and α actin, and the oxidative stress marker 3-nitrotyrosine in lung.

Conclusion
Melatonin improves vascular vasodilator function of the small pulmonary arteries dependent and independent of NO, enhance expression of vasodilator enzymes, decreased vascular remodeling and oxidative stress level. Our data support the use of melatonin in chronic hypoxic pregnancies to prevent detrimental perinatal pulmonary outcomes.
Validation of the Risk Index for Susceptible Persons (IRPS) as an Indicator to Identify the Association between Air Pollution in Mexico City and the Effects on Respiratory Health.

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Introduction
An air quality index is a quantitative tool to improve risk communication according to air quality based on health. The IRPS is an index that was developed using six years of health records and air pollution data from multiple monitoring sites in Mexico City in collaboration with the University of New York. Unlike indexes used in other countries, IRPS evaluates risk based on a multi-pollutant model. The Asthma Control Test (ACT) is a validated questionnaire to assess the status and control of asthma in the last month. With this study, we aim to provide statistical validation of the IRPS looking for an association between the concentrations of air pollutants and the control of asthma in each patient.

Materials & Methods
This is a clinical, observational, longitudinal and prospective cohort study that ascertained 150 patients diagnosed with asthma according to international guideline criteria. The IRPS was released on the 8th of December 2018 on a public website and registered daily. Patients were asked to answer the ACT daily on a digital platform during this month. The access to the ACT digital platform was closed on the 9th of January 2019 and the obtained information was gathered on a data basis. A bivariate analysis was made with a Pearson correlation to evaluate the association between the IRPS and the scores of the ACT questionnaire.

Results
Only thirty patients diagnosed with asthma were included in our pilot study. The mean age was 36.8 years (95% CI 21-65) and 70% of the patients were females. The average ACT scores were 9.65 (95% CI 5-35). The IRPS median during the 30-day follow-up was 7 (95% CI 3-12) meaning a moderate to bad air quality in Mexico City. A positive significant correlation between the mean ACT scores and IRPS was found (P=.049). Most common symptoms contributing to ACT scores were lacrimation and headache.

Conclusion
The results suggest that the daily use of IRPS can work as a predictive indicator to identify the association between exposure to environmental pollutants and its harmful acute effects in patients with asthma.
Impact of Hippo signaling in chick lung branching morphogenesis

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Introduction
Hippo signaling pathway and its effector YAP has been recognized as important growth regulator during embryonic development. The inhibition of this pathway in the liver causes overgrowth, whereas in pancreas – hypoplasia, therefore suggesting phenotypic differences depending on the organ system. Hippo signaling in lung organogenesis remains uncertain, this project aims to elucidate its role during pulmonary branching and, for the first time, in avian animal model.

Materials & Methods
All experiments were conducted in embryonic chick lungs during early branching stages (b1, b2, b3: one, two or three secondary bronchi/bronchus, respectively). The spatial distribution of Hippo signaling members were characterized by in situ hybridization. Moreover, in vitro lung explant culture was performed (lung culture medium) for 48 hours, and protein levels of phosphorylated-YAP (cytoplasmic)/total-YAP were assessed by Western blot at two time-points (0 and 48 hours). Additionally, lung explants were cultured (48 hours) in YAP-TEAD inhibitor verteporfin (5, 7.5 and 10 µM) and vehicle control (DMSO) supplemented media and analyzed morphometrically (D2/D0 ratio). One-way ANOVA and post-hoc Fisher Least Significant Difference test were used to determine the statistical differences between groups.

Results
In situ hybridization revealed that all Hippo signaling members are mainly expressed in mesenchymal, except for mst2 and lats2 in embryonic stages studied. Western blot analysis showed similar expression of total-YAP and phospho-YAP in three stages studied. The phospho-YAP/total-YAP ratio was assessed at Day-0 (0h) and Day-2 (48h) and no statistical differences were detected (p=0.171 and p=0.486, respectively). Lung explants treated with 7.5 and 10 µM VP (n≥10/condition) displayed statistically significant reduction in lung size (≈14 and 31%, respectively), branching (≈15 and 40%, respectively) and decreased expression of ctgf (n≥4/condition) when compared to controls. All experimental data is presented as mean ± SEM (p&lt;0.05, 95%CI).

Conclusion
This study demonstrates, for the first time, the presence of Hippo signaling in early stages of avian pulmonary branching. Gene/protein expression and pathway modulation indicate that Hippo is active and possibly involved in regulation of lung growth. This data brings new insights into the mechanisms underlying lung branching which ultimately may contribute in designing novel therapeutic strategies for congenital disorders.
Airway Occlusion Pressures in Mechanically Ventilated Paediatric Patients

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Introduction
Prolonged duration of mechanical ventilation can be associated with complications and an increased risk of extubation failure. At the same time, premature extubation and need for reintubation are also associated with increased morbidity and mortality. Measuring the maximum inspiratory pressure (MIP) and inspiratory pressure after 100ms (P100) during ventilation can possibly support the decision for extubation. No studies in paediatrics are known but it has proven its validity in adult ventilation. This study investigated the level and time course of MIP and P100 and studied the clinical applicability of such parameters.

Materials & Methods
This observational pilot-study was performed in a 20-bed tertiary paediatric intensive care unit (PICU). Patients eligible for this study were able to breathe spontaneously and measurements were made during a maximum of 5 consecutive days. Exclusion criteria were congenital or acquired neuro-/muscular damage. MIP – and P100 pressures were measured during occlusion of the inspiratory valve during 3-5 inspiratory efforts, at which the most negative value was chosen as best. The data was analysed with SPSS version 23.

Results
A total of 104 patients were included in the study. Median age of the cohort was 0.53 years (IQR 0.16; 2.16). Median MIP and P100 on the day of extubation were -17cmH2O(IQR -20.75; -11) and -5cmH2O(IQR -6.75; -4) respectively. A significant decrease in MIP was found on day of extubation (p= 0.036) compared to the day before extubation. There was significant correlation between the level of MIP and ventilation duration (p= 0.046). No correlation in MIP or P100 was found between patients who failed or succeed extubation.

Conclusion
This study found a significant decrease in MIP on day of extubation implicating that respiratory muscle strength is increasing towards extubation. Furthermore, the relationship between ventilation duration and level of MIP can possibly be explained by respiratory muscle atrophy. This might be helpful in further understanding the process of mechanical ventilation in paediatrics. The results provide a basis for further research to extend our knowledge concerning the treatment of respiratory insufficiency in paediatrics. For validating MIP/P100 as predictor of extubation, we extended the database. Inclusion so far provided 162 patients and is ongoing.
A Study of Certain Pulmonary Function Tests in professional Singers

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Introduction
It has universally been observed that trained professional singers have superior vocal ability as compared to a normal individual. It appears to be due to their better breathing capacity and better ventilating efficiency. Therefore we have tried to establish the fact that superior pulmonary capacity and breathing efficiency is because of training and presumably does not depend solely on heredity or other factors.

Materials & Methods
Pulmonary function tests namely FVC, FEV1, FEV1/FVC ratio (%), PEFR, and maximum breathing capacity (MBC) performed in 21 professional singers and 30 untrained persons as control. Both control and study groups were assessed for normality of distributions for all the parameters.

Results
It was found that in trained professional singers there is significant increase in FVC, FEV1, PEFR, and MBC while FEV1/FVC ratio (%) also showed a definite increase but it was not significant statistically. These parameters also showed improvement with length of vocal training. It was observed that mean FVC, FEV1, PEFR and MBC values in cases were significantly higher statistically, as compared to controls (p<0.05). Mean FEV1/FVC ratio (%) of cases was also slightly higher as compared to that of controls but the difference was not significant statistically (p=0.962).

Conclusion
It is suggested that these parameters have improved because of the ability of professional singers to utilize their residual volume for prolonged expiratory efforts during singing since total lung capacity cannot be increased. This result may also help the patients of respiratory disorders, like patients of COPD, etc. to improve their pulmonary functions.
DESIGN OF A LOW COST MONITORING AND DIAGNOSTIC MACHINE FOR PATIENTS WITH RESPIRATORY PROBLEMS IN RURAL MALAWIAN CLINICS

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Introduction
5.9 million Children under the age of 5 died in 2015. More than half of these early child deaths (in rural areas) are due to conditions that could be treated or prevented with access to simple, affordable interventions (in terms of treatment, early diagnosis and monitoring). In Malawi and most sub-Saharan countries children under five are not effectively treated from respiratory disorders (pneumothorax, asthma, asphyxia and pneumonia) due to lack of technical resources to diagnose and monitor body conditions. According to a research conducted at Queens Elizabeth Central Hospital (QECH) it was shown that nearly all under-five respiratory disorders are discovered at a late stage. We aimed at producing a low cost vital sign monitoring device.

Materials & Methods
The design was made to monitor, record and give recordings of body conditions to enable easy pre-diagnosis and treatment of respiratory disorders. This was done embedding a temperature sensor, simplified heart rate monitor, modified breath and chest movement sensors, a small oxygen medicator and a small nebulizer to a microprocessor.

Results
After a month prototype test at the Queens Elizabeth Central Hospital 11 nurses tested the device and 9 (81%) were able to diagnose over 89 more patients than days without usage (156 patients on average) of the design. This shows the device improved diagnosis efficiency by 57%. Multiple sensors eased disease identification by clinicians.

Conclusion
This design targeted quick vital signs diagnosis and monitoring of under-five children. With above results there was high increase in the patient monitoring not forgetting reduced time to diagnose a patient. This achieved early detection of respiratory diseases and improved patient monitoring in remote areas. At a low cost the device was able to provide the ability for rural clinics with enough diagnostic and monitoring equipment all in one set.
Vascular Medicine

Chair
Wybe Nieuwland MD PhD

Presenters
Anantawikrama, W. P. (Widyan Putra)
Ochneva, A.G. (Aleksandra)
Shilova, L. D. (Liubov)
Valk, M.M. (Martine)
Yang, DWY (Dawei)
Neutrophil-to-Lymphocyte Ratio is a predictor of short-term mortality in patients with Acute Limb Ischemia

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Introduction
Acute Limb Ischemia (ALI) is a dreadful disease that frequently resulted in mortality. In Dr. Sardjito General Hospital, ALI mortality rate is as high as 60.2%. Predictor of mortality can help the physician to decide the best treatment possible adjusted to mortality risk and predicting patient outcome. Neutrophil-to-Lymphocyte Ratio (NLR) is a medical indicator that already used to predict outcome in inflammatory diseases and malignancy. NLR has a big potential to be used as a low-cost mortality predictor in patients with ALI. This research is to establish an association between NLR and short-term mortality in Patients with ALI in Sardjito General Hospital.

Materials & Methods
Retrospective data of 103 patients diagnosed with ALI was collected from 2014 to 2018 at Sardjito General Hospital. NLR and mortality data were analyzed using Binary Logistic Regression in IBM SPSS Statistics 23 to establish significance and NLR associated mortality risk. ROC curve analysis was conducted using MedCalc 18.11 to determine NLR capability and cut-off point with optimal sensitivity and specificity.

Results
In the deceased group, NLR mean was 9.19 (95%CI 8.26-10.11). In the surviving group, NLR mean was 3.01 (95%CI 2.38-3.64). NLR was significantly associated with short-term mortality (p<0.01) and mortality risk increased by 3.48 times (95%CI 1.98-6.10) every unit increment of the NLR. ROC curve analysis showed that NLR has a distinctive ability to predict short-term mortality (p<0.01 with an area under the curve (AUC) of 0.972 (95%CI 0.918-0.994). The optimal cut-off point was 5.27, estimated using Youden J Index with value of 0.857 (95%CI 0.689-0.924) with sensitivity of 89.33% (95%CI 80.1 - 95.3) and specificity of 85.71% (95%CI 67.3 - 96.0).

Conclusion
Increase in NLR is meaningfully related to an upsurge in mortality risk. Besides, as a prognostic factor, NLR has a good ability to predict short-term mortality with 5.27 as the optimal cut-off point for classifying patients to high mortality risk. If these results are consistent and confirmed by succeeding investigations, NLR can be used as a prognostic tool to consider in management for patients with Acute Limb Ischemia, particularly before an invasive measure is taken.
Aspergillus sclerotiorum as a new producer of hemostatically active proteins


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Introduction
The hemostatic system of human blood is the most important system that provides blood flow, which prevents blood loss. Some processes of coagulation, anticoagulation, and thrombolysis are based on action of proteases. Many species of the genus Aspergillus produces proteases acting on proteins of the hemostatic system. These enzymes are capable of cleaving chromogenic peptide substrates specific for hemostatic proteins and activate a number of plasma hemostatic proenzymes (for example, protein C). It was shown that A. sclerotiorum has a high fibrinolytic activity. This may lead to the fact that micromycete may have other proteolytic activities of proteases of the hemostatic system.

Materials & Methods
Chromogenic peptide substrates, p-nitroanilides, were used to determine enzyme activities. The mechanism of action of chromogenic peptide substrates is based on specific enzyme cleavage, the active center of which targets at the amino acid sequence represented in the substrate. When the chromogenic substrate is cleaved, the colored p-nitroaniline (pNA) is released into the solution, which allows to determine the proteolytic activity by the color intensity of reaction mixture. Proteolytic activity is calculated from the amount of formed para-nitroaniline (pNA), proportional to the amount of hydrolyzed substrate. Activator activity towards protein C was determined by pre-incubating the sample with donor plasma.

Results
It was shown that A. sclerotiorum has a high thrombin-like (127 nanomoles pNA/(ml*min)), plasmin-like (194 nanomoles pNA/(ml*min)) activities and activator activity towards protein C (141 nanomoles pNA/(ml*min)). Activator activity towards protein C is significantly higher than that of A. oryzae (31.4 nanomoles pNA/(ml*min)), A. alliaceus (28.4 nanomoles pNA/(ml*min)) and A. nidulans (4.8 nanomoles pNA/(ml*min)).

Conclusion
Thus, A. sclerotiorum may be very promising producer of hemostatic-active proteolytic enzymes for therapy and diagnostic area. Preparations of fibrinolytic enzymes obtained using A. sclerotiorum will expand the range of existing drugs and reduce their average cost.
The influence of extracellular pH on the arterial contractile responses in early postnatal ontogenesis

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Introduction
Extracellular acidosis can accompany many cardiovascular disorders. It was shown to attenuate the contraction of resistance arteries in adult organism. However, it is well-known that arterial smooth muscle undergoes structural and functional remodeling during early postnatal development, but the effects of extracellular acidosis on arterial contraction during early postnatal ontogenesis have not been studied yet. Thus, the aim of this study was to investigate the effects of low pH on arterial contractile responses in the early postnatal period.

Materials & Methods
Experiments were performed on endothelium-denuded saphenous arteries from 10- to 15-days-old and 2- to 3-month-old (adults) male Wistar rats. Isometric force was measured using a wire myograph system (DMT A/S, Denmark). We studied isometric contractions to α1-adrenoreceptor agonist methoxamine (concentration range 10-8-10-4 M) in solutions with different pH (7.4, 7.1, 6.8 and 6.5). mRNA contents of NHE1 and NBCn1 transporters (regulate intracellular pH) were measured by qPCR.

Results
The solution with pH 7.1 did not change arterial contractile responses in both age groups. Solutions with pH 6.8 and 6.5 reduced contractile responses in adult (by 23,5±3,9% and 33,4±4,4%, respectively) and in 10- to 15-day-old rats (41,3±6,2% and 49,9±6,6%, respectively). Importantly, the low pH-induced reductions of contractile responses were more prominent in 10- to 15-days-old compared to adult rats. The mRNA expression level of NHE1 was higher in 10-to 15-day-old rats compared to adults, while NBCn1 mRNA was more abundant in adult animals.

Conclusion
Our data indicate that extracellular acidosis stronger affects α1-adrenergic arterial contractile responses in the early postnatal period compared to adults. This is associated with a higher mRNA expression level of NHE1 transporter in arteries of younger animals. Supported by the RFBR (grant N 18-015-00216-a).
The effect of rheological properties of extracellular matrix derived hydrogels on 3D vascularization

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Introduction
Tissue engineering is an interdisciplinary research field which combines knowledge of biology, physics and chemistry to in vitro create replacements for damaged tissues or organs. Because it uses autologous cells and natural polymers such as extracellular matrix derived hydrogels, in the future these tissue-engineered constructs could overcome the disadvantages associated with transplantation medicine, such as donor shortage and immunosuppressants dependency. However, a major limitation is that constructs often lack a vascular network to support the oxygen and nutrient supply to the tissues. Cell proliferation, differentiation and subsequent vascularization are influenced by many parameters, including the scaffold material. The aim of this project is to investigate the influence of the rheological properties of extracellular matrix derived hydrogels on vascularization. Vice versa, the influence that cell proliferation and matrix deposition has on the rheological properties of the hydrogel will also be examined.

Materials & Methods
Gelatin methacryloyl (GelMA) and decellularized porcine muscle tissue is used as the base for hydrogels of multiple compositions. Hydrogels are prepared by both casting and 3D printing with embedded adipose derived stem cells (ASCs) and human pulmonary microvascular endothelial cells (HPMECs) for cell culture. Rheological properties such as stiffness, stress relaxation and swelling are determined and compared between gels. Vascularization is imaged to determine the optimal composition of hydrogels for tissue engineering.

Results
Preliminary results show that the concentration of GelMA influences the swelling ratio, with a higher concentration of GelMA resulting in a lower swelling ratio. Different crosslinking photoinitiators also affect swelling with preliminary results showing higher swelling ratios for ruthenium crosslinked gels compared to lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) crosslinked gels. Further experiments will show how this and other rheological properties influence cell behaviour.

Conclusion
Although results are still preliminary, changes in compositions of extracellular matrix derived hydrogels influence rheological properties. This could influence cellular behaviour and improve vascularization in tissue engineering. In our group progress is made to investigate this further on a molecular scale by looking at cellular signalling.
Optical coherence tomography angiography discerns preclinical diabetic retinopathy in eyes of patients with type 2 diabetes without clinical diabetic retinopathy

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Introduction
The most common early clinically visible manifestations of DR include microaneurysm formation and intraretinal hemorrhage. At present, the ophthalmoscopy and color fundus photography are still the gold standard for the diagnosis and staging of DR. However, the occurrence of microvascular damage is known to occur before findings of retinopathy become apparent on clinical examination or fundus photography. Although fluorescein angiography (FA) is an important modality in revealing capillary leakage and nonperfusion in patients with DM, it is rarely used and not suggested for eyes without visible retinopathy or mild DR.

The aim of this study was to investigate retinal microvascular differences between diabetic eyes with no signs of DR and normal controls using OCTA.

Materials & Methods
A total of 71 DM2 and 67 healthy control subjects were included. All subjects underwent OCTA examination (RTVue-XR Avanti; Optovue, Fremont, CA, USA). Average vessel density in superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris, parafoveal vessel density in SCP and DCP, FAZ area (mm2) in SCP, microaneurysms and capillary nonperfusion were taken into analysis.

Results
Parafoveal vessel density in both SCP and DCP decreased in the eyes without clinical DR compared to normal controls (p < 0.001). Diabetic patients with no signs of DR also had a significant reduction in average vessel density of SCP, DCP and choriocapillaris (p < 0.001, p < 0.001 and p = 0.006, respectively). No significant difference was found in FAZ area of SCP between DM2 eyes and healthy controls (p = 0.253). The average vessel density of SCP and DCP is not correlated with HbA1c or serum creatinine in DM2 patients. Microaneurysms seen in OCTA but not in fundus examination were found in 8 out of the 71 (11.3%) diabetic eyes, and capillary nonperfusion was noted in 18 of 71 diabetic eyes.

Conclusion
We demonstrated that OCTA can identify preclinical DR before the manifestation of clinically apparent retinopathy in diabetic eyes. DM2 patients without DR have SCP, DCP and choriocapillaris impairment. Our results suggested that OCTA might be a promising tool for regular screening of diabetic eyes for DR.
Oral session 2
Cardiology II

Chair
Herman H.W. Sillje MD PhD

Presenters
Anpalagan, T.A (Tharani)
Chou, A.C. (Andre)
Dyrbuś, M.D (Maciej)
Jonatan, M. (Michael)
Liu, M L (Man)
vан der Linden, T. (Thijs)
Differences in Cardiac Rehabilitation Outcomes Between Complete and Incomplete Revascularization in post-PCI patients with multivessel coronary artery disease

Anpalagan, T.A (Tharani)1, Hartley, T.H (Tim)2, Suskin, N.S (Neville) Dr.3

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3 Western University, Epidemiology and Biostatistics, London, Canada

Introduction

Patients presenting with myocardial infarction (MI) may have multivessel disease. Ongoing studies are evaluating the benefits of multivessel complete revascularization with percutaneous coronary intervention (multiPCI) versus culprit only PCI (culpritPCI). Cardiac rehabilitation (CRSP) is recommended for all patients following myocardial infarction (MI). Systematic use of CRSP, to optimize medication, diet and exercise in patients post MI and PCI, may mitigate the difference in outcomes between multiPCI and culpritPCI patients with multivessel CAD. We evaluated the outcomes of multiPCI vs. culpritPCI in patients with multivessel CAD post MI following participation in CRSP.

Materials & Methods

Provincially mandated prospectively collected MI-PCI data from 2009-2017 at a single tertiary care centre in Southwestern Ontario were coded for multivessel CAD, multiPCI and culpritPCI (n=790). This data was linked with prospectively collected CRSP electronic patient records at the same centre. Patients common to both data sets were used for this study (n=80). The primary outcome selected for CRSP was the change in exercise performance (METs) derived from treadmill performance at entry and exit from the 6-month CRSP program, in accordance with national quality indicators. Secondary outcomes included blood glucose control, cholesterol, mood and anxiety.

Results

52 patients received MultiPCI while 28 had CulpritPCI. MultiPCI patients were younger (61±11y vs. 67±11y); and had a lower incidence of comorbidities (diabetes and HTN). MultiPCI was associated with improved treadmill performance from intake to exit (8.1±3.4METs vs. 9.9±3.6METs; p<0.05) while CulpritPCI was not (7.3±4.5METs vs. 9.0±5.6METs; p=ns). MultiPCI was associated with a significant improvement in total cholesterol (4.0±1.2mmol/L vs. 3.5±0.8mmol/L; p<0.05) while CulpritPCI was not (3.5±0.8mmol/L vs. 3.7±0.9mmol/L; p=ns). Anxiety and depression scores (HADS) decreased in MultiPCI patients but not in CulpritPCI patients. As well, MultiPCI was associated with significant improvements of Health Related Quality of Life.

Conclusion

In a retrospective review of post MI MultiPCI and CulpritPCI patients completing CRSP, only a minority of patients completed CRSP, the MultiPCI cohort had a significant improvement in treadmill performance vs. CulpritPCI. The preponderance of improvements in secondary outcomes, including total cholesterol, anxiety, depression and HRQoL, favoured the MultiPCI group. Further studies may evaluate the long term differences between the two cohorts.
New triple agent protocol for sternal closure decreased surgical site infections in cardiac surgery: A single centre experience

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Introduction
Deep sternal wound infections (DSWIs) are a type of surgical site infection (SSI) experienced in cardiac surgery. Despite their rare occurrence, DSWIs present a major complication. Mortality, length of hospital stay and costs are greatly increased thus DSWI prevention with antibiotic prophylaxis is widely used as a part of prevention protocol. Our previous protocol included bone wax as the haemostatic agent to prevent sternal bleeding. However, when compared to the literature, consistently unsatisfactory rates of DSWIs experienced in our department lead to the cessation of bone wax use and the implementation of a new protocol in 2017. Our study aimed to compare DSWI occurrence in patients subjected to vancomycin paste, gentamicin collagen sponge and oxidised cellulose with retrospective data based on bone wax use, with a focus on the effectiveness of the new protocol.

Materials & Methods
Retrospective data from 2009 to 2016 on patients who underwent cardiac surgery with the old protocol were compiled and compared with patient data subjected to the new protocol in 2017. Statistical analysis include Fisher’s exact test, performed with the R environment.

Results
Of the 6104 patients who were subjected to the old protocol, 154 (2.52%) suffered a DSWI. With the new protocol in 2017, only 7 incidences of DSWIs were reported out of 673 patients (1.04%). Fisher’s exact test showed statistical significance (P < 0.0154) and an odds ratio of 2.5 indicated the odds of suffering a DSWI to be 2.5 times smaller with the new protocol than with the old (95% CI: 1.16-6.25).

Conclusion
Perioperative use of vancomycin paste, gentamicin collagen sponge and oxidised cellulose significantly decreased DSWIs compared with the old protocol based on bone wax.
Post mortem pro life - should we analyse cardiac implantable electronic devices after death?

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Introduction
Post-mortem interrogation of cardiovascular implantable electronic device (CIED) implantation is not regularly practised. Studies conducted to date suggest that it provides additional data about the mechanism of the patient’s death and possible device malfunctions contributing to the death of the patient.

Materials & Methods
Between 24 August 2008 and 30 August 2018, consecutive subjects with an implanted CIED underwent either autopsy during which the CIED was removed and later interrogated by the qualified electrophysiologist or just had the device removed and interrogated. Baseline characteristics at the time of device implantation and at the time of death were collected from the patient’s records. The CIED interrogation results were then correlated with the final autopsy report and the clinical characteristics.

Results
Out of 1200 autopsies, 61 subjects with CIED had their device removed and stored. The devices consisted of 13 (21.3%) pacemakers (PM), 24 (39.3%) implantable cardioverter-defibrillators (ICD) and 24 (39.3%) cardiac resynchronisation therapy-defibrillators (CRT-D). Baseline characteristics from the time of implantation were available in 53 (86.7%) patients. Full autopsy was performed in 52 cases (85.2%). Three subjects (4.9%) died of asystole (2 PPMs and 1 ICD) and 4 (6.6%) patients died of pulseless electrical activity (1 with PPM, 1 with ICD and 2 with CRT-D). Ventricular tachyarrhythmias during the final 48 hours occurred in 17 (27.8%) patients, however, the vast majority was successfully terminated by the devices not being the terminal rhythms. There were seven (11.5%) patients who experienced electric storm (ES) in their final 48 hours. In three cases, the devices delivered only successful adequate shock therapies, and in four other cases, the devices required in average 3±2 unsuccessful shocks to finally terminate the ES. The average remaining battery longevity at the moment of interrogation was 5.1 years and in three devices (4.9%) an elective replacement indicator (ERI) was detected. Nevertheless, despite ERI, all those patients died of non-device related causes. Device concerns were presumed in 5 cases including 2 programming and 3 hardware issues.

Conclusion
Thanks to the addition of device interrogation we have found five CIED malfunctions potentially associated with death, which would not have been discovered in the routine clinical practice.
Red Blood Cell Distribution Width as A Novel Biomarker Predictor for Clinical Outcomes and Mortality Risk Among Patients with Coronary Artery Diseases: A Systematic Review and Meta-Analysis

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Introduction
Red blood cell distribution width (RDW) is a simple and cheap examination that usually overlooked. Recent studies have shown that RDW might reflect pathophysiological changes in human health. This study is aimed to evaluate the association between RDW and clinical outcomes among patients with coronary artery diseases (CAD).

Materials & Methods
We reviewed PubMed, Embase, and ScienceDirect literatures from 1946 to 2018 under the MeSH: “RDW”, “Mortality”, and “Clinical Outcomes”, with limitations on English published article only. The eligibility criteria were cohort observational studies and studies reporting clinical quantitative outcomes in association with RDW. Statistical analysis was conducted in accordance with PRISMA-MOOSE guideline and quality checklist and was computed using RevMan 5.3.

Results
Twenty-one studies (12 prospective and 9 retrospectives studies) consists of 26,226 patients were reviewed. Comparison of low RDW vs high RDW value was conducted. High RDW value was associated with higher age (p &lt;0.0001 to 0.067) and longer hospital stay (p 0.003 to 0.7). Low RDW represents a smaller number of impaired LVEF (EF&lt;40%) with risk ratio (RR) 0.8 (95% CI, 0.66-0.98; p=0.03). Low RDW exhibits smaller events of heart failure, re-infarction and major cardiac adverse events (MACE) with pooled RR 0.55 (95% CI, 0.47-0.64; p&lt;0.0001); RR 0.65 (95% CI, 0.56-0.74; p&lt;0.0001); and RR 0.49 (95% CI, 0.43-0.57; p&lt;0.0001), respectively. In terms of mortality, low RDW also indicates a smaller mortality rate than the high RDW group. The results for low RDW vs high RDW in in-hospital mortality, short term, and long term mortality were: pooled RR 0.46 (95% CI, 0.35-0.6; p&lt;0.0001); RR 0.27 (95% CI, 0.2-0.37; p&lt;0.0001); and RR 0.4 (95% CI, 0.36-0.45; p&lt;0.0001), respectively.

Conclusion
The meta-analysis indicates that low RDW (&lt;13-14) is associated with better prognostic and better clinical outcomes among patients with CAD. This result shows that RDW is an independent prognostic factor in CAD. A stratified risk assessment and future studies focusing on levels of recommended RDW in conjunctions with GRACE and TIMI score might provide breakthroughs in the cardiology field.
Nifedipin Ameliorates LTCC-/−H9c2 Cells H/R Injury via Regulating the Expression of Cyclooxygenase-2

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Introduction
It is evident that nifedipine can protect myocardium against Hypoxia/Reoxygenation(H/R) injury through blocking L-type calcium channel (LTCC). However, it has also been reported that nifedipine can also reduce H/R injury in a LTCC-independent way, which has been confirmed by our previous studies. How does nifedipine reduce H/R injury in addition to blocking LTCC? Cyclooxygenase-2 (COX-2), a key enzyme for the production of prostanoids, has been reported to be related to H/R injury. Whether or not nifedipine can regulate the expression of COX-2 to alleviate cardiomyocytes H/R injury in a LTCC-independent way?

Materials & Methods
LTCC-/−H9c2 cells were divided into: CON, H/R, H/R+DMSO, H/R+nifedipine, H/R+NS-398 (selective inhibitor of COX-2) group. COX-2 mRNA expression was detected by Quantitative PCR. COX-2 and cleaved caspase-3 protein expression were detected by Western Blot. Lactate dehydrogenase (LDH) leakage, malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were measured by relative kits. Apoptotic cells were measured by Annexin-V FITC/PI. Data were analyzed using one-way ANOVA followed by Newman–Keuls test.

Results
Compared with CON group, H/R group COX-2 mRNA and protein expression were up-regulated (p<0.05); H/R group LDH leakage, MDA content, cleaved caspase-3 protein expression and early apoptotic cells were increased (p<0.05) and SOD activity group was decreased (p<0.05).

Compared with H/R+DMSO group, H/R+NS-398 group LDH leakage, MDA content, cleaved-caspase3 protein expression and apoptotic cells were decreased (p<0.05) and SOD activity was increased (p<0.05).

Compared with H/R+DMSO group, H/R+nifedipine group COX-2 mRNA and protein expression was down-regulated (p<0.05) and LDH leakage, MDA content, cleaved-caspase3 protein expression was reduced (p<0.05).

Conclusion
Nifedipine can protect LTCC-/−H9c2 cells against H/R injury through regulating the expression of COX-2, which enriches the mechanism of protective role of nifedipine in cardiomyocytes H/R injury.
Determining aortic area and distensibility using deep learning on CMR images

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Introduction
The cross-sectional area of the aorta can accurately be determined on cardiovascular magnetic resonance (CMR) images. However, this is a time consuming process and prone to subjective bias, which is undesired, especially in large cohorts. The aim of this study was to investigate the use of deep learning for automated analysis of the aorta.

Materials & Methods
Aortic distensibility images of 21,137 subjects participating in the UK Biobank who underwent CMR assessment were included in this study. First, we developed a deep learning model on the Cosmosino platform (Groningen, the Netherlands) using an annotated training set of 2854 images. Next, aortic area (AA) and aortic distensibility (AD) was determined in a random sample of 200 subjects (54% male, mean age 63 ± 7.75 years). Mann-Whitney U test was used to compare AD between females and males. We validated the measurements derived from the deep learning model by comparing them to a group of manual measurements using post-processing software. Agreement between automated and manual measurements was evaluated using the dice similarity coefficient, the Pearson’s correlation coefficient and Bland-Altman analysis.

Results
Mean AD was 2.53 and 2.70, 10^-3 mmm Hg^-1 for females and males respectively (Mann-Whitney U test p=0.489). The deep learning model achieved a dice coefficient of 0.91. Correlation coefficient for manual versus automated derived AA was 0.86. Bias between automated and manual AA was 3.15 cm^2 (95% limits of agreement 1.10-5.19 cm^2).

Conclusion
Although we observed a consistent over-prediction by the deep learning model, high correlation with manually derived aortic measurements was achieved. Automated analysis of the aorta to derive area and distensibility measurements is promising for time-efficient and reproducible large scale measurements which can be used for individual risk prediction of cardiovascular disease.
Epidemiology

Chair
Marlou L. A. de Kroon MD PhD

Presenters
Cai, H.X (Haoxing)
Erpecum, CL van (Carel-Peter)
Schuch, G.A. (Guyonne)
Sibande, T. (Grace Thandekire)
Wang, C.Y.W. (Chenyang)
Xu, C (Cheng)
Elevated lead levels from e-waste exposure are linked to sensory integration difficulties in preschool children


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Introduction
Exposure to lead can have adverse effects on neurodevelopment. Sensory integration difficulties comprise a condition in which multi-sensory integration is not appropriately processed in response to environmental requirements. With approximately 30% of American children and 21%-28% of Taiwanese preschool children developing sensory integration disorders. The purpose of this research is to investigate the effect of lead exposure on child sensory integration.

Materials & Methods
A total of 574 children (3-6 years of age) from Guiyu (an e-waste recycling area, n = 358) and Haojiang (a non-e-waste recycling area, n = 216) were recruited. The Sensory Processing Measure (Hong Kong Chinese version, SPM-HKC) form was used to assess the sensory integration of children.

Results
The median blood lead level in Guiyu children was 4.88 μg/dL, higher than the 3.47 μg/dL blood lead level in Haojiang children (P < 0.001). The median concentration of serum cortisol in Guiyu children was significantly lower than in Haojiang, and was negatively correlated with blood lead levels. All subscale scores and the total score of the SPM-HKC in Guiyu children were higher than Haojiang children, indicating greater difficulties, especially for touch, body awareness, balance and motion, and total sensory systems. Sensory processing scores were positively correlated with blood lead, except for touch, which was negatively correlated with serum cortisol levels. Simultaneously, all subscale scores and the total SPM-HKC scores for children with high blood lead levels (blood lead > 5 μg/dL) were higher than those in the low blood lead level group (blood lead < 5 μg/dL), especially for hearing, touch, body awareness, balance and motion, and total sensory systems.

Conclusion
Our findings suggest that lead exposure in e-waste recycling areas may result in a decrease in serum cortisol levels and an increase in child sensory integration difficulties. Cortisol may be involved in touch-related sensory integration difficulties.
Obesogenic environments in the Netherlands: the cross-sectional association between neighbourhood fast-food outlet exposure and Body Mass Index among 137,361 adults of the Lifelines cohort study.

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Introduction
Overweight is a major risk factor for numerous non-communicable diseases, including cardiovascular diseases, cancer and diabetes type II. There is evidence that access to fast-food outlets is associated with overweight. However, this association has never been investigated in the Netherlands. This study aims to 1) investigate the association between neighbourhood fast-food outlet exposure and Body Mass Index (BMI) in the Dutch adult general population; and 2) examine whether this association is mediated by daily caloric intake.

Materials & Methods
In this cross-sectional study, data (N=137,361) of the Lifelines cohort study were used. Participants’ residential addresses were linked to LISA register data containing fast-food outlet locations. Independent variables reflecting fast-food outlet exposure included: proximity, and 500-meter, 1-kilometer and 3-kilometer density. Multilevel analysis was conducted to examine the association between fast food outlets with BMI. Analyses were adjusted for age, sex, educational level and employment status (model 1) and additionally for neighbourhood SES and urban level (model 2).

Results
Mean BMI of participants was 26.2 kg/m2 (SD 4.3; 56.3% was overweight with BMI ≥ 25.0). Fast-food proximity was inversely associated with BMI in model 2: compared with people living less than 500 m from a fast-food outlet, those living between 1,000 and 2,000 m away had a 0.13 (95% CI: 0.24, 0.03) kg/m2 lower Body Mass Index. Only up to model 1, high (compared to low) exposure to fast-food outlets was associated with BMI within densities of 500 meters (ES 0.17, 95% CI: 0.07, 0.26), 1 kilometer (ES 0.18, 95% CI: 0.06, 0.30) and 3 kilometers (ES -0.23, 95% CI: -0.11, -0.35).

Conclusion
This study demonstrates independent associations between nearby fast-food outlet exposure and Body Mass Index in the Dutch adult general population. Longitudinal and quasi-experimental study designs are needed to verify these findings. Policy-makers should consider tackling obesogenic environments in order to reduce overweight.
Challenging Patient Recruitment: Factors Related to Intrinsic Motivation of General Practitioners for Scientific Research Influencing Recruitment Success of Incidence Cases for Primary Care Based Trials.

Schuch, G.A. (Guyonne):

Introduction
Many primary care-based trials experience recruitment difficulties, especially concerning incident cases. This leads to underpowered studies, prolongation of inclusion periods, and prematurely ended trials, which is a waste of resources. In literature, explaining factors and improvement strategies are still inadequate, since inclusion problems persist. In general, intrinsic motivation is a moderate to strong predictor of performance. Therefore, intrinsic motivation might be of influence on inclusion success.

Aim: To investigate whether intrinsic motivation of the recruiting GP influences recruitment success of incident cases in primary care-based research.

Materials & Methods
A cross-sectional survey aimed at GPs that had been recruiting for PIM-POM (UMCU), PRICE (UMCU), RAPIDA (MUMC) or URinControl (UMCG). The questionnaire consisted of proxies measuring intrinsic motivation and the validated short-version Utrecht Work Engagement Scale (UWES-9) for both the recruiter and GP job. ≥3 inclusions per GP was considered successful. Logistic regression analysis was used to identify predictors.

Results
256 GPs were invited to fill out the questionnaire. 113 complete responses were received (44% response rate). A positive relationship with inclusion success was shown for interest in the research topic (OR 2.0, 95% CI [1.2 – 3.4]), returning the questionnaire (OR 2.4, 95% CI [1.4 – 4.0]), assistant involvement (OR 1.7, 95% CI [1.0 – 2.8]), subjective inclusion success (OR 2.4, 95% CI [1.5 – 3.9]), 6-10 expected inclusions (OR 7.2, 95% CI [2.2 – 23.4]), and >10 expected inclusions (OR 12.6, 95% CI [2.8 – 56.1]) compared to 0-5 expected inclusions. A negative relationship with inclusion success was shown for the factor ‘considering one could have included more patients’ (OR 0.6, 95% CI [0.4 – 0.9]).

Conclusion
Intrinsic motivation for scientific research of recruiting GPs might be of importance in successful patient recruitment. UWES-9 scores for both the recruiter and GP job could not predict inclusion success, however.
Introduction
Antimicrobial resistance (AMR) is a major concern in health care worldwide. In Malawi rates of AMR, in particular extended spectrum beta-lactamase rapidly increased between 2003-2016. Antibiotic guidelines are a key component of antimicrobial stewardship. As part of stewardship, Queen Elizabeth Central Hospital in Blantyre, Malawi developed an antibiotic guideline in form of a smart phone application in June 2016. We conducted a study to assess clinicians’ adherence to the antibiotic guideline on the adult medical wards.

Materials & Methods
A cross-sectional audit study was carried out. 230 case files of adult patients were audited against the antibiotic guideline. Adherence to the guideline in terms of indication for antibiotic, choice of antibiotic and antibiotic review time were reviewed. Analysis was done using SPSS and presented with descriptive statistics.

Results
Median age of patients was 40 years and 111(43%) were males. Average length of hospital stay was 2 days. 194(84.3%) of the antibiotic prescriptions were adherent to the local antibiotic guideline, 28(12.2%) non-adherent and 8(3.5%) had no clear indication why they were prescribed antibiotics. The main indication for antibiotic prescriptions was documented in 89(38.7%) of case files and the most common indication was Pneumonia. 191(76.1%) of prescriptions were for Ceftriaxone. There was no evidence of utilising blood culture to guide therapy as only 81(35.2%) had culture taken before antibiotic initiation. 175(76.1%) of files had their antibiotics reviewed within 48 hours.

Conclusion
The study showed there is still need to work on rational prescribing of antibiotics as ceftriaxone was potentially overused during this study period. Interventions should be implemented quickly to reduce the impact of antibiotic resistance and to improve individual patient care.
Impaired lipid metabolism associated with high PM2.5-bound PAH levels on children from an e-waste area

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Introduction
Epidemiological studies link airborne organic contaminants or release from electronic waste (e-waste), including polycyclic aromatic hydrocarbons (PAHs), to adverse effects of immune inflammation and physical growth. Data on PM2.5-bound PAHs and children urinary hydroxylated PAHs (OH-PAHs) are lacking for e-waste area. Lipid metabolism disorder has been suggested as one of the underlying mechanisms of PAH-induced obesity. We aimed to examine the effects of exposure to PM2.5-bound PAHs and urinary OH-PAHs on inflammation and lipid metabolism disorder in preschool children.

Materials & Methods
The study population consisted of 217 preschool children from Guiyu (n =110) and Haojiang (n =107). We collected PM2.5 samples and measured their sixteen PAH components, we also measured ten urinary OH-PAHs, and serum stromal cell-derived factor 1 alpha (SDF-1α) and fatty acid synthase (FASN) levels, from October 2017 to July 2018 in Guangdong, China. Linear regression analysis was performed to estimate the effects of PAHs on lipid metabolism disorder, and a generalized linear model was used to estimate the effects of PAHs on the risk of childhood overweight or obesity.

Results
We found a statistically significant increase in the PM2.5-bound PAH, urinary OH-PAH and serum SDF-1α levels (all P < 0.001), decrease in serum FASN levels (P < 0.05) in Guiyu compared to Haojiang children. PM2.5-bound PAHs were synergistically correlated with urinary OH-PAH and serum SDF-1α levels and negatively correlated with serum FASN levels. Urinary OH-PAH levels also showed a positive association with serum SDF-1α levels, negative association with serum FASN levels, which was statistically significant in the generalized linear model (P < 0.05). Urinary OH-PAH levels had positive associations with the proportion of obese or overweight children.

Conclusion
PAHs exposure both in vivo and in vitro is serious in e-waste areas, which may increase the risk of childhood obesity.
Reduced serum NPY in relation to adverse emotion in preschool children with e-waste lead exposure

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Introduction
Lead (Pb) poisoning can affect the developing brain of young children, and lead to central nervous system dysfunction, as in the case of behavioral problems and emotional disorders. Neuropeptide Y (NPY) plays a very important role in emotion-related brain circuitry. Therefore, we evaluated the relationship between Pb and emotional difficulties through NPY in children from an e-waste recycling area, China.

Materials & Methods
We recruited 213 preschool children, 3- to 7-years of age, among whom 112 children were from Guiyu (exposed area) and 101 from Haojiang (reference area). The emotional health of children was assessed using the ‘emotional symptoms’ subscale of the Strengths and Difficulties Questionnaire. We measured blood Pb level (BPb) and serum NPY level. Statistical analyses were performed by using SPSS 22.0.

Results
Approximately 48.2 % of Guiyu children were categorized in the ‘at risk’ group for emotional difficulties, in contrast to 13.9 % for the Haojiang. BPb of Guiyu children was higher than Haojiang children (p < 0.001). The median serum NPY in Guiyu children was lower than in Haojiang children and was negatively correlated with BPb (rs = -0.25). In addition, emotional symptom scores positively correlated with BPb and whether left-behind child, and were negatively associated with serum NPY levels and maternal education levels. Emotional symptom scores on children in the high BPb group (BPb ≥ 5.00 µg/dL) were higher than those in the low group (BPb < 5.00 µg/dL), suggesting that Pb exposure increases the risk of emotional difficulties in children. After adjusting for confounding factors, children with lower NPY levels were at higher risk of having emotional difficulties.

Conclusion
Our results indicate that Pb exposure in e-waste recycling areas could lead to a decrease in serum NPY concentration and an increase in the risk to child emotional health. In addition, NPY might be involved in emotional difficulties.
Gastrointestinal Medicine

Chair
Aad P. van den Berg MD PhD

Presenters
Cupitra-Vergara, N.I. (Nelson Ivan)
Gowani, SG (Shahnoor)
Li, C.W.L (Chenwen)
Ullah, S. (Saif)
Verkade, E. (Esther)
Wijaya, WW (Wynne)
Differences in vascular function of arteries of colon tumors vs healthy arteries in humans: role of diverse agonists and their receptors

Cupitra-Vergara, N.I. (Nelson Ivan) BSc.; León, J. (Jimmy) MD; Calderon, J.C. (Juan Camilo) MD, PhD.; Narvaez-Sanchez, R. (Raul) MD, MSc. PhD.

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Introduction
Cancer is a public health problem that can be treated modifying its vasculature. Generating knowledge about differences in vascular function of tumoral arteries compared with extratumoral and healthy arteries will improve our understanding of structural and functional changes of the vasculature induced by the tumor. Multiple agonists are involved.

Materials & Methods
Colonic arterial segments were taken from the edge of macroscopically identifiable tumor tissue, from 24 cancer (67±5years) and 10 no cancer (53±6years) patients. Arteries were analyzed histologically to measure intima and media thickness. Arteries were mounted in an organ bath to measure vascular reactivity (VR) in response to KCl (n=7patients,3controls), phenylephrine (PE; n=7,4), U46619 (thromboxane-A2 analog;n=9,4), endothelin-1 (ET-1;n=8,4), carbachol (CCH;4,2), vascular endothelial growth factor (VEGF;n=3,2) or bradykinin (n=8,4). By Western blot and RTqPCR, protein and gene expression of ET-1, VEGF, COX-2, ECE-1 and HIF-1A were measured. Differences among tumoral (TU), extratumoral (ET, surrounding the tumor but not irrigating it) and non-tumoral (NT, from patients colectomized by non-tumoral causes) arteries were determined by ANOVA, being p<0.05 significant.

Results
Histology: intimal hyperplasia in TU (155±24µm) versus NT (13±3µm,p=0.04). VR: Increased sensitivity to PE in TU (pD2:6.1±0.2) and ET (6.09±0.4) vs NT (5.7±0.1;p=0.001), to U-46619 in TU (pD2:7.4±0.2) and ET (7.4±0.11) vs NT (7.8±0.03;p=0.01), and to CCH between TU (pD2:6.2±0.23) and ET (5.8±0.18) vs NT (6.7±0.15; p=0.04). Gene expression: The preliminary results show an increase of ECE-1 expression in TU (1.55 arbitrary units-AU) and decrease in ET (0.056AU) compared with NT (1AU) and decrease of VEGF expression in TU (0.74AU) and increase in ET (2.31AU) compared with NT (1AU).

Conclusion
Colon cancer induces hyperplasia of the intima, which is not attributable to radiotherapy, since none of our patients received that kind of treatment. As well, induces functional changes in the arteries that irrigate it, favoring the response to FE and U-46619 and decreasing the response to CCH, possibly due to endothelial dysfunction, evident using nitric oxide blockers (results will be shown in the meeting). Preliminary results in gene expression suggest that increase in the signaling (and perhaps in the production) of ET-1 in the endothelium of TU arteries. Our results agreed with those of Ferrero, 2008, although differ from those of Voss, 2019.
Comparative Evaluation Of Efficacy of Omeprazole versus Lansoprazole for Relief of Functional Dyspepsia: A Systematic Review

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Introduction
Functional dyspepsia (FD) is defined as a condition chronically presenting symptoms centered in the upper abdomen, such as epigastric pain or discomfort, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. Proton pump inhibitors are main line agents to treat functional Dyspepsia. Omeprazole is conventional PPI and Lansoprazole is a new PPI both are said to be effective option to treat functional dyspepsia in individual trials.

Materials & Methods
All randomised control trials which follows PRISMA guidelines 2009 and in which Omeprazole and Lansoprazole were first compared with placebo for the treatment of functional dyspepsia. Clinical trial registries, MEDLINE, SCOPUS, EMBASE database were searched for MeSH terms Omeprazole, Pantoprazole, Placebo which resulted in the treatment of Functional Dyspepsia. Observational studies, Unpublished studies, RCTs not following PRISMA guidelines were excluded. Data was analyzed using RevMan version 5.3 and Odd’s Ratio was calculated to determine the difference in Early and late phases. Both Fixed and Random effect model was utilized to calculate the difference. To compare the difference between Omeprazole and Lansoprazole Fischer’s exact test was used. P value less than 0.05 was considered as statistically significant. The I2 will be used to measure the heterogeneity between studies and a value &gt;30.0 will be considered to reflect heterogeneity.

Results
A total of 10 studies were included consisting of 3934 patients. Omeprazole was effective than placebo to treat functional dyspepsia(Odd’s ratio=1.603, CI=1.264 to 2.033, p value less than 0.01) Lansoprazole was also effective when compared to placebo to treat functional dyspepsia. (Odd’s ratio=0.748, CI=0.553 to 1.011, p=0.058). When Omeprazole was compared to lansoprazole indirectly statistically significant difference was seen (P=0.0001).

Conclusion
Both Omeprazole and Lansoprazole are effective to treat functional dyspepsia when compared to placebo. Omeprazole is more effective than Lansoprazole to treat functional dyspepsia.
Site-specific therapy of inflammatory bowel disease by regulating proinflammatory microenvironment and gut microbiota

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Introduction
The incidence and prevalence of inflammatory bowel disease (IBD) increases steadily worldwide, without effective therapeutics currently. Accelerated resolution of inflammation is a new strategy for the management of IBD. For effective and safe IBD treatment, herein we aimed to develop a smart nanotherapy capable of selectively releasing a proresolving peptide Ac2-26 and simultaneously normalizing proinflammatory microenvironment and dysbiosis of gut microbiota, in response to high reactive oxygen species (ROS) at diseased sites.

Materials & Methods
In vivo efficacy of orally administered Ac2-26 was first examined in mice with dextran sulfate sodium (DSS)-induced colitis. Due to the negative result, Ac2-26 was packaged into nanoparticles derived from a ROS-responsive and biocompatible material OxbCD to obtain a nanotherapy AON. ROS-triggerable release profiles under intestinal conditions were demonstrated, while stability of Ac2-26 in AON was examined in simulated gastrointestinal fluids. We then investigated oral targeting capability of AON in colitis mice. Therapeutic effects of AON were studied in mice with acute or chronic colitis. Furthermore, in vitro and in vivo experiments were performed to explore anti-colitis mechanisms of AON. In vivo safety of AON was preliminarily evaluated.

Results
Oral administration of free Ac2-26 showed no therapeutic benefits in colitis mice, due to its instability in the gastrointestinal tract. AON effectively protected Ac2-26 from degradation. By targeting delivery of this nanotherapy to the inflamed colons of colitis mice, ROS-responsive release and site-specific accumulation of Ac2-26 at the inflammatory sites were achieved. Mechanistically, AON significantly decreased the expression of proinflammatory mediators, attenuated infiltration of inflammatory cells, promoted efferocytosis of apoptotic neutrophils, and increased phenotypic switching of macrophages. Therapeutically, AON reduced inflammation symptoms, accelerated intestinal mucosal wound healing, reshaped the gut microbiota composition, and increased short-chain fatty acid production. Moreover, oral delivery of AON showed excellent safety profile in mice.

Conclusion
Simultaneous regulation of proinflammatory microenvironment and gut microbiota is an effective approach for IBD treatment. AON can be further developed as a targeted precision nanotherapy for IBD and other inflammatory diseases.
Endoscopic retrograde appendicography: an effective diagnostic method for acute appendicitis

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Introduction
Appendicography had been used for the diagnosis of chronic appendicitis. But, to our knowledge, there is no study about endoscopic retrograde appendicography (ERA) for the diagnosis of acute appendicitis (AA). This retrospective study was designed to describe the ERA features of appendicitis and the viability for diagnosis of AA.

Materials & Methods
Thirty-three patients (20 men and 13 women, average age 44±18.5) with suspected acute appendicitis were enrolled and endoscopic retrograde appendicography findings and complication were analyzed retrospectively.

Results
Twenty-three patients (70%) were definitely diagnosed with AA through ERA. Twenty-one patients became asymptomatic after endoscopic therapy and follow up (median 12 months; 2 months to 46 months) confirmed complete recovery in 19 patients. Appendectomy and histological results also confirmed AA in 4 patients for unrelieved or recurrent pain. Accordingly, the diagnostic accuracy of ERA was 100%. Interestingly, of the 23 patients, the diagnosis of ultrasonography (US) and CT scan was negative or equivocal in 7 patients (false negative rate: 31% and 3%) and 4 patients was misdiagnosed as AA by US and CT scan (false positive: 57% and 33%). In 23 patients with AA, colonoscopic findings showed mucosal hyperemia and edema of appendiceal orifice (83%), pus outpouring from appendiceal orifice (70%) and swollen surrounding mucosa in cecum (61%). Appendicographic findings included diffuse dilation (Diameter: 0.8±0.4mm), partial stenosis (43%), inflexibility (87%) and filling defect sign (22%). During follow-up, there were no long-term complications in all of the patients during or after the ERA.

Conclusion
Endoscopic retrograde appendicography is a reliable and useful method for visualization of appendiceal lumen which provide an alternative diagnostic method for acute appendicitis. However, a prospective controlled study need to be performed subsequently.
Effects of A Humanized Bile Acid Pool Induced by Deletion of Cyp2c70 on Pharmacological FXR Activation in Mice


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Introduction
Bile acids (BAs) facilitate fat absorption but also modulate various metabolic pathways through activation of the BA receptors FXR and TGR5, which have been identified as targets for therapeutic interventions. However, fundamental differences in BA metabolism between humans and mice complicates translation of preclinical data. CYP2C70 was recently proposed to catalyze the formation of rodent-specific muricholic acids (MCAs). We generated mouse models of Cyp2c70-deficiency, to clarify its role in BA metabolism in vivo and to evaluate whether humanization of the murine bile acid pool modulates the effects of pharmacological FXR activation.

Materials & Methods
Two different mouse models of Cyp2c70-deficiency were generated, an acute hepatic knock-out model, in which the Cyp2c70 gene was ablated in adult mouse livers by CRISPR/Cas9-mediated somatic genome editing employing adenovirus-mediated delivery of single-guide RNA to Cas9-transgenic mice (Cyp2c70 acute knock-out, Cyp2c70ako), as well as a full-body Cyp2c70 knock-out model.

Results
Hepatic CYP2C70 protein levels were reduced by ~95% in Cyp2c70ako mice. This translated into strongly increased contributions of chenodeoxycholic (CDCA) and ursodeoxycholic (UDCA) acids and a concomitantly reduced contribution of mouse-specific β-MCA, resulting in a more hydrophobic BA pool (p&lt;0.001). Evaluation of in vivo CDCA and UDCA metabolism using D4-labeled tracers revealed 6β-hydroxylase as well as C7-epimerase activity of CYP2C70, delineating its importance in generating the characteristic murine BA pool. The reduction of fractional cholesterol absorption in control mice upon FXR activation with PX20606 (54% to 20%, p&lt;0.001) was blunted in Cyp2c70ako mice (47% to 34%, p&lt;0.01). Additionally, augmented fecal cholesterol disposal in response to FXR activation was impaired in Cyp2c70ako mice (p&lt;0.05), predominantly due to reduced stimulation of transintestinal cholesterol excretion (TICE).

Full-body Cyp2c70-KO mice were completely devoid of MCAs, indicating that CYP2C70 is the only enzyme responsible for MCA production in mice. In contrast to acute ablation of Cyp2c70, lifelong exposure to the more hydrophobic bile acid pool induced moderate cholangiocyte proliferation.

Conclusion
Deletion of Cyp2c70 in mice translates into a human-like BA pool composition and impacts the response to pharmacological FXR activation, thereby emphasizing the importance to carefully consider the consequences of species-specific (BA) metabolism in pre-clinical studies.
Neutrophil-to-Lymphocyte Ratio as a Predictor of Ascites Formation in Patients with Hepatic Cirrhosis

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Introduction

Hepatic cirrhosis is one of the diseases with the highest morbidity and mortality. Ascites is the most common complication in cirrhosis and has quite a high mortality rate. Therefore, laboratory markers are required to determine the prognosis in cirrhotic patients, especially the formation of ascites. Systemic inflammation plays an important role in the pathophysiology of hepatic cirrhosis and is a result of portal hypertension together with ascites. Neutrophil-to-lymphocyte ratio (NLR) is one of the inflammation markers often used to predict the outcome in cancer, heart disease, and cirrhosis. Thus, NLR may be used to predict the development of complication such as ascites in cirrhotic patients.

Materials & Methods

Patients are selected based on inclusion and exclusion criteria. Neutrophil-to-lymphocyte ratio is acquired from laboratory examination of patients’s blood sample. Ascites is diagnosed by ultrasonography. Difference in mean NLR in ascitic patients and non-ascitic patients is tested using two-sample independent t-test or Mann-Whitney test according to data distribution. With significant difference, chi square test or Fisher exact test will be conducted. Cut-off value for NLR will be obtained by conducting ROC analysis. Results are statistically significant if p value<0.05.

Results

There are 61 subjects (39 male and 22 female) with the mean age of 54.56 years old, 31 patients with ascites and 30 patients without ascites. Significant difference in NLR mean were found with the values of 2.72 in patients with ascites and 3.53 in those without (p=0.022). Based on ROC curve analysis, the cut-off value is 2.70 with AUC 0.660 (p=0.032) and then chi square test with 2x2 table is conducted and the odds ratio is found to be 4.354 (95% CI: 1.471-12.885) with p=0.006.

Conclusion

A statistically significant difference was found between NLR mean values and the presence of ascites in cirrhotic with the NLR mean value lower in patients with ascites. NLR<2.70 in cirrhotic patients can be used to predict the presence of ascites.
Gynaecology and Paediatrics

Chair
Prof Paul P. van den Berg MD PhD

Presenters
Aslancan, R. (Reyhan)
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EFFECT OF INTRAVENOUS LIPID (SMOFLIPID®) USE ALONG IN VITRO FERTILIZATION (IVF) TREATMENT IN WOMEN WITH FAILED IVF CYCLES DESPITE GOOD QUALITY EMBRYO TRANSFER

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Introduction
Repeated IVF failure despite successful embryo transfer is a discouraging fact for couples and doctors. In order to defeat this situation, some different techniques such as intravenous lipid supplementation are used in IVF cycles. The aim of this study is to investigate the effect of intravenous lipid use on clinical pregnancy and live birth rate.

Materials & Methods
In this two years retrospective cohort study, 222 women with at least two cycles of IVF failed despite good quality embryo transfer were included. Among these women, 106 of them received intravenous lipid (SMOFlipid®) in addition to antagonist IVF protocol (intravenous lipid group), while 116 of them did not receive any supplementation and underwent antagonist IVF protocol (control group). Intravenous lipid was given on the day of embryo transfer, on the day of positive pregnancy test and after the positive test it was given weekly until the tenth week. Past pregnancy history of two groups were similar. Statistically significant p value was defined as lower than 0.05.

Results
Rate of positive pregnancy test was 50.9% in intravenous lipid group while it was 22.4% in the control group (p<0.05). 41.5% of women in intravenous lipid group had clinical pregnancy while the rate was 19.8% in the control group (p<0.05). Live birth rate was 29.2% in intravenous lipid group and 10.3% in the control group (p<0.05). Chemical pregnancy rate was 9.4% in intravenous lipid group and 2.5% in the control group (p<0.05). The rate of spontaneous abortion was similar between two groups (p>0.05).

Conclusion
Addition of intravenous lipid supplementation may overcome negative IVF outcomes and increase clinical pregnancy rates. Further studies might help the scientists to investigate the efficiency of intravenous lipid.
The Relationship between Anemia and Postpartum Depression: A Systematic Review and Meta-Analysis

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Introduction

The relationship between anemia and postpartum depression (PPD) has been reported to be controversial in different studies. Therefore, this study aims to provide a comprehensive assessment of anemia and PPD.

Materials & Methods

This review study was conducted on the basis of the PRISMA Guidelines. We searched epidemiologic studies conducted until January 2018 without time limit in nine English databases including Scopus, PubMed/Medline, Science Direct, Embase, Web of Science (ISI), CINAHL, Cochrane Library, EBSCO and Google Scholar search engine using English MeSH keywords: Anemia, Anaemia, Hemoglobin, Ferritin, Pregnancy, Pregnant Woman, Prenatal Care, Complications of Pregnancy, Depression, Postpartum Depression, Mental Disorders, and Mental Health. A combination of words was used with functions “AND” and “OR”. Inclusion criteria according to PICO (related to Evidence-Based Medicine). Exclusion criteria were: 1) sample size other than postpartum women; 2) sample size with a history of mental illness or use of antidepressants; 3) letters to the Editor without original data, review and case report and 4) duplicate studies. The modified Newcastle Ottawa Scale (NOS) for non randomized studies was used to assess the quality of the studies. P-value and sample size were used for analyzing data and finally, the relative risk (RR) and 95% confidence interval (CI) were calculated for each of the studies. Considering the GRADE guidance, the heterogeneity of the studies was assessed using the Cochran’s Q test and I2 index. Data were analyzed using Comprehensive Meta-Analysis (CMA) Version 2.

Results

In 10 studied, PPD was significantly higher in anemic women than non-anemic women based on the random effects model (heterogeneity test: P<0.001, I2=74.62%), and RR = 1.887 (95%CI: 1.255-1.838, P=0.002). In 8 studies, anemia significantly increased the risk of postpartum depression (Heterogeneity test: P=0.116, I2=36.422%), RR=1.240 (1.001-1.536, P=0.048). Publication bias for postpartum anemia and anemia during pregnancy and PPD indicating that publication bias did not affect the results of the studies.

Conclusion

Meta-analysis results showed anemia during pregnancy and after pregnancy significantly increased the risk of postpartum depression. Therefore, prevention, identification and treatment of anemia in pregnant women seems necessary.
A more accurate predictive model for successful labour induction to replace the Bishop Score

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Introduction
The Bishop score was originally created to estimate the expected date of delivery, which is valuable in determining the optimum time for labour induction or C-section.(1) Today this score, which consists of the components cervical dilation, effacement, consistency, position, and station of the fetus, is used as a predictive model for labour induction success. A systematic review (2) determined that the Bishop score is inadequate for this purpose, resulting in unnecessary C-sections, including emergency C-sections, as well as labour and surgical complications. Our aim was to investigate if a model can be developed with a better predictive capacity.

Materials & Methods
A combined dataset of the HYPITAT I + II Trials and the DIGITAT trial was used, including women randomized for labour induction and excluding women who requested a C-section. A literature search was done to find variables which influence labour induction success; with these variables a series of logistic regressions were run using the database. The performances of both models were compared using an receiver operating characteristic (ROC) curve and a calibration plot.

Results
The binary logistic regression produced a model containing the following variables; maternal systolic blood pressure, parity status, abortion status, maternal age, cervical effacement, gestational age, ethnicity, cervical length and cervical dilatation. The ROC curve and calibration plots confirmed that our model has a higher predictive capacity; the area under the curve (AUC) of the Bishop score is 0.682, while the AUC of the new model is 0.721.

Conclusion
Our model has a higher predictive capacity than the Bishop Model, when applied to our study population of hypertensive women, and should give medical professionals a more accurate idea of whether labour induction will be successful. This could lead to fewer emergency C-sections, and their complications. This model still requires testing alongside the Bishop model in a clinical setting to compare these two models.
Prenatal exposure to polychlorinated biphenyls and their hydroxylated metabolites influences motor performance in adolescence negatively

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Introduction
Persistent organic pollutants (POPs), such as polychlorinated biphenyls and their hydroxylated metabolites (OH-PCBs), are environmental chemicals. There is evidence that PCBs and OH-PCBs are neurotoxic to the brain. Knowledge about the effects of background prenatal exposure to PCBs and OH-PCBs on motor performance on the age of 13 to 15 years is limited.

Materials & Methods
This study is part of the Development at Adolescence and Chemical Exposure (DACE)-study. Maternal pregnancy levels of 10 PCBs and 6 OH-PCBs were measured at the third trimester of pregnancy in this Dutch study. The developmental coordination disorder questionnaire (DCDQ) was used to assess the adolescent’s motor performance on an age of 13-15 years. Fine motor skills, coordination, control of movement and total motor performance were assessed. The questionnaire was filled in by a parent.

With the partial Spearman test we explored the correlations between PCB and OH-PCB levels and the DCDQ score in total and on the sub scores. The total score can range from 15 to 75. The higher the score the better the motor performance is.

Results
115 adolescents were included, 62 boys and 53 girls. The mean total score in the DCDQ was 64.7. Higher levels of 4-OH-PCB-172 were associated with lower DCDQ total scores (P=0.072; Rho=-0.303), as well as lower coordination scores (P=0.045; Rho=-0.336). 4-OH-PCB-187 was associated with lower scores on fine motor skills (P=0.058; Rho=-0.279) and coordination (P=0.056; Rho=-0.281). Higher levels of all OH-PCBs measured together were associated with lower scores on coordination (P=0.071; Rho=-0.304). Correlation coefficients between the other POPs and DCDQ scores were not significant.

Conclusion
Prenatal exposure to higher levels of 4-OH-PCB-146, 4-OH-PCB-172 and 4-OH-PCB-187 and the sum of the 6 OH-PCBs is negatively associated with motor performance in 13- to 15- year old children. Our study suggests that prenatal Dutch background exposure to several OH-PCBs can influence motor performance outcomes into adolescence.
Electronic cigarette aerosol: impact on embryonic lung morphology

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Introduction
Smoking is a major public health problem responsible for 700000 deaths/year in Europe. Conventional cigarettes (c-cig) exacerbates several health issues, such as chronic obstructive pulmonary disease, fibrosis and cancer. Tobacco use during pregnancy has serious consequences to infants, since they become more susceptible to develop congenital disorders, lung diseases and sudden death. Electronic cigarettes (e-cig) have emerged as an alternative to c-cig. Previous studies revealed that c-cig exposure impairs lung development, aggravates wheezing and triggers inflammation. However, nothing is known about the impact of e-cig aerosol during pulmonary development. Our aim was to evaluate the effect of e-cig aerosol and c-cig smoke in the early chick embryonic lung.

Materials & Methods
Ex vivo lung explants were cultured in smoke/aerosol medium or unexposed medium (control) for 48 hours. Explants were assessed morphometrically. Additionally, TNF-α levels were evaluated by ELISA. One-way ANOVA and post-hoc Fisher Least Significant Difference test (SPSS IBM 25.0) were used to determine the statistical differences between groups.

Results
When compared to controls (p<0.05, 95%CI), c-cig treated explants revealed a significant decrease, in all morphometric parameters, between 15 to 30%, while e-cig treated explants displayed a significant reduction only in lung total area and mesenchymal perimeter (roughly 10%). Lastly, c-cig explants presented a decrease in all morphometric parameters, between 11 to 26%, when compared to e-cig treated explants (p<0.05, 95%CI). Additionally, e-cig and c-cig treatment induced similar TNF-α release (p<0.001, 95%CI), that was nearly 7 times higher than control (p<0.001, 95%CI).

Conclusion
This study describes, for the first time, the impact of e-cigs on early lung development. The results revealed that e-cig aerosol impairs lung growth and promotes lung inflammation. However, its impact on early lung growth seems to be less detrimental than conventional cigarette smoke. Nevertheless, more studies are required to fully understand the effect of the aerosol in embryo development. The validation of these effects will eventually lead to the development of new tobacco control recommendations to pregnant women in order to protect the fetus and child’s health.
Smoking during pregnancy and developmental outcomes in childhood in the Longitudinal Preterm Outcome Project (LOLLIPOP) cohort

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Introduction
In the last decades, the introduction of many preventive interventions has led to a declining prevalence of smoking during pregnancy. However, the prevalence is still rather high in the Netherlands, where 8.6% of all pregnant women were reported to smoke at some point during the pregnancy, and 4.7% of all pregnant women were reported to smoke throughout pregnancy. Findings concerning the association between smoking during pregnancy and developmental outcomes are inconclusive due to conflicting reports on the role of confounding variables and the different domains of developmental outcomes in studies.

Materials & Methods
In this longitudinal study, we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP) cohort (n=2,517), in which 339 mothers (18.2%) smoked during pregnancy. Developmental outcomes were measured for 1914 and 1367 children at age 4 and 5 respectively, using the Ages and Stages Questionnaire for the total scores and five sub-scores on five domains (fine motor, gross motor, problem-solving, psychosocial skills and communication skills). Logistic regression was applied. The analyses were adjusted for socioeconomic status (SES), mother’s age, gestational age, breastfeeding, and family structure.

Results
170 (8.8%) and 119(8.7%) of the children in LOLLIPOP cohort were found to have abnormal total ASQ scores at age 4 and 5, respectively. Children from mothers who smoked during pregnancy more frequently had an abnormal ASQ score at age 4 and 5 (10.3% and 11.0%, respectively) comparing to children from non-smoking mothers (8.4% and 8.1%, respectively), but this difference was not statistically significant (p>0.05). In the univariable analysis, the relationship between smoking during pregnancy and an abnormal score in the fine motor domain of the ASQ was statistically significant (95% CI of the OR 0.018-p0.097). After adjustment for SES, mother’s age, breastfeeding, gestational age, and family structure the association was not significant anymore. We did not find an association between smoking during pregnancy and developmental outcome in the other domains at age 4 and 5.

Conclusion
This study could not show a relationship between smoking during pregnancy and developmental problems. A more detailed study on biological pathways, including gestational age, might give better insight if the effects of smoking are mediated by other factors.
Immunology

Chair
Karina de Leeuw MD PhD

Presenters
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Gorlenko, K.L. (Kirill)
Lagos, J. (Jonathan)
Milani, A. (Alireza)
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Antibiotic resistance and physicians’ choice of antibiotic in urinary tract infections in Western Bangladesh

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Introduction
Antibiotic resistance is an important obstacle for treatment of UTI specially in low cost health setup of developing countries. The aim of this study is to investigate the resistance pattern of the common pathogens responsible for UTI in Bogra, Bangladesh. Specific factors associated with antibiotic resistance and prescription pattern were also explored to render data for appropriate empiric evidence-based antibiotic guidelines for this area.

Materials & Methods
This retrospective analysis was done among the patients presented with clinical suspicions of UTI for a period of 1 year from October 2016 to September 2017. A total 1256 patients were included in the study. A single clean catch midstream urine sample was collected per patient and samples with more than 105 CFU/mL bacteria were considered positive. 552 samples met the inclusion criteria and in these samples, the bacteria were identified by standard microbiological techniques and the profile of antibiotic susceptibility was obtained using Kibry-Bauer method following Clinical and Laboratory Standards Institute (CLSI) guidelines. Patients’ characteristics, self reported previous antibiotic consumption history within last 1 year, presenting symptoms, empirical antibiotic prescription given at presentation are also recorded and statistical analysis was done using Stata 15 to investigate the possible factors associated with resistance.

Results
UTI was more common in women (61.5%) and its incidence varied with age, affecting more the elderly patients (29.6%). E coli was the predominant isolate (61.05%,n=337), followed by klebsiella (22.28%,n=123). E. coli showed very high frequency of resistance ranging from 54.30% to 77.15% to cefixime, ciprofloxacin, cotrimoxazole and nalidixic acid, moderately high resistance (47.18% to 48.96%) to cefipime, ceftazidime, ceftriaxone and azithromycin and low resistance (1.19% to 16.62%) to imipenem, amikacin, nitrofurantoin and netilimycin. Previous antibiotic consumption history revealed macrolides, cephalosporins and quinolones are mostly consumed antibiotic and 36.34% was based on self medication and 25.78% was recommended by quacks and drug sellers. 78.29% registered physicians used empirical antibiotic at presentation. Mismatching differences of antibiotic prescription and resistance were slightly evident.

Conclusion
High percentage of resistance to most of first line low cost antibiotics made the choice of empirical therapy critical. Continued surveillance, educational interventions and antibiotic stewardship programs for clinicians are necessary to fight the rising problem of antimicrobial resistance. Further exploration of physician prescribing behavior with development of evidence based empirical therapy for infectious diseases is recommended.
Gallic acid shows promising antimicrobial efficiency comparing to amoxicillin and amoxicillin with clavulanic acid drugs

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Introduction
Antimicrobial resistance is a major health problem rapidly spreading across the world that is associated with health and economic impact. Since ancient time plants were well-known sources of cure. They produce whole range of bioactive molecules known as phytochemicals, such as flavonoids, tannins and phenols that become increasingly attracting to scientists due to antioxidant and antimicrobial effect that can be exploited in medicine. Supposed, that secondary metabolites of plants (SMoP) can potentiate the efficiency of antibiotics. Gallic acid is a SMoP also known as common antioxidant of tea formulation. In our research we aimed to compare antimicrobial activity of mentioned antibiotics and gallic acid.

Materials & Methods
The MIC test was performed to determine the minimal inhibitory concentrations of gallic acid in comparison to chosen drugs. Strains of bacteria B. subtilis, E. coli, P. aeruginosa, K. pneumoniae, and C. albicans yeasts were tested using standardized procedure. On the next step we determined the possible interaction between gallic acid and antimicrobial drugs using diffusion method in Müller-Hinton Agar (Merk, Germany). In this assay, 8-well agar plate was seeded with pure cultures of the microbial strains and 50 μl of 2.5% alcohol solution of gallic acid were added to the center well, and then we placed two-times dimensions (from 25 mg/ml to 0.39 mg/ml) of antimicrobial drug tested bringing it by 50 μl to peripheral wells. The MICs were determined by measuring the diameter of growth inhibition zones.

Results
The MIC of gallic acid to all tested strains was much lower (average MIC(mg/ml): gallic acid = 0.21-0.41; amoxicillin = 17.88-20.7; amoxicillin with clavulanic acid = 6.41-7.66) and measured diameters of growth inhibition zones were much bigger than that of antimicrobial drugs.

Conclusion
The results have demonstrated that gallic acid shows a significantly higher antimicrobial activity than antibiotics used in the experiment. Our coming study calls for antimicrobial activity examination of the mixtures (gallic acid + antimicrobials), detection of possible synergistic or antagonistic effects with Isobolograms and fractional inhibitory concentration calculating.
Pathogen associated molecular patterns diminish antigen presentation in B cells by modifying lysosomal trafficking to the immune synapse.

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Introduction
Recognition of pathogen associated molecular patterns (PAMPs) by immune cells is critical to mount a response to invading pathogens. However, their modulation on immune effector functions is not fully elucidated. For instance during sepsis, a systemic inflammatory response to an infection, antigen presentation by macrophages is blunted. Similarly, B cells exposed to 16-24h treatments with CpG, a PAMP that binds TLR9, display diminished antigen-presenting capacity accompanied by increased autophagy. Activation of B cells relies on the formation of an immune synapse (IS) where lysosomes are recruited to facilitate the extraction and presentation of surface-tethered antigens. Given the pivotal role of lysosomes in these processes, we studied whether PAMPs regulate autophagosome formation and their interplay with lysosome trafficking to the IS.

Materials & Methods
We used a B lymphoma cell line, which was incubated with a CpG or LPS for 24 hrs. Autophagy was evaluated by measuring levels of LC3-II and P62 by western blot. The polarization of organelles to the IS was determined by immunofluorescence and imaging analysis. Antigen extraction was measured by monitoring the disappearance of ovalbumin fluorescence coupled to the beads interacting with B cells for different time points. Antigen presentation was evaluated in a co-culture assay with an antigen-specific T cell line.

Results
Our results show that pretreatment with CpG or LPS, decreases the antigen extraction capacity of B cells. This leads to diminished antigen presentation albeit the higher expression of costimulatory molecules on B cells. In the presence of CpG and LPS, we also observed increased levels of LC3-II, associated to a higher production of autophagosomes as well as changes in lysosome distribution, which become repositioned to autophagosomes, diminishing their recruitment to the IS.

Conclusion
CpG and LPS modify both autophagy and lysosome trafficking to the IS of B cells. This impacts on antigen extraction and presentation, which could be important in humoral immune memory formation during sepsis.
Small heat shock protein 27: The most effective adjuvant for development of therapeutic HPV vaccine

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Introduction
Human papilloma virus (HPV) infection is the primary cause of cervical cancer in women worldwide. Practical consideration of vaccines as an alternative to other therapeutic methods against HPV depends on the improved delivery systems and different adjuvants. Hsp20 and Hsp27 belong to small heat shock protein family whose have multiple roles such as chaperon activity, anti-apoptotic properties and recently vaccine adjuvants in infections. Cell penetrating peptides (CPPs) such as hPP10 and MPG were known as major keys for successful protein and DNA transfer into cells with high efficiency and low cytotoxicity. Herein, we evaluated the roles of Hsp20 and Hsp27 proteins as an adjuvant and also hPP10 and MPG peptides as a delivery system for HPV16 E7 antigen in tumor mouse model.

Materials & Methods
The recombinant HPV16 E7 (rE7), Hsp20 and Hsp27 proteins were expressed in prokaryotic expression system and purified by affinity chromatography on Ni-NTA resin. Also, HPV16 E7 gene was fused to the nucleotide sequence of hPP10 and purified under denaturing conditions. For using MPG as a delivery system, the MPG solution was added to 1μg of pcDNA-E7 at an N/P ratio of 10:1 (peptide: DNA). Inbred C57BL/6 female mice were immunized with pcDNA-E7, pcDNA-E7/MPG, rE7 and rhPP10-E7 with and without adjuvants. The mice sera and splenocytes were analyzed for humoral and cellular responses, respectively as well as the evaluation of anti-tumor effects.

Results
Our data showed that the combination of Hsp27 with the recombinant hPP10-E7 protein in homologous protein/protein (hPP10-E7 + Hsp27) and heterologous DNA/protein (pcDNA-E7 + MPG/ hPP10-E7 + Hsp27) significantly enhanced the E7-specific T cell responses. Indeed, these regimens induced high levels of IgG2a, IFN-γ and IL-2 directed toward Th1 responses and also Granzyme B secretion as compared to other immunization strategies, and also displayed complete protection more than 60 days after treatment.

Conclusion
Generally, Hsp27 protein could induce the effective E7-specific immune responses compared to other groups. Furthermore, both MPG and hPP10 as a gene and protein carrier would represent promising applications for improvement of HPV therapeutic vaccines.
The influence of N-acetylocysteine on surgical wound healing - the animal model

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Introduction

N-acetylocysteine (NAC) has been known for its anti-oxidative effect, while the chronic inflammation is a well-recognised factor impairing wound healing. The aim of the study was to evaluate the pre-incision NAC injection influence on the process of wound formation.

Materials & Methods

The study was approved ethically (Resolution no. 304/2017). Each of 24 Sprague-Dawley rats had 2 rows of 3 incisions each planned on the dorsal side. In the one row (chosen randomly), injections with lidocaine and epinephrine solution were made, while in the other injections with 3 different concentrations of NAC were used additionally. Photographic documentation of wounds was performed. Rats were sacrificed on the 3rd, 7th, 14th and 60th day after the operation (6/timepoint). Wounds were excised and preserved for histological (ongoing study) and gene expression analyses. qPCR included 94 targets related to wound healing process. Photographic documentation underwent planimetric measurements (wound area, length, width) with ImageJ 1.48v. Mann-Whitney U and ANOVA Kruskal-Wallis tests were used for data statistical analysis.

Results

All the concentrations of NAC rendered higher expression of growth factors (FGF2, FGF10, IGF1, IGF2), selected cytokines (TNF, VEGFB, TGF-a, TGF-b2, IL-10, ELANE), cell adhesion molecules (CDH1, ITA5) and remodeling factors (MMP2, CSK) (p\textless 0.05). Wound area in NAC-treated groups was smaller starting from the 28th day after incision (p\textless 0.01). The length of wounds on the 14th day in NAC-treated groups were shorter than in the control group (p\textless 0.01). Optimal results occurred with 0.03% NAC solution.

Conclusion

NAC in pre-incisional anesthetic solution decreases wound size, acting as an activator of growth factors and cytokines involved in wound healing. Our study is verifying molecular and macroscopic findings.
Immunotherapy based in macrophages M2 for the treatment of Impaired glucose tolerance in a murine model

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Introduction
Impaired glucose tolerance (IGT) is an intermediate hyperglycemia state, 140-199mg/dl after an Oral glucose tolerance test (OGTT). The IGT is characterized by the increased number of pro-inflammatory M1 macrophages in adipose tissue of obese humans, while the number of anti-inflammatory M2 macrophages is reduced. The M1 macrophages overproduce TNF-α and contribute to insulin resistance as well as hyperglycemia, apoptosis of pancreatic β cells and promote IGT. In adipose tissue of lean mice M2 macrophages secreted IL-10 which increase the insulin sensitivity and glucose tolerance. The aim of this study was to administered M2 macrophages in obese mice as treatment for the IGT.

Materials & Methods
To generate a mice obese model mimicking IGT, we used a combination of high-fat diet (HFD) and low-dose streptozotocin (STZ). The M2 macrophages administrated were obtained from monocytes bone marrow-derived and cultured in vitro with IL-4/IL-13. Every other day per a week, 7x10^6 M2 macrophages CD206+ were administrated intraperitoneally in the mice. Total RNA was extracted from retoperitoneal adipose tissue and cDNA was synthesized. Quantitative RT-PCR for IL-10 gene was performed with premade primer sets. Significance between experimental groups was determined by the p value ≤0.05, using one-way or two-way ANOVA.

Results
In week 16, the mice increased 50% of body weight and subsequent low-dose STZ led a substantial hyperglycemia, therefore the combination of HFD and STZ generated a mice obese model mimicking IGT. After 9 days with M2 macrophages treatment, the glucose levels measured with a glucose tolerance test (GTT) reduced 89% compared with controls. We also found that the upregulated expression of IL-10, an anti-inflammatory cytokine, was associated with the administration of M2 macrophages in adipose tissue.

Conclusion
The current study demonstrated that administration of M2 macrophages decreased IGT in a mice obese model mimicking IGT. These study findings may open new therapeutic options against impaired glucose tolerance by using anti-inflammatory M2 macrophages.
Nephrology and Transplantation

Chair

Prof. Henri G.D. Leuvenink MD PhD

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Biomarkers of renal hypoxia in the experimental model of intra-abdominal hypertension

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Introduction

Kidneys are vulnerable to even a small increase of intra-abdominal pressure due to alternations in renal blood flow, which leads to hypoxia and renal injury. Biomarkers of renal hypoxia can detect the initial stages and degree of renal injury in patients with intra-abdominal hypertension (IAH). We aimed to compare the levels of hypoxia biomarkers HIF, VEGF-C, sVEGF-R1 in renal homogenate and blood serum to the morphologic changes in renal tissue in rats with different severity and time of duration of experimental IAH.

Materials & Methods

The experiment was conducted in 50 newborn Wistar rats. Rats were divided into 5 groups of 10 rats each: rats with mild IAH, exposition of IAH of 5 and 10 days (1, 2) and severe IAH, exposition of IAH of 5 and 10 days (3, 4), and the control group. IAH was modelled via the injection of sterile vaseline into the abdominal cavity under control of intravesical manometry. Blood serum and tissue homogenate were assessed for biomarkers by ELISA. Statistical analysis was performed using SPSS Statistics 22.0.

Results

The HIF level in renal homogenate increased significantly in 2, 3, 4 groups compared to the control group (p<0.001); the degree of increase depended on the severity and time of IAH duration (p<0.05). In contrast, the blood serum level of HIF was lower in all groups compared to the control group (p<0.05). The VEGF-C level in renal homogenate was higher in all rats with IAH (p<0.001); the degree of increase depended on the severity of IAH (p<0.05). The VEGF-C concentration in blood serum increased only in the 3rd group (p=0.013). The level of sVEGF-R1 in renal homogenate was higher in rats with an exposition of IAH of 10 days; the degree of increase depended on the time of IAH duration (p<0.05). The sVEGF-R1 concentration in blood serum increased only in the 3rd group (p=0.022). Morphological analysis showed hydropic dystrophy and the degree of morphological changes depended on the severity and time of IAH duration.

Conclusion

Changes in HIF, VEGF-C and sVEGF-R1 levels assessed in renal homogenate correlated with morphological changes in renal tissue in rats with different severity and time of duration of IAH.
Renal tubular exosomes modulate extracellular levels of ATP in a nephron-segment specific fashion

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Introduction
In the kidneys, exosomes secreted by different nephron portions carry segment-specific proteins. Furthermore, proximal-tubule exosomes regulate collecting duct sodium channels, suggesting a role as intrarenal regulators. Extracellular ATP released by renal epithelial cells in a polarized manner regulates renal physiological processes and electrolyte handling. In this regard, exosomes from non-renal cells (e.g. seminal-fluid exosomes) modulate ATP signalling, for instance, by carrying ectonucleotidases. However, it remains unknown whether renal tubular exosomes exert this function. We aimed to investigate the role of exosomes from different nephron segments in the regulation of extracellular ATP levels.

Materials & Methods
Exosomes were isolated from human proximal tubule (HK-2) and collecting duct (HCD) non-polarized and polarized epithelial cells by ultracentrifugation and precipitation, respectively. Exosomes were characterized by electron microscopy, nanotracking-analysis and immunoblotting. Cultured cells were incubated with their corresponding exosomes, and HCD cells were also incubated with HK-2 exosomes after which extracellular ATP was measured by chemiluminescence. In parallel, HK-2 and HCD-derived non-polarized and polarized and exosomes were incubated in vitro (i.e. non-cellular system) with synthetic ATP (0.1μM, 6h), after which ATP was measured.

Results
Isolated exosomes displayed a round-shape and modal size of 84±2nm and 87±30nm for HK-2 and HCD-exosomes, respectively. Exosomes carried exosomal markers (CD9, CD63, TSG101). HK 2 cells exposed to HK-2-derived exosomes showed no effect on extracellular ATP, while HCD cells exposed to HCD exosomes for 6h and HK-2 exosomes for 24h exhibited a reduction of extracellular ATP (0.60±0.22 vs 1.00±0.11 and 0.29±0.07 vs 1.00±0.08, respectively). When exosomes were incubated with synthetic ATP, only HCD exosomes reduced ATP concentration (0.65±0.01* vs 1.00±0.02). The latter was prevented by sodium orthovanadate. HK-2 cells released more exosomes to the apical than to the basolateral compartment (1.30e+10±1.66e+09* vs 2.40e+09±6.70e+08 particles/ml), while HCD cells showed no differences between compartments (9.73e+08±6.11e+07 vs 1.04e+09±1.63e+08 particles/ml, n=3). In vitro, apical or basolateral HK-2 exosomes had no effect on ATP concentration, while only apical HCD exosomes reduced ATP concentration (0.49±0.05 vs 1.00±0.03). * p<0.05; n=3

Conclusion
HCD apical exosomes modulate extracellular ATP-levels, probably due to ATPases in their cargo, suggesting a segment-specific potential to regulate ATP-dependent processes.
Plasma Vitamin C Levels are Inversely Associated with Risk of Death due to Malignancy in Renal Transplant Recipients

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Introduction
Renal transplant recipients (RTR) are at higher mortality risk compared to controls, and have an increased risk of developing malignancies mainly due to long-term use of immunosuppressive medication. Vitamin C is a well-known radical scavenger and reducing agent that may exhibit protective properties against malignant diseases. We aimed to investigate the association between plasma vitamin C and long-term mortality due to malignancy in a large cohort of RTR.

Materials & Methods
Observational prospective cohort study. RTR with a functioning allograft ≥1 year were recruited at a single university setting between 2001 and 2003. Plasma vitamin C was measured at baseline using reversed phase liquid chromatography with fluorescence. RTR visited the outpatient clinic with declining frequency, in accordance with the American Transplantation Society Guidelines. There was no loss during follow-up. Death due to malignancy was defined as death due to any type of malignancy (International Classification of Diseases, 10th revision (ICD-10) codes C00-C97). Multivariable Cox-proportional hazards regression analyses were performed to assess the association between vitamin C and mortality risk due to malignancy diseases.

Results
We included 598 patients (mean age 51±12 years, 55% male, 97% caucasian). Mean plasma vitamin C was 44±20 µmol/L. After a median follow-up of 7.0 [IQR, 6.2-7.5] years, 131 (22%) patients died, of whom 32 (24%) were due to malignancy. In multivariable Cox regression analyses, plasma vitamin C was inversely associated with risk of death due to malignancy (HR 0.42; 95% CI 0.24-0.75, P=0.003), independent of several potential confounders including age, sex, body mass index, estimated Glomerular Filtration Rate, proteinuria, dialysis vintage time since transplantation, and immunosuppressive therapy. Similar results were found through tertiles of vitamin C.

Conclusion
Malignancy is a substantially prevalent individual cause of death after renal transplantation. Plasma vitamin C levels are inversely and independently associated with risk of mortality due to malignancy. These findings suggest that vitamin C may be an overlooked modifiable risk factor of death due to malignancy in RTR. Whether a novel therapy based on vitamin C supplementation may represent an opportunity to decrease deaths due to malignancy in RTR requires further studies.
Prophylactic effect of N-acetyl-cysteine plus Atorvastatin against contrast-induced nephropathy in patients undergoing elective angiography with or without percutaneous coronary intervention: a prospective, randomized, controlled trial

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Introduction
Contrast-induced nephropathy (CIN) is the main complication of cardiac catheterization with considerable morbidity and mortality. Therefore, this preventive investigation was conducted to examine the reno-protective effect of N-acetyl-cysteine (NAC) plus Atorvastatin against CIN during coronary angiography.

Materials & Methods
This randomized, controlled, clinical trial (IRCT20180417039347N1) consisted of 120 patients with normal and abnormal (creatinine clearance between 15 and 60 mL/min or serum creatinine (SCr) ≥1.1 mg/dl) renal function undergoing elective cardiac catheterization with or without PCI. These individuals were randomly categorized in 4 groups with the following protocols: Group I (considered as control), Group II (Atorvastatin 80 mg), Group III (NAC 1800 mg) and Group IV (NAC 1800 mg plus Atorvastatin 80 mg). CIN was characterized as ≥ 25% or ≥0.5 mg/dl increase in serum creatinine level above the baseline within 48 h after coronary angiography or PCI.

Results
The occurrence of CIN was 30 (25%) patients with the lowest incidence in group IV (13%) as compared to other groups (26.7% vs. 36.7% vs. 23.3%). The statistical analysis identified that group IV had a lower (P <0.05) incidence of CIN (P= 0.04) indicating desirable efficacy for the prevention of CIN (ANOVA). Although statistically significant in both group III and IV (P <0.05), the CIN incidence in group IV (P <0.001) was remarkably lower than group III (P <0.003) in individuals with both normal and abnormal kidney functions confirmed by Chi-square test. In addition, group IV (P <0.003) had a substantial effect than group III (P <0.01) in decreasing CIN in patients with abnormal kidney function (glomerular filtration rate between 15 and 60 mL/min) (Chi-square test). Subgroup analysis also revealed a lesser incidence of CIN in diabetic patients receiving NAC plus Atorvastatin (P= 0.04)

Conclusion
Co-pretreatment of NAC plus Atorvastatin demonstrated significant differences among the four groups and this modality of preventive regimen did reduce CIN.
Successful transplantation of high-risk donor livers after ex situ sequential hypo- and normothermic machine perfusion

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Introduction

Despite persistent donor organ shortage, a high number of donor livers is currently not used for transplantation because of a supposed too high risk of early graft dysfunction/loss. We aimed to increase the number of transplantable livers by resuscitating and assessing viability of liver parenchyma and biliary tree of initially declined high-risk donor livers, using a protocol of sequential ex situ hypothermic (10°C) and normothermic (37°C) machine perfusion.

Materials & Methods

In this prospective clinical trial, all nationwide declined donor livers were eligible for inclusion (Netherlands Trial Registry: NTR5972). The protocol consisted of one hour hypothermic oxygenated perfusion for resuscitation, one hour of controlled oxygenated rewarming, and subsequent normothermic machine perfusion (NMP) for viability testing. A novel perfusion fluid containing a hemoglobin-based oxygen carrier was used for all temperature phases. During the first 150 min of NMP, viability of the liver and biliary tree was assessed using the following criteria: perfusate lactate <1.7mmol/L, pH 7.35-7.45, cumulative bile production >10mL and bile pH>7.45. Livers meeting these criteria were subsequently accepted for transplantation. All recipients gave written informed consent. Primary endpoint was safety and feasibility, as reflected by a 3-months graft survival rate of at least 80%.

Results

Between August 2017 and October 2018, 16 livers underwent machine perfusion after an average of 288 (241-480) min of preservation on ice. All livers were derived from donation after circulatory death donors with a median age of 63 (range 42-82) years. During NMP, all livers cleared lactate and produced sufficient bile volume, but in 5 cases biliary pH remained <7.45. The 11 (69%) livers that met all viability criteria were successfully transplanted, resulting in a 20% increase in the number of deceased donor liver transplants in our center. Patient and graft survival at 3 and 6 months was 100%.

Conclusion

Sequential hypo- and normothermic machine perfusion for initially declined high-risk donor livers enabled resuscitation and successful transplantation. This method offered a valuable tool to safely increase the number of transplantable livers by 20%.
Plasma Malondialdehyde Is Associated With Higher Risk Of Cardiovascular Mortality In Renal Transplant Recipients: A Prospective Cohort Study.

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Introduction
Oxidative stress (OS) has been associated with cardiovascular disease and adverse survival outcomes in chronic kidney disease and end-stage renal disease patients. In successful renal transplant recipients (RTR), OS remains exacerbated when compared to healthy controls, however, to date no study has assessed whether it may prospectively impact long-term survival. The current study aims to investigate whether the OS biomarker malondialdehyde (MDA) is prospectively associated with long-term risk of cardiovascular mortality in an extensively phenotyped cohort of stable RTR.

Materials & Methods
Prospective cohort study of stable RTR with a functioning allograft ≥1 year, recruited between 2001 and 2003 in a university setting. Plasma MDA was measured by thiobarbituric acid reaction assay. Associations of circulating MDA with cardiovascular mortality were assessed using Cox regression analyses in the overall RTR cohort and within subgroups of patients according to significant effect-modifiers. For all analyses IBM SPSS software version 23.0 was used.

Results
In 604 RTR (51±12 years-old, 55% male, at a median of 6.0 [interquartile range (IQR) 2.7–11.5] years after transplantation), baseline median plasma MDA concentration was 5.38 [IQR, 4.31–6.45] μmol/L. During a median follow-up of 6.4 [IQR, 5.6–6.8] years, 110 (18%) RTR died, 44 (40%) deaths due to cardiovascular causes. An increase in one standard deviation of circulating MDA was positively associated with risk of cardiovascular mortality (hazard ratio [HR] 1.31, (95% confidence interval [95% CI] 1.03–1.67)). This association was independent of adjustment for potential confounders, including immunosuppressive therapy and traditional cardiovascular risk factors. In RTRs with a relatively low plasma vitamin C concentration (<42.5 µmol/L) or relatively low estimated glomerular filtration rate (<45 mL/min/1.73 m²), MDA was associated with a more than two-fold higher risk of cardiovascular mortality (HR 2.22 (95% CI 1.48–3.32), and HR 2.05 (95% CI 1.43–2.92), respectively).

Conclusion
Circulating MDA is independently associated with higher long-term risk of cardiovascular mortality, particularly in RTR with relatively low plasma vitamin C or renal function. Further studies are warranted to investigate whether OS-targeted interventions may decrease the burden of excess premature cardiovascular mortality in RTR.
Neurology II

Chair
Prof. J.B.M. (Jan) kuks MD PhD

Presenters
Aken, E.S.M. van (Evert)
Babaie, M (Mahsa)
Brzegowy, K. (Karolina)
Rowling, HR (Hannah)
Yang, DWY (Dawei)
Yeganyan, G. (Garik)
Risk of ischemic cerebrovascular events is associated with carotid artery radiation dose in head and neck cancer patients

Aken, E.S.M. van (Evert) 1, Bijl, H.P. (Henk) drs. 1, Laan, H.P. van der (Hans Paul) PhD 1, Bosch, L. Van den (Lisa) drs. 1, Hoek, J.G.M. van den (Anne) drs. 1, Dieters, M. (Margriet) drs. 1, Steenbakkers, R.J.H.M. (Roel) dr. 1, Langendijk, J.A. (Hans) prof. dr. 1

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Introduction
Radiotherapy in the head and neck area may cause vascular damage to the carotid arteries, increasing the risk of ischemic cerebrovascular events (ICVEs). However, limited data exists on the relationship between radiation dose and the risk of ICVE. This information is crucial to identify patients at risk and to optimize radiotherapy treatment plans. Therefore, the purpose of this study was to determine the relationship between radiation dose to the carotid arteries and anterior circulation ICVE risk and to identify the most relevant dose-volume parameters.

Materials & Methods
A retrospective analysis was performed using data of a prospective cohort study of 750 patients treated with definitive radiotherapy (either or not combined with systemic treatment) for head and neck squamous cell carcinomas. Based on treatment planning CT scans, carotid arteries were delineated and dose-volume parameters were calculated bilaterally for the entire carotid arteries (external carotid arteries were excluded) and for the common carotid artery (CCA), bifurcation and internal carotid artery (ICA). ICVEs were scored prospectively and additional information was added by reviewing patient records. Cox proportional hazards analysis was performed to analyse the relationship between radiation dose and the risk of ICVE.

Results
In the univariate analysis, anterior circulation ICVE risk was significantly associated with dose variables to the entire carotid arteries, particularly to the CCA and the bifurcation. Multivariable analysis showed that the absolute volume (cc) of the entire carotid arteries that receives at least a radiation dose of 10 Gy (absolute V10) was the most important prognostic factor for ICVE, with a HR of 1.14 per cc (95% CI 1.064-1.222; p<0.001). No relevant confounding patient and treatment characteristics were found, meaning that the absolute V10 to the entire carotid arteries can be considered as an independent prognostic factor for the cumulative incidence of ICVE.

Conclusion
This is the first prospective cohort study that demonstrates an independent dose-effect relationship between radiation dose to the carotid arteries and the risk of ICVE. These findings may lead to more adequate ICVE risk prediction and prevention in these patients. ICVE prevention can be achieved by radiotherapy treatment optimization, regular screening or pharmacological treatment.
Comparison of intraoperative and early postoperative efficacy of hypertonic saline versus mannitol as anti-edema therapy among patients with cerebral low grade glioma: A randomized clinical trial.

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Introduction
Increased intracranial pressure followed by brain swelling can cause problems during operation. The main approach to this complication is the use of osmotic fluids. Mannitol is a well known agent for reduction of ICP. But regarding the various side effects of Mannitol administration, researchers has become interested in hypertonic solutions for brain relaxation in neurosurgies. In addition to osmotic property of hypertonic saline, it seems to have anti-inflammatory and neuroprotective effects which has been studied in recent years. But no study has evaluated the intra and postoperative efficacy and safety of HS and its anti-inflammatory role in patients undergoing elective craniotomy for brain tumors.

Materials & Methods
Via a randomized controlled clinical trial, 60 patients suspected to have supratentorial low grade glioma were enrolled in the study. Patients were randomly divided into intervention (HS) and control (Mannitol) groups. As the primary outcome, amount of brain edema after dural opening, reported by the neurosurgeon, and pre-and postoperative serum S100B levels were documented and measured. The volume of intraoperative blood loss, operation time, length of ICU and hospital stay, duration of mental confusion after surgery, extent of tumor resection and duration of anti-edema therapy after surgery were documented as secondary outcome measures.

Results
All cases completed the study. There was no significant difference between the two groups regarding age, sex, tumor size and location and preoperative S100B levels. The postoperative serum level of S100B was significantly lower in patients who received HS (0.584) in contrast to patients received Mannitol (0.851) (P: 0.001). There was no significant difference regarding the severity of brain edema based on surgeon’s reports, extent of tumor resection, volume of intraoperative blood loss, operation time and hospital stay between the two groups. (P\textless;0.05)

As secondary outcomes, length of ICU stay (0.04), duration of mental confusion after operation (0.003) and duration of corticosteroid therapy as an anti-edema approach (0.03) were significantly lower in hypertonic saline group.

Conclusion
HS infusion just before the onset of craniotomy seems to be effective and safe in brain relaxation during surgery and have neuroprotective effects in addition to its osmotic features, resulting in better control of cytotoxic edema after craniotomy.
The internal cerebral vein: new classification of branching patterns based on computed tomography angiography

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Introduction
The internal cerebral vein (ICV) is a deep cerebral vein that begins in the region of the foramen of Monro by the union of the thalamostriate (TSV) and the anterior septal (ASV) veins. Other main tributaries of the ICV include the lateral direct (LDV) and the medial atrial (MAV) veins. Gross anatomy of the ICV is well known, however its branching patterns and their relationship to the basal nuclei have not yet been fully investigated. The aim of this study was to evaluate the anatomy of the ICV and its main tributaries and to classify them depending on their course patterns using computed tomography angiography (CTA).

Materials & Methods
Head CTA of 250 patients were evaluated in this study, involving 500 ICVs. We identified the number and characteristics of the ASV, TSV, LDV and MAV. The ASV-ICV junctions and their location in relation to the foramen of Monro were also evaluated.

Results
We classified the ICV branching patterns into 6 types, depending on the presence of an extra vessel draining the striatum. The most prevalent pattern included the ICV continuing further as one TSV (77.00%). The LDVs were identified in 22.00% of the hemispheres. They usually terminated at the middle portion of the ICV (65.45%). In 38.95% of the hemispheres with an LDV, the TSV had a reduced diameter. The most common location of the ASV-ICV junction was anterior (57.20%), with the ASV terminating at the venous angle.

Conclusion
Significant variations in the ICV branching patterns are relatively frequent. Detailed knowledge of the anatomy of deep cerebral veins is of a great importance for neurosurgery of the cerebral ventricles, especially minimally invasive endoscopic approaches. A thorough preoperative understanding of the variation of their patterns may aid in reducing the risk of iatrogenic injury to the veins resulting in basal nuclei infarcts. To our best knowledge, a classification of the ICV branching patterns with their prevalence based on large-scale radiological anatomical study has not yet been published.
Large vessel occlusion patients with milder baseline symptoms have better collaterals and less harm from transfer delays

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Introduction
Severity-based clinical triage tools, aim to allocate suspected large vessel occlusion (LVO) patients at high risk of requiring thrombectomy to comprehensive stroke centers, but miss a proportion of patients with milder symptoms. Our hypothesis was that LVO patients with milder symptoms have better collateral quality and less impact of delayed thrombectomy due to inter-hospital transfer on functional outcome, as compared to patients with more severe symptoms.

Materials & Methods
We compared pre-thrombectomy CT-perfusion markers of collateral circulation, including cerebral blood flow (CBF)&lt;30% volume and hypoperfusion intensity ratio (HIR) between patients with National Institutes of Health Stroke Scale (NIHSS) &lt;10 and ≥10 in thrombectomy patients admitted to the Royal Melbourne Hospital from 2007-2018. The association between transfer and functional outcome (90-day modified Rankin Scale, mRS) adjusted for age, sex, site of occlusion and reperfusion, was compared between patients with NIHSS &lt;10 and ≥10 using logistic regression.

Results
Of 607 patients, 111 (18.3%) had NIHSS &lt;10. Patients with NIHSS &lt;10 had smaller baseline CBF &lt;30% volume (median 5.5 vs 17 mL, p &lt; 0.001) and lower HIR (0.33 vs 0.49, p &lt; 0.001), indicating better collaterals. For mRS/0/1/return-to-baseline, there was a significant transfer-by-NIHSS(&lt;10/≥10) interaction (p = 0.0001). NIHSS ≥10 patients: adjusted odds ratio, aOR = 0.647 (95% CI, 0.40 – 1.06); NIHSS &lt;10 patients: aOR = 0.896 (0.32 – 2.53); Ordinal logistic regression analysis demonstrated a shift towards higher mRS score for transfer patients with NIHSS ≥10 (p = 0.02), but not for transfer patients with NIHSS &lt;10 (p = 0.95).

Conclusion
Thrombectomy patients with lower baseline NIHSS have better collateral circulation. Delays due to inter-hospital transfer were not significantly associated with worse outcome for these patients, mitigating the reduced sensitivity of triage tools in milder patients.
Optic nerve head perfusion changes preceding peripapillary retinal nerve fiber layer thinning in preclinical diabetic retinopathy

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Introduction
Diabetic retinopathy (DR) is the leading cause of blindness in working-age adults. There are approximately 93 million people with DR worldwide (the overall prevalence rate of DR for all adults with diabetes mellitus is 34.6%). Microvascular and neural complications have been associated with DR, however, our understanding of the molecular and cellular pathogenesis of DR remains incomplete. DR has been classically considered as a microvascular disorder. However, growing evidences suggest that retinal neurodegeneration is present before the development of clinically detectable microvascular damage. Recent studies have showed positive correlation between peripapillary vessel density and RNFL thickness at 3.45-mm circle diameter around the optic nerve head (ONH). Since peripapillary RNFL thinning is significant in preclinical DR, it is of interest to investigate the blood flow of ONH in diabetic patients. With the development and application of optical coherence tomography angiography (OCTA), a novel non-invasive imaging technique that can demonstrate ONH microcirculation, ONH blood flow can now be easily quantified and visualized. In the present study, peripapillary perfusion and RNFL thickness were measured and compared among control subjects and diabetic patients with no signs of DR using OCTA.

Materials & Methods
All participants underwent 4.5×4.5 mm rectangle scans centered on the optic nerve head (ONH) using OCTA (RTVue-XR Avanti; Optovue, Fremont, CA, USA). Peripapillary retinal nerve fiber layer (RNFL) thickness and capillary perfusion density inside the ONH and in the peripapillary region were compared between the two groups.

Results
Vessel density values in both peripapillary and inside the disc were significantly lower in diabetic patients without DR compared to normal controls. The reduction of vessel density was prominent in all eight peripapillary sectors in diabetic eyes (all P <0.05). Thinning of RNFL thickness was significant in the nasal superior (P<0.001), inferior nasal (P = 0.023) and superior nasal quadrant (P < 0.001) in diabetic eyes in comparison to normal controls.

Conclusion
ONH perfusion and peripapillary RNFL thickness were significantly decreased in preclinical DR patients compared to normal controls. Microvascular alterations in ONH may occur earlier than peripapillary RNFL defect in the course of DR.
Sleep bruxism is more common in patients with epilepsy

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Introduction
Epilepsy is one of the most common neurological disorders (up to 1% in general population). Determining factors, which affect the severity of epilepsy is important for modern epileptology. Such factors could be also various sleep disorders; however, they are insufficiently investigated. The role of some sleep disorders, like obstructive sleep apnea (OSA) or parasomnias, in epilepsy is well studied. Considering a huge variety of primary sleep disorders and their prevalence, investigation of the effects of others on epilepsy is essential. Bruxism is a common phenomenon (up to 31% in general population), which is defined as a repetitive jaw-muscle activity characterized by clenching or grinding of teeth and/or by bracing or thrusting of mandible (International Classification of Sleep Disorders, 3th ed.). Sleep bruxism (SB) is a bruxism which occurs exclusively during sleep, and is classified in sleep related movement disorders (SRMD). It is associated with frequent microarousals. The prevalence of SB is reach to 15.9% in adults. The aim of this study was to identify the prevalence of SB in patients with epilepsy (PWE).

Materials & Methods
257 adults were involved into this study. They were divided into two groups: group 1 (G1) - PWE with proven diagnosis of both partial and generalized epilepsy and with at last 3-month regular pharmacotherapy or without any treatment. Group 2 - subjectively healthy participants. SB was identified through interviewing; reports of regular tooth grinding or jaw clenching during sleep were evaluated as SB. Nobody was taking antidepressants (possible cause of secondary SB). Chi-squared test was used for statistics.

Results
157 PWE (G1) and 100 healthy individuals were involved. Mean age of G1 and G2 was 34.8 and 33.7 years respectively. Prevalence of SB in G1 was 25.5% (n=40) and 7% in G2 (n=7) (p<0.0001).

Conclusion
According to our findings SB is more common in PWE than in healthy population. As a SRMD associated with microarousals, SB may provoke nocturnal seizures like OSA or other sleep disorders. Our results could be an important addition to understanding of drug-resistant epilepsy.
Oncology II

Chair
Annemiek Walenkamp MD PhD

Presenters
Anderson, E.M.A. (Elizabeth)
Cheplova, N. (Natalya)
Dieckmann, S.M. (Sophie)
Hui, W (Wang)
Sapach, A.
Stutvoet, TS (Thijs)
Differential effects of cannabigerol and epigallocatechin-3-gallate on SKOV3 ovarian cancer cell migration and matrix metalloprotease expression

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Introduction
Phytochemicals from both Cannabis sativa (cannabinoids) and Camellia sinensis (catechins) exhibit cytotoxicity to many different types of cancer cells, including ovarian. In this study, we examined the effects of the phytocannabinoid cannabigerol (CBG) and green tea derivative epigallocatechin gallate (EGCG) on SKOV3 ovarian cancer cell proliferation and migration on a murine tumor-derived basement membrane extract (BME) to test our hypothesis that these phytochemicals will affect the two major hallmarks of cancer cells, namely proliferation and migration.

Materials & Methods
All experiments were performed in serum-free DMEM:F12 medium in the presence or absence of CBG and EGCG on tumor-derived BME. After 48-hours in culture, cell viability was determined in the presence of WST-8 reagent. For cell proliferation studies, the phytocompounds were tested on subconfluent cells. For migration assay, scratch wounds were made on confluent cells with a pipette tip. Subsequent closure of the wound by migrating cells was determined in the presence of the test compounds. The activity of matrix metalloprotease-2 (MMP-2) was assayed by zymography on gelatin gels. Data were analyzed by one-way ANOVA followed by Bonferroni post-hoc test.

Results
At micromolar concentrations, both CBG and EGCG inhibited the proliferation of the cancer cells. In the presence of CBG, the cells rounded up and detached from the culture surface. In the presence of EGCG, however, some cells also remained attached to the substratum. In the scratch wound assay, migration of the cells was significantly inhibited only by EGCG. The cellular secretion of MMP-2, a gelatinase associated with tumor cell migration and metastasis, was also markedly inhibited by EGCG.

Conclusion
The results of our studies suggest that both CBG and EGCG are cytotoxic to SKOV3 ovarian cancer cells growing on the tumor BME. However, only EGCG inhibited both cell migration and MMP-2 secretion. Thus, the differential actions of CBG and EGCG on SKOV3 cancer cells suggest different mechanisms of action of these compounds.
Drug repurposing: nitroxoline and digoxin as candidates for breast and colon cancer treatment.

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Introduction
Drug repurposing in cancer treatment is the reuse of drugs with non-cancer application in cancer therapy. The advantages of this approach are well-known toxicity profiles of existing licensed drugs and reasonable prices. The aim of this study were to investigate: 1) the anticancer effects of enalapril, metoprolol, digoxin and nitroxoline on tumor cells; 2) its combinations’ effects with standard chemotherapy used against breast and colon cancer.

Materials & Methods
Enalapril, metoprolol, digoxin and nitroxoline were selected from the database of ReDO project (“Repurposing drugs in oncology”) as candidates for treatment of breast and colon cancer. MCF-7 breast cancer and SW480 colon cancer cell lines were used as a model cells. Cells were treated with non-cancer drugs and with their combinations with specific anticancer agents tamoxifen and oxaliplatin. Cell viability and synergism effects of drugs combinations were evaluated by MTT assay. Drug effects to cell cycle were evaluated by flow cytometry with PI staining.

Results
Nitroxolin and digoxin inhibited the cell growth with IC50 values of 110µM and 0.3 µM for MCF-7, 87.0 µM and 0.09 µM for SW480. Cell cycle analysis showed, that digoxin and nitroxoline inhibit the cellular proliferation via G2/M phase cell cycle arrest and apoptosis. The combinations of nitroxolin or digoxin with oxaliplatin and tamoxifen showed a dose-dependent synergistic cytotoxic effect both in SW480 cells, and in MCF-7 cells, as compared to single agents oxaliplatin and tamoxifen. Enalapril and metoprolol showed no effects for cancer cells.

Conclusion
We demonstrated that antibiotic nitroxoline and cardio drug digoxin revealed anticancer effects in MCF-7 and SW480 cells. Synergy of these compounds was shown for their combination with oxaliplatin in SW480 cells and with tamoxifen in MCF-7 cells. Moreover, the cytotoxic effect of the combinations was achieved with nontoxic doses of anticancer drugs. Thus, in this study we offer perspective drugs nitroxolin and digoxin for colon cancer and breast cancer treatment.
Preclinical validation of the adapter chimeric antigen receptor (aCAR)-modified NK-92 cell line for melanoma therapy

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Introduction

Melanoma is the most dangerous type of dermatological tumor, linked to 80-90% of skin cancer associated deaths. The incidence of melanoma has been steadily increasing. Therapy options remain limited.

In recent years, immunotherapy has shown great potential for cancer treatment. CAR-modified T cell therapy, an immunotherapeutic strategy, gained much attention due to impressive clinical responses in the treatment of malignancies. However, they have a risk of side effects, such as cytokine-release-syndrome and neurotoxicity. A promising alternative to CART cells are NK cells. CAR NK cells can be safely delivered as an off-the-shelf-product, when using the FDA-approved NK-92 cell line.

The newly developed aCAR-system is based on the properties of a novel scFv targeting a “neo”-epitope formed by conjugating biotin to the Fc part of an antibody. Splitting antigen recognition and CAR-immune cell activation and introducing biotinylated antibodies, allows precise quantitative as well as qualitative regulation of immune cell function.

Materials & Methods

To evaluate aCAR-modified NK-92 cells for melanoma treatment, eight different cell lines were used. Real-time quantitative PCR was used to compare gene expression profiles and confirm the origin of the melanoma cell lines. Using FACS the cell lines were screened for the expression of several therapeutic antigens. aCAR NK-92 cells were tested in combination with biotinylated antibodies directed against the most promising antigens and the cytolytic effects were measured by calcein release assays and FACS-based live/dead assays.

Results

In the presence of biotin-conjugated antibodies against different expressed antigens on melanoma cells, aCAR NK-92 cells were highly cytotoxic in a time-dependent manner, thus verifying the specificity and potency of the aCAR system. The aCAR NK-92 cells induced a maximum cell lysis of up to 70%. Using longer incubation times (24h) with the FACS based cytotoxicity assay cell lysis of up to 85% could be achieved.

Conclusion

The activation and effector function of the aCAR NK-92 cell line can be tightly regulated by the presence of biotinylated antibodies, allowing effective, universal targeting of multiple antigens expressed on melanoma cell lines. aCAR NK-92 therapy may provide a safe, economic, “off-the-shelf on demand” standardized cellular product for the treatment of melanoma and other cancers.
Non-cancer-specific Immunoglobulin G4 as a Blocking Molecule in Cancer

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Introduction
IgG is one of the most important molecules in immunity. IgG4 is the least abundant IgG subtypes in the human body. Current studies about IgG4 are mainly focused on IgG4-RD, inflammatory diseases and autoimmune diseases, rarely involved malignant tumors. And the role of IgG4 in the immune system has not been fully understood. In this study, significantly increased number of IgG4 positive cells was first time discovered in esophageal cancer tissue compared with other IgG subtypes, the aim of this study was to investigate the structural uniqueness of IgG4 and its possible functions in cancer immunity.

Materials & Methods
Serum IgG4 and IgG levels were measured by Roche immune Turbidimetry method in 88 cases of esophageal cancer patients’ serum. IgG4 positive cells were assessed by immunohistochemistry in 55 cases of cancer tissues and adjacent tissues. the stain-destain-restain technique was used in this study to verify four IgG subclasses on the same tumor slice. Electrophoresis was used to examine the reaction between IgG1 and IgG4.

Results
IgG4 positive lymphocytes in esophageal cancer mass (n=55) are significantly more abundant than those in adjacent cancer tissue (n=33) and normal tissues (n=35). (unpaired t-test, both P<0.001). The levels of serum IgG4(P<0.001) and IgG4/IgGtotal(P<0.001) of patients with esophageal cancer(n=82) were higher than those in the control group (n = 70). Both were related to patients’ prognoses(Pearson’s correlation, P<0.05). IgG4 extracted from the serum of cancer patients did not react to cancer antigens but IgG1 did. However, the non-cancer-specific IgG4 reacted to IgG1 that was bound to cancer antigens. Electrophoresis confirmed that this reaction was via Fc fragment of IgG4 to Fc of IgG1.

Conclusion
The concentration of IgG4 elevated significantly in cancer patients’ tissue and serum and the unique reacting properties of this IgG4 molecule with other subtypes can interfere with anti-tumor IgG1 activities. These results indicate the specificity of IgG4 as a role of immune suppressor in humoral immunity of cancer microenvironment and further investigations are needed to clarify the biological functions of IgG4 in vivo.
FOLATE-ASSOCIATED CATIONIC LIPOSOMES OBTAINED BY POST-MODIFICATION TECHNIQUE FOR ACTIVE TARGETED DRUG DELIVERY

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Introduction
Cationic liposomes are promising drug delivery systems, since they allow to encapsulate both lipophilic and hydrophilic compounds, as well as genetic material. Presently, for targeted drug delivery, liposomes are modified with ligands by thin film technique. However, ligands are localized both inside and outside of the liposome membrane which limits drug loading. A novel click-chemistry approach (post-modification technique) to control ligand localization only at outer liposome surface was developed. Folic acid (FA) was used as a ligand for active tumor targeting. The aim of the study was to obtain doxorubicin (DOX)-loaded FA-associated cationic liposomes (FLPs) and to study their cytotoxicity in vitro.

Materials & Methods
The DOX-loaded FLPs (40% DOX w/w) were obtained by two techniques: 1) by mixing native lipids and FA-associated lipids (98:2, w/w) at thin film formation step (FLPs-1) and 2) by post-modification of previously prepared DOX-loaded liposomes (FLPs-2). FLPs accumulation was evaluated by confocal microscopy and flow cytometry. In vitro cytotoxicity was studied by MTT-test. Human breast adenocarcinoma (MCF-7), human cervical cancer (HeLa), human brain glioma (U-87 MG), rat brain glioma (C6), human mesenchymal stem cells (MSC) cells were cultivated in DMEM supplemented with 10% FBS in a 5%-CO² humidified atmosphere at 37ºC.

Results
Characterization of FLPs was performed. The FLPs-2 were 2-fold smaller in size (135±13 nm) compared to FLPs-1 (254±20 nm). Both FLPs had high ζ-potential (+51±10 mV) and were stable for 3 weeks. To study FLPs accumulation and cytotoxicity, C6 and MCF-7 (both with overexpression of folate receptors), HeLa, U-87 MG and MSC cells were chosen. Liposomes without FA (LPS) were used as a control. All samples penetrated the cells after 15 min incubation. However, after 1 h FLPs were localized mainly in the nuclei, while LPS were observed in cell membranes. LPS accumulation levels were similar for all cells, while FLPs uptake was faster and promoted higher cytotoxicity in C6 and MCF-7 cells than in other cells.

Conclusion
FLPs and LPS were obtained and characterized. The FLPs accumulation and cytotoxicity were higher than those for LPS. The post-modification technique is promising for ligand attachment only at liposome surface. The study was supported by RFBR grants 18-34-00919 and 18-04-01087.
MAPK pathway activity plays a key role in PD-L1 expression of lung adenocarcinoma cells

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Introduction

Immune checkpoint inhibitors targeting programmed death-ligand 1 (PD-L1) function have improved survival of non-small cell lung cancer (NSCLC). Still, many patients do not respond. PD-L1 expression influences efficacy of immune checkpoint inhibitors, but is very dynamic. Here, we studied PD-L1 regulation in NSCLC without targetable genetic alterations to provide a rationale for combination strategies of immune checkpoint inhibitors with other targeted agents.

Materials & Methods

Using TCGA RNA sequencing data of lung adenocarcinoma (n = 159) and squamous cell lung carcinoma (n = 166) without targetable genetic alterations, we investigated the correlation of EGFR and IFNγ signaling with PD-L1. Next, the influence of EGFR and IFNγ signaling on PD-L1 mRNA (by qPCR), total protein (by Western blotting) and membrane expression (by flow cytometry) was determined in 5 lung adenocarcinoma cell lines. The role of JAK/STAT, MAPK and PI3K signaling were studied using specific inhibitors and siRNAs. Results were validated using cocultures of tumor cells with peripheral blood mononuclear cells (PBMCs).

Results

TCGA data revealed that inferred IFNγ and MAPK signaling correlated with PD-L1 expression in lung adenocarcinomas. In our cell line panel, EGF and IFNγ strongly increased PD-L1 mRNA, protein, and membrane expression, which was further enhanced by combining EGF and IFNγ. Similarly, activated PBMCs increased tumor cell PD-L1 expression. PI3K signaling was marginally related to PD-L1 levels, but inhibition of MAPK signaling using EGFR and MEK1/2 inhibitors almost completely prevented EGF- and IFNγ-induced PD-L1 mRNA, protein, and membrane upregulation. This did not influence IFNγ-induced MHC-I upregulation. Interestingly, MAPK signaling moderately activated PD-L1 transcription inducer STAT1 and primarily acted through stabilization of PD-L1 mRNA.

Conclusion

Inhibition of MAPK signaling reduces PD-L1 mRNA stability, disrupting IFNγ- and growth factor-induced PD-L1 expression in lung adenocarcinoma without targetable genetic alterations, but does not disrupt MHC-I expression. These results support further investigation of MAPK pathway inhibition to improve the efficacy of immunotherapy in NSCLC.
Pharmacology II

Chair

Prof. Martina Schmidt PhD

Presenters

Chauhan, S (Shashi)
Hassanipour, M. (Mahsa)
Jain, K.J. (Kriti)
Khezrnia, S.S. (Sana)
Mehrbakhsh, N.M (Negar)
Patel, Y.S.P (Yatri)
To evaluate anti-Parkinson’s potential of simultaneous blockage of adenosine A2A receptor and glutamate receptors against 6-OHDA-induced lesions in mice

Not Applicable, S (Shashi)

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Introduction
Parkinson’s diseases (PD) is a progressive neurodegenerative disorder in which degeneration of nigrostriatal dopaminergic neurons causes the dopamine depletion resulting the motor and nonmotor symptoms. Simultaneous blockage of adenosine A2A receptor and glutamate receptors are shown to be effective in preventing excitotoxic degeneration of dopaminergic neurons. Among glutamate receptors NR2B, mGlu5, AMPA and both metabotropic and NMDA are often targeted. However, it is unclear blocking which receptors is most effective in preventing development of motor and non-motor indicator of PD.

Materials & Methods
In an animal experiment, PD was induced in mice by unilateral infusion of 6-OHDA(4µg/µl/mice) into the striatum and evaluated by using different biochemical and behavioral parameters. Adenosine A2A receptor and glutamate receptors (NR2B, mGlu5, AMPA and both metabotropic and NMDA simultaneously) were blocked using four different drug combinations. Experiment had 6 groups: Group 1-control group, Group 2-vehicle, Group 3-blocking NR2B using istradefylline(0.1mg/kg, i.p) traxoprodil(10mg/kg, i.p.) for, Group 4-blocking mGlu5 using istradefylline(0.1mg/kg, i.p)+MPEP(2-methyl-6-(phenylethynyl)pyridine)(20mg/kg, i.p), Group-5 blocking AMPA istradefylline(0.1mg/kg, i.p) + topiramate (10mg/kg, p.o) for and Group-6 blocking both metabotropic and NMDA using istradefylline(0.1mg/kg, i.p)+acamprosate(300mg/kg, p.o). To assess motor function, Bart test and Rota rod test were performed. To assess locomotor activity, open field performance test was performed. To test an effect size of 20 (SD=8) at power of 80% and type I error rate of 5%, we needed 5 mice per group. Sample size calculation was performed using one way ANOVA. Mice were randomly assigned to treatment groups and treatment allocation was blinded.

Results
Mean cataleptic duration in Group 1 – Group 6 were (10.6±6.26), (105.4±21.58), (11±4.3), (41.6±6.95), (39.6±9.56) and (81.8±15.2) respectively. Results from one-way ANOVA test indicated that mean was not same across 6 groups (p-value <0.001). Post-hoc test showed that the group 3 differed significantly from other groups except Group 1. Results were essentially similar for other parameters including falling latency time, number of lines crossed, dopamine levels, GABA and glutamate levels.

Conclusion
Results in this study show that blocking adenosine A2A receptor and NR2B glutamate receptors (i.e. Group 2) offers most improvement in behavioral and biochemical PD indicators in mice.
The effects of Pistacia vera seed oil on anxiety and depressive-like behaviors in rats with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is associated with many complications. Neurobehavioral deficits are reported in woman with PCOS. Evidence showed a high prevalence of affective disorders in women with PCOS which impair their quality of life. Pistacia vera, a member of the Anacardiaceae family, plays beneficial roles in central nervous disorders such as seizures and anxiety. Current study is designed to evaluate the effects of Pistacia vera oil on depression and anxiety-like behaviors in female rats with letrozole-induced PCOS.

Materials & Methods
Female Wistar rats weighing 150-200 g were used in this study. Animals were cared and treated in accordance to the institutional Guideline for the Care and Use of Laboratory Animals with the approval of Rafsanjan University Research and Medical Ethics Committees. Letrozole was administered orally for 21 days (once daily) at the dose of 1 mg/kg. Pistachio with genetic code M30 and from species Akbari was purchased and the seed oil was obtained via cold press technique. This oil was administered once daily orally with doses of 1 and 4 ml/kg concurrently with letrozole. After 21 days, elevated plus maze, forced swimming test and open field tests were performed. Data analysis was performed using Graphpad Prism data analysis program version 6. One-way analysis of variance (ANOVA) followed by Tukey’s multiple comparisons were used. P value<0.05 was considered statistically significance. Female rats were randomly assigned into four groups (N=7 each group):

1: Control group: healthy normal animals without PCOS.
2: PCOS group: rats with polycystic ovary syndrome.
3: PCOS+PO 1: PCOS rats treated with pistachio oil with the dose of 1 ml/kg.
4: PCOS+PO 4: PCOS rats treated with pistachio oil with the dose of 4 ml/kg.

Results
Our data showed that PCOS condition led to immobility time enhancement in the FST (P<0.001). PCOS animals significantly exhibited anxiety-like behaviors (P<0.05). Treatment with pistachio oil with doses of 1 and 4 ml/kg completely blocked deleterious effects of PCOS on behavioral parameters (all P<0.01).

Conclusion
Administration of Pistacia vera oil in female rats with PCOS could alleviate depression and anxiety.
Cognitive and behavioural effects of lamotrigine in juvenile rats

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Introduction
Lamotrigine, new generation anti-epileptic, acts by slowing the rate of recovery of Na+ channels from inactivation, an action that is both voltage- and use-dependent. It also inhibits voltage-gated calcium channels, particularly the N- and P/Q-type. Moreover, it decreases the synaptic release of glutamate. These multiple actions explain its efficacy in varied types of seizures like partial seizures and generalized seizures including absence seizures in children and women of child-bearing age. Considering the heterogeneous actions of lamotrigine, and the predictably long-term use of anti-epileptics in children, behavioral and cognitive adverse effects cannot be ruled out. Hence this study was planned to investigate the cognitive effects on long term treatment with lamotrigine in younger wistar rats.

Materials & Methods
In-house bred Wistar rats of either sex were maintained at standard laboratory conditions for the experiment. Institutional animal ethics committee approval was obtained. All experiments were conducted according to the guidelines laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Eighteen rats were divided into three groups of six each. Group 1 (Control) received Normal Saline, Group 2 received lamotrigine 50 mg/kg and Group 3 received lamotrigine 100 mg/kg. All drugs/vehicles were administered once daily orally for 3 weeks starting from 3rd postnatal week to 6th postnatal week. Study parameters evaluated cognitive function using the Condition avoidance test and Hebb-William Maze. The Forced Swim Test was used as a model for learned helplessness behavior.

Results
In the conditioned avoidance test, there was no significant difference in the retention trial between the three groups. In the Hebb-William maze too there was no significant difference in the time taken to reach the reward chamber between the three groups. Also, there was no difference in the duration of immobility in the Forced Swim test between the three groups.

Conclusion
Lamotrigine did not adversely affect cognition and behavior in the relatively high doses used in juvenile rats. This demonstrates that lamotrigine may safely be used even in children without any effect on cognition and behavior.
Phenobarbital pharmacokinetics change in critically brain-injured patients, the story of converting a long-acting drug to a short-acting one

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Introduction
Phenobarbital, a member of the barbiturate family, with a strong and old history has revolutionized the treatment of epilepsy. It continues to be one of the potential treatment options because of neuroprotective and anti-oxidant properties and beneficial clinical effects through the effect on the GABAA receptor and non-NMDA receptors even at low doses. Physiological changes can significantly alter the pharmacokinetics of prescription medications in critically ill patients.

The aim of this study was to evaluate the pharmacokinetic parameters of intravenous (IV) phenobarbital in critically ill patients with brain injury admitted to the intensive care unit (ICU).

Materials & Methods
Seventeen Patients with severe traumatic or non-traumatic brain injury at high risk of seizure were included and monitored for 7 days. All patients initially received a loading dose of 15-20 mg/kg of total body weight through an IV infusion, and the maintenance dose of 2 mg/kg every 8 hours after 12 hours. Multiple blood samples were obtained on the first and fourth day of study at 1, 2, 5, 8, and 10 hours after the end of infusion. Serum concentrations of phenobarbital were measured by high-pressure liquid chromatography (HPLC) with a UV detector. Pharmacokinetic parameters were calculated based on the one-compartmental model.

Results
According to our preliminary results, the average of phenobarbital half-life in brain-injured population is about 1.67±0.51 day on the first day of the study (mostly first 72 hours of admission to ICU) whereas this parameter is about 4 days in healthy adults and geriatrics population. Based on the primary evaluation, this significant decreasing of half-life is related to increases in clearance of the drug (16.4±6.15 ml/kg/h) which is almost 4 times comparing to healthy individuals. Considering therapeutic range of 20 to 40 mg/L as the therapeutic goal of phenobarbital therapy, most patients experienced sub-therapeutic levels.

Conclusion
Phenobarbital pharmacokinetic parameters change remarkably in brain-injured patients. It is expected that clearance of phenobarbital, known as a long-acting barbiturate increases significantly so the half-life will be decreased and this emphasizes on the higher initial doses and the need for individualized dosing to achieve therapeutic goals in critically brain-injured patients.
The protective effects of Dexmedetomidine on the neurological scores, brain edema and brain -blood barrier after severe traumatic brain injury in male rats

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Introduction

Dexmedetomidine DEX is known as a α2-adrenergic receptor agonist. It is used as a short-acting analgesic drug. In this study, we investigated the effects of neural protection of the DEX after induction of cerebral inflammation in rats

Materials & Methods

Materials and methods: The male Albino wistar rats received different doses of DEX (15, 30, 60 mg/kg, i.p.). All rats were intubated before TBI. In the TBI groups, diffuse TBI was induced by Marmarou method using a TBI induction device. The severe TBI was induced using a weight 300 gr. In the sham groups, all stages of induction of TBI were performed except dropping weight on the head. The disruption of Blood brain- barrier (BBB) was evaluated 6 h post- TBI. The neurologic score( VCS ) and brain water content, the beam-walk –balance task (WB) were determined before trauma, on trauma time(D0), and 1 day(D1) and 2 Day (D2) and 3 Day (D3) After TBI. after 72 hour CSF samples are collected from cisterna magna and then analysis mmp9 in CSF with Elisa assay.

Results

Our results showed that traumatic brain injury led to significant brain edema and disrupt of blood brain- barrier and neurological defect and vestibular-motor dysfunction in the rat brain and increase mmp9 in CSF serum. DEX (15,30mg/kg) could attenuated brain edema, improved BBB, vestibular-motor dysfunction and decreased mmp9 in compare with TBI control group (P&lt;0.001). in 30mg/kg dose results were better than 15mg/kg. Dex didn’t have neuroprotective effect in 60mg/kg dose.

Conclusion

These findings showed that DEX has a prominent role in TBI outcome’s and perhaps protect neurons through modulating inflammatory and antioxidant pathways By inhibition of increasing intracellular calcium and decreasing mmp9 factor. By adding α2-adrenergic antagonist, neuroprotective effect of Dex has been disappeared. it indicates that neuroprotective effect of DEX is through α2-adrenergic receptor.we found that in higher dosage we came across a different respond from DEX, that can cause reduction in producing cortisol.the second reason is that the higher dosage can effect the α1-adrenergic receptor.
Efficacy of Rasagiline as an adjunct in patients with long term treated Parkinson’s disease: A Meta-analysis

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Introduction
Parkinson’s disease is a common, progressively disabling, neurodegenerative disorder. Motor complications especially “on-off” fluctuations and dyskinesias commonly occur in patients with Parkinson’s disease after months to years of dopaminergic therapy. Administration of Rasagiline, a MAO-B inhibitor aims at least controlling motor fluctuations and in facilitating symptom control.

Materials & Methods
A systemic review with the comparative evaluation of efficacy of rasagiline and placebo in patients with Parkinson receiving dopaminergic therapy was evaluated. All the scientific database like clinicaltrials.gov, Pubmed central, NCBI, NIH, Cochrane Library & Googlescholar were used for search. The search was done based on preferred reporting system for meta-analysis and systematic review (PRISMA) guideline. Primary outcome measure was reduction in MOTOR ON time of Unified Parkinson’s disease rating scale (UPDRS) from baseline. Secondary outcomes such as change in ADL OFF of UPDRS and total daily off time were also measured. Direct comparison between active drug and placebo was done using fixed and random effect model and (standard mean deviation) SMD was calculated. RevMan®Version5.3 were used for analysis. P-value less than 0.05 was considered significant.

Results
Data were synthesized from six randomized controlled trials. These placebo controlled trials compared rasagiline with placebo. The primary outcome of UPDRS MOTOR ON (total participants of rasagiline - 863 and that of placebo - 886) has SMD 3.080 and 95% CI is 0.260 to 1.173 and p-value in random effect is 0.002 and in Fixed effect < 0.001 which is significant in both model. The secondary outcome of UPDRS ADL OFF (total participants of rasagiline - 863 and that of placebo - 886) has SMD 2.213 and 95% CI is 0.106 to 1.755. p-value in random effect is 0.027 and in Fixed effect < 0.001 which is significant in both model. Total daily off time has p value less than 0.05 in both random and fixed effect which is considered as significant.

Conclusion
In chronically-treated patients with Parkinson’s disease and motor fluctuations, adjunct rasagiline 1 mg/day statistically reduced the motor fluctuations, and improved daily function and overall well being as compared to placebo.
Public Health

Chair
Sander K.R. van Zon PhD

Presenters
Aung, Dr. (Pyae Linn)
Carter, S.E. (Sarah)
Chan, SK (Sik Kwan)
Gannu, AG (Abhishek)
Kangwerema, A (Allan)
Riyaz, R. (Rizana)
Regular health education through mass media announcements by loudspeakers about malaria care: prevention and practice among people living in a malaria endemic area of Banmauk township, Sagaing region, Myanmar

Aung, Dr. (Pyae Linn)1, Pumphaibool, Tepanata2, Kyaw, Myat Phone1

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Introduction
Various approaches towards community awareness-raising interventions have been delivered through a variety of channels, but evidence for the effect of these practices has been minimal. This study aimed to determine the effectiveness of announcements made through loudspeakers regarding malaria care and prevention practices among people living in the malaria endemic villages of Banmauk Township, Sagaing Region, Myanmar.

Materials & Methods
Four villages among the most malaria-burdened areas were randomly chosen: two villages were assigned as the intervention group and another two as a control. Before the peak season of malaria (June 2018), a baseline study was conducted. The announcement was regularly repeated at 7:00pm every other day using local messages that were conveyed through loudspeakers. A six-month follow-up survey was carried out in both groups using the same questionnaire to compare them against the baseline results. Descriptive statistics, chi-square, and the t-test for addressing statistical differences were determined.

Results
Among a total of 270 respondents with similar socio-economic characteristics, the baseline knowledge, attitude and practice mean scores were not found to be significantly different between intervention and control groups. After six months’ post intervention, improvements in scores were observed at p-value<0.001 in both groups, but the increase in score was much greater in the intervention group. The declining trend of malaria was also noticed as an impact. In addition, more than 75% of people showed positive opinions of the intervention.

Conclusion
The intervention was found to be effective, as shown by the significant improvement in scores relating to prevention and care-seeking practices for malaria in the targeted community. An expansion of study areas and long-term follow-up measures will be encouraged in addition to the maintenance of sustainability.
Blurring research-care boundaries: mining professional perspectives on organoid biobanking

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Introduction
With increased excitement surrounding organoid technology, it is critical to explore optimal ethics and governance models for organoid biobanking. This is especially relevant for cystic fibrosis (CF), where organoids are being utilized in the European-wide HIT-CF drug screening initiative. Using parallel research ethics, or ethical research conducted concurrently with scientific advancement, this study aimed to assess the needs and perspectives of organoid experts as a first step in providing governance recommendations for organoid biobanking. While previous qualitative research into biobanking perspectives has been conducted, this study specifically explores organoids as a unique precision medicine tool and considers their distinct characteristics from other tissues.

Materials & Methods
10 English-speaking and 11 Dutch-speaking interviews were conducted, with questions semi-structured based on previous literature. Interviewees had commercial, academic, or medical expertise, and came from 6 different countries. Themes were identified using qualitative thematic analysis and coded in NVivo software.

Results
Four major themes were identified: 1) the critical role of informed consent; 2) contradictions surrounding organoid ownership; 3) privacy tensions; and 4) further defining researcher duties in precision medicine. Within these themes, respondents were overall supportive of broad consent for practical reasons, but noted the importance of ethical oversight committees in balancing stakeholder interests and maintaining public trust. While ownership claims were often contradictory, many agreed that donors should maintain withdrawal rights. Significant anxieties were also present about the blurred research-care boundary in precision medicine, where researcher duties to patients remain unclear. Most advocated to further define researcher duties to report incidental findings in the consent form; some respondents, however, struggled with reporting findings due to privacy concerns.

Conclusion
Professional stakeholders differentially prioritized ethical duties and practical considerations in issues of consent, privacy, ownership, and researcher duties. Based on these results, it may be advantageous to strike a balance between practical and moral concerns in both governing organoid biobanking and further defining the elusive research-care boundary in precision medicine.
A 10-year Territory-wide Review of Palliative Care Service for Hong Kong Cancer Patients: Implications for Future Development

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Introduction
In a view of sizable cancer patient population, which was expanding due to aging of society and ever-improving cancer treatment, palliative care (PC) needs are growing. This study was the first territory-wide assessment in Hong Kong to assess the PC service coverage in advanced cancer patients in the past decade. Healthcare resources utilization and various PC outcome indexes were reviewed to evaluate the efficacy of PC service provision. Predictors of PC service gap were analyzed which would help future service planning.

Materials & Methods
Based on Hong Kong Hospital Authority’s electronic patient record system, cancer deaths of all 43 public hospitals were screened. Randomly selected 2,800 cancer deaths from 4 time points (2006, 2009, 2012, 2015) formed a representative cohort. Individual patient records were thoroughly reviewed to analyze PC coverage, outcomes and healthcare resources utilization.

Results
In the decade 2006 to 2015, PC coverage improved steadily from 55.4% to 68.9% (P<0.001). For duration of PC provision, median was stable at 21-22 days before death for in-patient PC. For out-patient PC, the median time improved slightly from 53 days in 2006 to 70-96 days in subsequent years. Such duration was similar to internationally reported standard –21 days for hospitalized patients and 90 days for out-patients. PC provision was associated with improved end-of-life care outcomes including more prescription of strong opioids, fewer CPR, fewer ICU admissions, less futile chemotherapy usage in the end-of-life period (all P<0.001). Patients receiving PC service had more clinic visits (6.2 v. 4.9 times, P<0.001), similar AED visits (2.6 v. 2.3 times, P<0.01) and more hospital stay in the last 6 months of life (41 v. 28 days, P<0.001). Multivariable Cox model identified factors associated with lower PC coverage: male (HR 0.787, 95%CI 0.652-0.95, P=0.013), younger patients, (HR 0.628, 95%CI 0.459-0.858, P=0.003), surgical cancers (HR 0.736, 95%CI 0.612-0.887, P=0.001) and rapid deterioration (HR 0.74, 95%CI 0.616-0.889, P=0.001).

Conclusion
There was concrete achievement in PC service in the past decade. However, the current PC system heavily relied on hospital resources. Further works are needed to identify patients whom we failed to help, and to strengthen community hospice care and build up quality monitoring systems.
CHRONOBIOLOGICAL EFFECTS OF BLUE LIGHT: A COMPARATIVE STUDY TO ASSESS THE IMPACT OF TWO TYPES OF BLUE LIGHT FILTERS

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Introduction
There is a steep increase in the use of personal electronics, these are sources of blue light. Our over-exposure to this is leading to disruption of the normal circadian rhythm or the sleep-wake cycle. Several methods are being introduced for screening blue light. These blue light filters can be classified into two types one which cuts off the light at the source and the other which screens at the eye level.

The objective of this study was to assess the impact of blue light on sleep cycle and also compare the effectiveness of the filters to find the best way to screen blue light from its sources.

Materials & Methods
Students attending college have been chosen for the study, they are most exposed to blue light among all age groups hence they have been selected for the study. Their sleep pattern was tracked for three consecutive days under different conditions, using a sleep tracker wristband. A pretested questionnaire was provided which had questions related to their cognitive abilities. On the first day, no precaution was taken to prevent exposure to blue light, on the second day blue light screened at source itself and on the third day blue light was filtered at eye level. The duration of deep sleep, light sleep and total sleep were tracked by the band and data was fed into an application later on. The mean ratio of deep sleep and total sleep of all the 1200 students for three consecutive days was calculated and then compared by Bonferroni “t” test.

Results
The mean ratio of deep sleep on the three consecutive days were (0.294± .071), (0.328± .067) and (0.309± .066). When compared with day 1, there’s a significant change in the ratio on day 2 (p=0.036) as well as day 3 (p=0.048). But then it’s more significant in comparison to day 2 than day 3.

Conclusion
The results validate the severe effect blue light has on the sleep cycle, also provides evidence that screening of blue light at the level of source is better hence people frequently using gadgets should utilize the screening methods to reduce its influence on sleep cycle.
POST-TREATMENT RELAPSE TO SEVERE ACUTE MALNUTRITION AND ASSOCIATED FACTORS IN UNDER-FIVE CHILDREN AT TWO HEALTH FACILITIES, BLANTYRE, MALAWI: A RETROSPECTIVE STUDY.

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Introduction
Severe acute malnutrition (SAM) remains major problem in Africa. Evidence suggests that children who are successfully treated for acute malnutrition relapse back to acute malnutrition or develop other adverse outcome. Although there is an increase in the number of children being treated for SAM, comprehensive information on the follow up outcomes of children who recover from SAM is often not available. This study aimed at determining rates of post-treatment relapse to severe acute malnutrition and associated factors in children aged 6 to 59 months at Queen Elizabeth Central Hospital (QECH) and Ndirande Health Centre in Blantyre, Malawi.

Materials & Methods
This was a retrospective study. We reviewed medical records of 170 under-five children who were admitted and treated for severe acute malnutrition in outpatient therapeutic program (OTP) between May 2017 to October 2018. Chi-square test and logistic regression analysis were performed to identify factors that were associated with relapse. The results were regarded statistically significant at p-value of < 0.05.

Results
Of 170 children who had complete medical records, 132 (77.6%) were discharged cured, 3(1.8%) died, 11(6.4%) were not cured, 12(7.1%) defaulted and/or transferred out to other centers respectively. Relapse rate among those that were cured was 21.2 % (n= 28). The mean age of those who had relapse was 21.4 months. Among factors associated with relapse, HIV positive children (OR=4.05, p=0.001), child living in the rural area (OR=2.80, p=0.020), and being admitted from Nutrition Rehabilitation Unit (NRU) (OR=3.93, p=0.003) were significantly associated with post-treatment relapse.

Conclusion
This study has demonstrated that post-treatment relapse rate at these two health facilities is high (21.2%). HIV positive status, living in rural area and being admitted into OTP from NRU were significantly associated with high relapse. Routine follow up of children who are discharged from SAM treatment program must be enhanced for early identification of children who are at risk of relapse. And further studies are needed to investigate factors associated with relapse.
Telemedicine Based Diabetes Management Protocol and Its Effect On Chronic Kidney Disease Progression

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Introduction
Chronic Kidney Disease (CKD) is a complication of diabetes and results in organ failure, therefore, requiring frequent dialysis and kidney transplant. A telemedicine-based diabetes management program (DTMS®) had been implemented at a comprehensive diabetes care centre in Trivandrum, South India since 1999. During the DTMS® follow-ups by the multidisciplinary diabetes care team, patients are given timely and customised lifestyle and therapeutic advice. It also helps ensure patients’ adherence to medications, self-monitoring of blood glucose (SMBG), home blood pressure monitoring and achievement of major therapeutic targets.

Our aim was to assess the extent to which type 2 diabetes (T2DM) patients diagnosed with CKD show a progression in the condition when followed up via a telemedicine-based protocol as opposed to a conventional treatment approach.

Materials & Methods
T2DM patients with CKD (Stage 1 to 4) with a minimum of 5 years DTMS® follow-up were chosen for the study (DTMS® group, n=25). A Control group included T2DM patients with CKD followed up through conventional treatment plan (Conventional group, n=10), where there was no home blood pressure monitoring, and no telemedicine follow up done. Serum creatinine, serum urea, eGFR, Hb, HbA1c and BP at baseline and from recent visits were retrieved from the EMRs.

Results
Serum creatinine and serum urea levels were significantly elevated (p<0.05) and eGFR was significantly declined (p<0.05) in the conventional group compared to the DTMS® group. Diastolic blood pressure significantly improved (p<0.05) in the DTMS® group. With regard to the CKD stages, as indicated by the eGFR levels, 64% of the patients in the DTMS® group successfully withstood CKD progression, and 24% of the patients achieved a regression in the severity of CKD. In the conventional group, a progression was seen in 60% of the patients, and no regression was noted.

Conclusion
T2DM patients with CKD when followed up through a structured telemedicine protocol, gets benefited in terms of a delay in their disease progression when compared to those following a conventional treatment plan. Telemedicine proves to be a feasible and affordable diabetes management approach while avoiding complications.
Rheumatology and Orthopaedics

Chair
A. L. (Lex) Boerboom MD

Presenters
Chen, Z.M. (Ziming)
Eerden, J (Justine)
Jonatan, A.J. (Andrew)
Kolltveit Skeie, T.K.S (Terje)
Ozcifci, G.O. (Guzin)
Urrego, T (Tomás)
Selective Thromboembolism Prophylaxis after Total Hip Arthroplasty or Total Knee Arthroplasty with Risk Stratification by Thromboelastography in Asian Populations: A Randomized Controlled Trial

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Introduction
Asian populations have a lower rate of high-risk gene mutations in venous thrombosis. Therefore, individual patient risk assessment, rather than a “blanket policy,” is considered the best thromboembolism prophylaxis for Asians. The purpose of this study was to evaluate the effectiveness and safety of selective thromboembolism prophylaxis compared with conventional thromboembolism prophylaxis by risk stratification with thromboelastography (TEG) after joint arthroplasty in Asian populations.

Materials & Methods
Asian patients who underwent hip or knee arthroplasty were randomly divided into a selective anticoagulation group (SAG) and a conventional anticoagulation group (CAG). In the SAG, an anticoagulant was used when TEG indicated hypercoagulability; while in the CAG, an anticoagulant was regularly used until one month after surgery. Data, including patients’ basic characteristics, perioperative clotting index, volume of blood loss, TEG result, postoperative complications, volume of drainage, and blood transfusion, were evaluated.

Results
A total of 197 patients (79 in the SAG and 118 in the CAG), aged 65 ± 12 years on average, were included in the study. There was 1 case of deep vein thrombosis (DVT) in the SAG and 2 cases of DVT in the CAG, but there was no significant difference between the two groups. Hidden blood loss in the SAG was 707.4 ± 539.8 ml and hidden blood loss in the CAG was 617 ± 565.0 ml, respectively (P > 0.05). No significant difference was observed in perioperative blood loss between the SAG and the CAG (1024.9 ± 597.9 ml and 1139.3 ± 620.9 ml, respectively). Volume of blood transfusion was 92.4 ± 270.2 ml in the SAG and 224.6 ± 416.3 ml in the CAG, respectively, while rate of transfusion was 13.9% in the SAG and 33.9% in the CAG, respectively, which were significantly different between the two groups (p < 0.05).

Conclusion
In Asian patients who underwent hip or knee arthroplasty, the efficacy of selective anticoagulation was comparable to that of conventional anticoagulation. Furthermore, blood transfusion volume and rate of transfusion were low after using selective anticoagulation. This suggests that the safety of selective anticoagulant prophylaxis was superior to that of conventional anticoagulant prophylaxis.
3D visualisation of collagen fibre orientation at the Achilles tendon-bone junction

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Introduction
A good understanding of collagen fibre orientation at the tendon-bone junction (enthesis) is essential for improvement of tendon rupture repair surgery. Currently, destructive histological analysis is necessary to visualise collagen orientation at the enthesis. This study aims to optimise and compare contrast-enhancing staining protocols for microCT scanning to achieve non-destructive 3D visualisation of the collagen fibre orientation in the human Achilles tendon enthesis.

Materials & Methods
Samples of human Achilles tendon and enthesis were acquired from cadaveric specimens. Four different stains were used: sodium tungstate (Na2WO4), Lugol’s solution (I2KI) and two different concentrations of phosphotungstic acid (PTA), 2.5% and 1%, in methanol. X-ray scans were taken at 24-hr, 3-days and 7-days. An additional scan was performed after destaining the samples for 24-hr using either water, ethanol or phosphate buffered saline. After optimising the staining protocol samples were scanned with microCT to obtain 3D images of the Achilles tendon enthesis.

Results
Both PTA concentrations showed staining of the collagen fibres. 2.5% PTA resulted in an optimal diffused staining after 24 hours and overstaining at 3 and 7 days. 1% PTA lead to pronounced staining on the edges without diffusing well into the sample. Sodium tungstate weakly stained collagen and staining increased slightly over time, whereas Lugol’s solution did not improve the visibility of collagen fibres, even after 7 days. Destaining protocols showed a decrease in staining in all samples.

Conclusion
2.5% PTA is very effective as a contrast enhancing stain for 3D visualisation of collagen fibres in the human Achilles tendon enthesis. Destaining of the tissue is possible and allows subsequent histological analysis of the same samples.
Apolipoprotein B-100 and E Attenuates Acute Inflammatory Response of Monosodium Urate Crystal-Induced Gouty Arthritis Rats

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Introduction
Gouty arthritis is a common joint disease. If gout continue to chronic state it can cause irreversible joint damage. Apolipoprotein B-100 (ApoB-100) and Apolipoprotein E (ApoE) possess immunomodulatory effect in acute inflammatory response by altering both cellular and humoral immunity through various mechanisms. Thus, our study was aimed to investigate the effects of ApoB-100 and ApoE administration toward activation of acute inflammatory response of MSU crystal induced gouty arthritis rats.

Materials & Methods
We conduct an in vivo true experimental research with randomized post-test only controlled group design in 18-20 weeks old male Wistar strain Rattus norvegicus. Acute gouty arthritis was induced using 0.25mg/50μl monosodium urate crystal injection in the right genu. Forty rats were divided into eight groups, with group I and II served as non-treated gouty and gouty controls receiving oral colchicine therapy respectively. Group III, IV, V served as ApoB-100 treatment groups and received three different doses of intra articular ApoB-100 injection (1.25 µg, 2.5 µg, and 3.75 µg ApoB-100 respectively). Group VI, VII, VIII served as Apo E injection treatment groups and received three different doses of intra articular ApoE injection (0.5 µg, 1 µg, and 1.5 µg ApoE respectively). Activation of acute inflammatory response was evaluated by histopathological examination of PMN cells count in synovial tissue of the right genu and analyzing the release of inflammatory mediator by measuring serum TNF-alpha level using ELISA method. We use SPSS 16 for WIndows with confident interval of 95%

Results
Administration of 0.5 µg Apo E resulted in marked reduction of PMN cells count compared to control group (LSD, p=0.000). Analysis of serum TNF-alpha level also shown significant difference between groups (Kruskal Wallis, p=0.021) in Apo E treated groups. Administration of 3.75 µg ApoB showed significant reduction in number of PMN cells compared to control group (LSD, p=0.001). No significant different in serum TNF-alpha level among Apo B treated group compared to control group (Mann-Whitney, p &gt; 0.05).

Conclusion
Intra articular injection of ApoB-100 and ApoE attenuates the inflammatory response within synovium of acute gouty arthritis rats and therefore holds promise as a novel intervention strategy for the treatment of gouty arthritis.
The influence of aging on the insertion of the Achilles tendon: a magnetic resonance study.

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Introduction

Fundamental to the treatment of pathologies in the foot and ankle is a good understanding of the underlying anatomical relationships between the Achilles tendon (AT) and its surrounding structures. Knowledge regarding the correlation between this anatomical variation, age and pathologies may improve prevention and treatment of AT pathologies, as well as improve surgical techniques and reduce the risk of iatrogenic injuries.

This study aimed to determine the variation of the AT insertion point into the calcaneal bone (CB) with respect to age and gender using high quality MRI.

Materials & Methods

Two-hundred and two foot and ankle MRIs were reviewed, and patients were allocated into three age groups: \(\leq 18\), 18-65, and \(>65\) years old. All measurements were obtained on a mid-sagittal scan. The mean values obtained from these measurements were used to assess the relationship between the AT insertion point, gender and age.

Results

Our main findings revealed that the (1) distance between the most inferior point of the CB and the most inferior part of the AT insertion into the CB increases with age, (2) height of the AT insertion into the posterior aspect of the CB decreases with age, and (3) length of the AT insertion into the posterior aspect of the CB decreases with age.

Conclusion

The terminal insertion point of the AT on the CB in younger subjects revealed a more distal insertion, whereas older individuals revealed a more proximal insertion. This data may help to develop novel strategies in the treatment and prophylaxis of AT injuries for people in particular age groups. Anatomical data on the AT insertion is crucial in the development of a computer model of the AT and for biomechanical considerations regarding this tendon.
Can soluble SLAMF7 quantification be used as a diagnostic tool for IgG4-related disease?

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Introduction
IgG4-related disease (IgG4-RD) is a multiorgan, chronic, fibro-inflammatory disorder. Its diagnosis is made by biopsy and measuring serum IgG4 level which is actually not a consistent and robust indicator. Also, it requires the exclusion of a broad variety of differential diagnosis. Although IgG4-RD pathophysiology has not been fully elucidated, it is believed that CD4+ SLAMF7+ cytotoxic T cells in affected tissues drive disease onset. Our aim is to quantify soluble SLAMF7+(Signaling lymphocytic activation molecule family member 7) concentration in healthy control and patient serum to assess whether it correlates with the disease state.

Materials & Methods
Soluble SLAMF7 concentration is measured in human plasma samples from 38 healthy donors, 40 untreated systemic sclerosis patients, 40 untreated idiopathic pulmonary fibrosis patients and 42 untreated IgG4-related disease patients by using ELISA kits for SLAMF7. Next step, we measured IgG4 concentration in serum and compared results with SLAMF7 concentration. All p-values were determined by Mann-Whitney test. Our patient cohort is taken from Massachusetts General Hospital.

Results
SLAMF7 concentration is the highest in IgG4-related disease group compared to the other three groups. Systemic sclerosis (SS) and healthy donor groups (HD) have the lowest results in a close range. P value = 0.002 between IgG4-related disease and and healthy donors. Serum IgG4 levels and soluble SLAMF7 levels also correlate (p value = 0.0013 and r value = 0.55) (p value = 0.23 between HD-SS; p = 0.0001 between HD-IPF).

Conclusion
Soluble SLAMF7 concentration is the highest in IgG4-related disease among the four groups. Hence, serum SLAMF7 quantification can be used as a diagnostic tool for IgG4-related disease. For future directions, we are going to investigate whether this concentration correlates with CD4+ SLAMF7+ T cell number to study the relationship between the level of soluble SLAMF7, immune cell activity, and IgG4-RD progression.
Urinary Biomarkers in Lupus Nephritis – A model of involvement of a medical student in a research project

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Introduction
Lupus nephritis (LN) can present in up to 50% of patients with systemic lupus erythematosus (SLE), and it can complicate disease course ending in end-stage renal disease. A renal biopsy is usually required for classification and further treatment. Although it is reliable, a biopsy is a procedure that carries various risks such as bleeding or infection. Therefore, urinary biomarkers have emerged as a candidate non-invasive diagnostic and prognosis method.

Materials & Methods
We included patients with systemic lupus erythematosus (SLE) according to ACR criteria. LN diagnosis was based on ACR criteria. Urinary levels of transferrin (uTF), ceruloplasmin (uCP), VCAM-1, TWEAK, monocyte chemoattractant protein-1 (uMCP-1), neutrophil gelatinase-associated lipocalin (uNGAL) and alpha-1-acid glycoprotein were measured by ELISA commercial kits. Also, histologic features for activity and chronicity indices were analyzed according to Austin’s Index. A Student’s T-test was used for variables with a normal distribution; and for those variables whose data had a non-normal distribution, the Mann-Whitney U test was used. On the other hand, receiver operator curves (ROC) were constructed.

Results
LN was documented in 64.4% of patients, from a total of 120. CP concentrations were significantly higher on those patients with a higher activity index in Austin’s index (498,924 ± 481,717 vs 222,621 ± 221,933 ng/ml; p&lt;0.05). MCP-1 concentrations were significantly higher in patients with a higher chronicity index (4172,050 ± 5881,132 vs 1480,787 ± 969,923 pg/ml; p&lt;0.05). ROC curves underscored good diagnostic values of uNGAL (area under the curve (AUC) 0.70, 95% confidence interval (CI) (0.61–0.80), uMCP-1 (AUC 0.73, 95% CI 0.63–0.82), uCP (AUC 0.84, IC 95%: 0.76-0.92) and uTF (AUC 0.86, IC 95%: 0.79-0.93) for LN diagnosis.

Conclusion
Urinary biomarkers seem a plausible non-invasive method for LN diagnosis. Furthermore, they could aid to differentiate active and chronic lesions.
Poster session 1
Cardiology

Chair
Herman H.W. Sillje MD PhD

Presenters
Croon, S.I. (Sophie)
Dani, A.S. (Avichal)
Gebreyohannes, E.A.G. (Eyob)
Kiganda, R (Raymond Sembatya)
Prasetyadi, Y.L.P (Yosafat)
Smit, L.
vан Blokland, I.V. (Irene)
Surgical Treatment and Long-Term Outcome of Aortic Valve Endocarditis with Periannular Abscess


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2 Catharina Ziekenhuis Eindhoven, Department of Cardiothoracic Surgery, Eindhoven, Netherlands

Introduction
Aortic valve endocarditis is occasionally complicated with periannular spreading of the infection and abscess formation, leading to a more aggressive course of the disease and life-threatening complications. We investigated the long-term outcomes of patients having this complication, which was surgically managed with annular reconstruction and aortic valve replacement.

Materials & Methods
Between 1998 and 2018, 69 patients from the Catharina Ziekenhuis Eindhoven were identified with aortic valve endocarditis complicated by a periannular abscess. Patients were all treated with debridement of the infected tissue, gentamicin filling of the abscess cavities, annulus reconstruction with bovine pericardium and valve replacement. Long-term follow-up was performed to detect the rate of recurrence of endocarditis, aortic valve reoperation and survival.

Results
Mean age was 58 ± 15 years, 81% of patients were male, and the infected valve was native in 51% of all patients. Five- and 10-year survival was 69.4 ± 12.0% and 55.7 ± 14.3%, respectively. Freedom from recurrent endocarditis at 10 years was 83.5 ± 13.3%. A significantly negative effect on survival time was found for prosthetic endocarditis (χ²(1)=5.472, p=0.019), having a tricuspid aortic valve (χ²(1)=5.083, p=0.024), receiving a biological valve (χ²(1)=7.049, p=0.008), and suffering from diabetes mellitus (χ²(1)=4.878, p=0.027), peripheral vascular disease (χ²(1)=5.276, p=0.022), or prior transient ischemic attack (χ²(1)=10.714, p=0.001).

Conclusion
Endocarditis with annular abscess remains associated with high morbidity and mortality and aggressive treatment of the infected tissue and abscess cavities is crucial. Compared with the available literature, long-term outcome of annular reconstruction in this series is comparable with aortic root replacement.
Evaluation of Prescription Pattern, Health-Related Quality of Life and Adherence to Standard Treatment Guidelines in Patients who have undergone Percutaneous Coronary Intervention.


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Introduction
Advances in medical therapy have significantly improved the prognosis of patients with CAD and PCI is one of the them. ACCF/AHA/SCAI Guidelines for PCI aim to reduce cardiovascular disease mortality by encouraging GBMT. Prescription analyzing studies will help the policy makers to prioritize and promote the rational use of medicines. QoL assessment would help to assess the functional capacity of patients, effects of drugs and cardiac rehabilitation.

Materials & Methods
It is a prospective, longitudinal study where prescriptions were evaluated for adherence to 2011 ACCF/AHA/SCAI Guidelines for PCI. Adherence was adjudged by the application of Class of Recommendation (COR) and Level of Evidence (LOE) as the criteria. The QoL was assessed thrice i.e. at the end of 1 week, 1 month and 3 months respectively by using 12-question long DASI questionnaire. Pearson correlation coefficient was used to find correlation between different variables and QoL. Unpaired t-test was used to compare the distribution of variables such as age, no. of prescribed drugs and the assessment of QoL on three follow-ups of all patients suffering from different ACS types. p value ≤0.05 was taken significant.

Results
Total 81 patients were included with about 9 drugs on average being prescribed to each. Antiplatelet drugs and statins were prescribed to all; followed by β-blockers(92.6%), potassium-channel openers(35.8%), anti-coagulants(28.4%), diuretics(28.4%) and ACE inhibitors(26.2%). The adherence to guidelines is 89.75%. Triple-antiplatelet therapy was followed instead of recommended dual-antiplatelet therapy (DAPT). The mean ± SD for QoL at first week, first month and third month was 6.4617 ± 2.08330, 26.3932 ± 14.66368 and 40.9222 ± 11.48307 respectively. There was a negative correlation between age & DASI score on 2nd (p=0.037) and 3rd follow-up (p=0.000). On comparing DASI score across different groups on 1st follow-up, UA v/s NSTEMI and UA v/s STEMI was found significant (p=0.001). On 2nd follow-up, UA v/s STEMI was found significant (p=0.0374).

Conclusion
Antiplatelet drugs and statins were prescribed indiscriminately and the prescriptions were highly adherent to the guidelines. At the end of third month, irrespective of the diagnosis, all groups (UA/STEMI/NSTEMI) achieved similar physical activity status with age being the key factor influencing the DASI score.
Poor outcomes associated with antithrombotic undertreatment in patients with atrial fibrillation attending Gondar University Hospital: a retrospective cohort study

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Introduction
Atrial fibrillation (AF) is a major risk factor for stroke as it increases the incidence of stroke nearly fivefold. Antithrombotic treatment is recommended for the prevention of stroke in AF patients. However, majorly due to fear of risk of bleeding, adherence to recommendations is not observed. The aim of this study was to investigate the impact of antithrombotic undertreatment, on ischemic stroke and/or all-cause mortality in patients with AF.

Materials & Methods
A retrospective cohort study was conducted from January 7, 2017 to April 30 2017 using medical records of patients with AF attending Gondar University Hospital (GUH) between November 2012 and September 2016. Patients receiving appropriate antithrombotic management and those on undertreatment, were followed for development of ischemic stroke and/or all-cause mortality. Kaplan-Meier and a log-rank test was used to plot the survival analysis curve. Cox regression was used to determine the predictors of guideline-adherent antithrombotic therapy.

Results
The final analysis included 159 AF patients with a median age of 60 years. Of these, nearly two third (64.78%) of patients were receiving undertreatment for antithrombotic medications. Upon multivariate analysis, history of ischemic stroke/transient ischemic attack (TIA) was associated with lower incidence of antithrombotic undertreatment. A significant increase (HR: 8.194, 95% CI: 2.911–23.066) in the incidence of ischemic stroke and/or all-cause mortality was observed in patients with undertreatment. Up-on multivariate analysis, only increased age was associated with a statistically significant increase incidence of ischemic stroke and/or all-cause mortality, while only history of ischemic stroke/TIA was associated with a decrease in the risk of ischemic stroke and/or all-cause mortality.

Conclusion
Adherence to antithrombotic guideline recommendations was found to be crucial in reducing the incidence of ischemic stroke and/or all-cause mortality in patients with AF without increasing the risk of bleeding. However, undertreatment to antithrombotic medications was found to be high (64.78%) and was associated with poorer outcomes in terms of ischemic stroke and/or all-cause mortality.
Active hydraulic ventricular support drug delivery system

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Introduction

ASD is an initiative hydraulic attachment support and drug delivery system abbreviated as Active hydraulic ventricular support drug delivery system. It is a net cover having a heart-shaped configuration. It consists of hollow flexible tubules, which are intercommunicated with each other and covering both the ventricles. It’s a multi functional therapeutic platform intended and designed for real time heart monitoring, physical support to dilated ventricles, therapeutic agent delivery to the heart muscles and bridging the gaps of the available single therapeutic platforms.

Materials & Methods

ASD is composed of a net cover having hollow flexible tubules, which are intercommunicated with each other. It covers both ventricles and has two tubules which are channeled outside and connected with a desired medical equipment. A 3D computer model of ASD was developed by using Rhinoceros 5.0 software. Then a blue wax model of was printed using 3D printing technology. The blue wax model was then immersed in liquid silicon and was dried in an oven at 50˚C. The was then melted and a pure silicon built ASD model was obtained. Leak testing was then performed to ensure any leakage or blockage in the ASD tubules. This was then followed by Laser production of the dosing micro pores and attachment of external and internal connecting tubes/pipelines. It was then placed surgically into a heart failure animal model

Results

Animal studies have been established and the results demonstrated that the treatment of HF, through delivery of Salvia miltiorrhiza by ASD had better curative effect, treatment of arrhythmia with lidocaine via ASD had a higher survival rate as compared to the control groups, and treatment of myocardial infarction with bone marrow stem cells by ASD can reduce ventricular fibrosis and may inhibit ventricular remodeling.

Conclusion

ASD device is structurally composed of silicon a non-immunologic and bio-compatible material not only improved the efficiency of the drug, reduced the side effects but also provides promising restraint therapy as compared with previous standard restraint therapies and improves cardiac function and reverses ventricular remodeling.
Coronary Heart Disease Risk factors and in-hospital mortality among patients with ST-Elevation Myocardial Infarct: Analysis of 2-years cohort registry in National Cardiovascular Center Harapan Kita

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Introduction
The highest numbers of mortality among patients with ST-Elevation Myocardium Infarct (STEMI) become the main concern of risk factor modification as the primary intervention. In Indonesia, little is known about the impact of each risk factors on in-hospital mortality. Therefore, this study aims to investigate the implication of each coronary heart disease risk factors on in-hospital mortality among patients with STEMI.

Materials & Methods
Retrospective analysis study was conducted on the data obtained from National Cardiovascular Center cohort registry on 2695 consecutive STEMI patients who were admitted between 2014 and 2016. The association between variables was analyzed using a bivariate method and logistic regression analysis.

Results
The overall in-hospital mortality rate exceeds 9%. Based on bivariate analysis, variables as age >65 years (OR=2.28; 95%CI: 1.66-3.14) and diabetes mellitus (OR=1.81; 95%CI: 1.36-2.40) was independently associated with in-hospital mortality. These factors associated with several comorbidities which enhancing death. Some other factors like dyslipidemia, family history, gender, and hypertension have small implication. This study finds out that smoking history is a protective factor for in-hospital mortality rate (OR=0.6; 95%CI: 0.46-0.80), a phenomenon called “smoker’s paradox”. This paradox might be caused by a different response between smoker and non-smoker in pharmacological therapy of anti-platelet. Age >65 years is the most significant risk factor based on logistic regression analysis, followed by diabetes mellitus. The presence of these factors in concordance will have three-fold increase in in-hospital mortality among patient with STEMI.

Conclusion
Diabetes mellitus as the second most significant risk factor must become the focus of risk factor modification among STEMI patients considering age as the most influential factor is unmodifiable. Also, analysis of both risk factors and clinical intervention should be conducted to obtain a better accuracy result for studying in-hospital mortality rate predictor.
Introduction
Recent studies have shown that patients with heart failure have an increased risk of developing cancer, compared to patients without heart failure. We believe this is partly caused by the shared risk factors between cancer and cardiovascular (CV) diseases. Therefore, we aimed to investigate the associations between HF biomarkers and risk factors and new-onset cancer in the general population.

Materials & Methods
For this research, the PREVEND (Prevention of Renal and Vascular End-stage Disease) cohort was used. The median follow-up of this cohort was 17.6 years. We evaluated the association between HF biomarkers and risk factors with new-onset cancer using cox regression, corrected for age, sex, smoking and BMI. Next to this, the predictive utility of biomarkers were evaluated in high and low CV risk groups, based on diabetes, hypertension and hypercholesterolemia. High-risk was defined as having ≥ 2 of the aforementioned conditions.

Results
The PREVEND cohort consisted of 8311 participants of which 1171 participants developed new-onset cancer (14.2%), excluding skin cancer. The subjects that develop cancer were often male, older, and had more comorbidities, including decreased renal function. Out of the risk factors tested, age, smoking and waist-hip ratio were significantly associated with an increased risk of developing new-onset cancer in a multivariable-adjusted model; P-value < 0.05. For the HF biomarkers, Cystatin-C, UAE and hs-CRP were associated with an increased risk of developing new-onset cancer. Cystatin-C showed the highest risk for new-onset cancer (HR: 1.22 ; 95% CI:1.03–1.45). UAE was associated with an increased hazard-ratio in the high-risk population (HR 1.14 ; 95% CI: 1.06 – 1.23).

Conclusion
Age, smoking and waist-hip ratio are CV risk factors associated with an increased risk of new-onset cancer. The CV biomarkers associated with an increased risk of new-onset cancer were Cystatin-C, UAE and hs-CRP, with an increased risk for UAE in the high-risk population. With this, we have shown that an increase in inflammation and kidney markers lead to an increased risk of developing cancer.
Increased epicardial fat in patients with coronary artery disease

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Introduction
Adipose tissue located around the heart, also known as epicardial fat, may play a key role in the inflammatory mechanism underlying cardiovascular disease. It is hypothesized that epicardial fat secretes inflammatory cytokines promoting a systemic state of inflammation due to the lack of an anatomical border between epicardial fat and the myocardium and coronary arteries. However, it is unknown whether epicardial fat is increased in individuals with cardiovascular disease. We therefore investigated epicardial fat in individuals with coronary artery disease (CAD), myocardial infarction (MI) and healthy controls.

Materials & Methods
A total of 60 participants were selected from the UK Biobank cohort, who were matched on age, sex and body mass index (20 healthy controls, 20 CAD, 20 MI), with equal amounts of men and women. All participants had undergone cardiac magnetic resonance imaging (CMRi). Epicardial fat was quantified on short-axis CMRi stacks in end-diastolic state using CVI42. Total epicardial volumes were related to inflammatory cell counts using regression analysis. Statistical significance was considered at a level of P=0.05.

Results
Epicardial fat volumes were significantly higher in participants with previous CAD in comparison to the control group (169 mL ± 42.5mL vs. 120 mL ± 30.0mL, P<0.001). Epicardial fat volumes were positively associated with circulating levels of neutrophils and lymphocytes (R=0.42, P=0.048 and R=0.66, P=0.025 respectively).

Conclusion
Epicardial fat was increased in CAD patients compared to controls and MI patients. Furthermore, epicardial fat was associated with inflammatory cells as neutrophils and lymphocytes, suggesting that epicardial fat may contribute to the systemic inflammatory state prior to MI. Studying the exact inflammatory mechanism of epicardial fat, using biopsies of epicardial fat in patients undergoing coronary artery bypass graft (CABG) might be of interest, as this could open up for potential therapeutical targets in cardiovascular disease.
Cell Biology I

Chair
Prof Cor F. Calkhoven MD PhD

Presenters
Berrens, A.C. (Anne Claire)
Carolina, E.C. (Erica)
Drygina, K. (Ksenia)
Esteban Valdebenito, G.E.V (Gabriel)
Handziuk, Z.. (Zuzanna)
Klepe, A.K. (Adrián)
Mandra, E.V. (Ekaterina)
Zhao, X.Y.Z (Xiaoyu)
Stem cells as the main source of pro-inflammatory chemokines in the intestinal epithelium during microbe-epithelial interaction

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Introduction
Inflammatory bowel disease (IBD) is caused by chronic inflammation of the gastrointestinal tract. Up to date the pathogenesis of IBD remains unclear but it is found that a disturbed balance between responsiveness and tolerance to bacterial antigens is involved in the pathogenesis of IBD. Previously, in our main study, the stem cells were identified by single cell sequencing as the main source of inflammatory response and that they become hyporesponsive and hypoproliferative on RNA level after continuous stimulation. The aim was to objectify these results on protein level, focusing on the NFkB-pathway and answering the question why differentiated cells seem to respond less than stem cells upon microbe-epithelial interaction.

Materials & Methods
The use of intestinal organoids provided the possibility of culturing patient-derived tissue from colon, ileum and duodenum, while maintaining all functional and phenotypic characteristics. To mimic a stem cell or differentiated cell environment, the organoids were grown in either expansion medium (EM) or differentiation medium (DM) and were stimulated with bacteria lysate for different periods of time. All organoids were then harvested, embedded in paraffin and stained for the proliferation marker Ki67 and the responsive protein NFkB (p65). By using secondary antibodies with a fluorescent tail images could be made using a confocal microscope.

Results
When quantified, immunohistochemistry showed a significant decrease of proliferation, shown by Ki67, in EM-organoids after continued stimulation (20.26% of positive cells in 0 hours vs. 0.71% in 72 hours p<0.05). NFkB portrayed an increase in translocation to the nucleus, which is a clear marker for activation of the NFkB-pathway, starting at (0.42% of positive nuclei) with its peak at 2 hours of stimulation (68.85%, p<0.0001) and a decrease after 72 hours (13.47%p<0.0005), both in EM- and in a significantly lesser way in DM-organoids (p<0.0002).

Conclusion
These results showed that it is possible to observe and quantify the inflammatory response on protein level and that intestinal stem cells become hypoproliferative and hyporesponsive after 72 hours of continuous stimulation. Furthermore, both EM- and DM-organoids have an active NFkB pathway, which leads us to believe we have deciphered an important part of the question, but there may also be other factors at play.
Extracellular vesicles recover the dysfunctional mesenchymal stem cells derived from type 2 diabetes mellitus patients through AKT and EGR1 signaling

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Introduction
Chronic wound is one of the most common complications in type 2 diabetes mellitus (T2DM). Although stem-cell therapy holds promise to accelerate wound healing, unfortunately earlier studies demonstrated the dysfunction of T2DM-derived stem cells (dAT-MSCs). Recently, extracellular vesicles (EVs) derived from mesenchymal stem cells that contain a cargo of miRNA, mRNA, and proteins showed the ability to be transferred and alter the target cell phenotype. Hence, this study aims to assess EVs potency as an alternative to improve the function of dAT-MSCs before clinical application.

Materials & Methods
Mesenchymal Stem Cells (MSCs) and dAT-MSCs was sorted by FACS and characterized. EVs obtained from the supernatant of MSCs by differential centrifugation method were characterized using western blotting. PKH labelled EVs transfection efficiency was determined using FACS analysis. In vitro scratch assay and in vivo wound-healing model, were performed to compare cells function. Gene expression analysis was identified through PCR and western blot. Data were analyzed using Student t-test after one-way ANOVA analysis of variance by GraphPad Prism5 software.

Results
EVs were successfully transfected to dAT-MSCs (99.8% [SE: 1.1]). EV transfection elevates angiogenesis related gene expressions such as SDF-1, CXCR4, CXCR7 and CCL2 by two-fold that of dAT-MSCs group (n=3, P<0.05) and improve the dAT-MSCs in vitro migration to two folds higher (n=3, P<0.01) and in vivo wound-healing capacity to two folds higher than control group (n=6, P<0.05). The constitutive activation of EGR-1, which is responsible for dAT-MSCs dysfunction, was repressed to 72% after EV transfection (n=12, P<0.05). The impaired AKT signaling in dAT-MSCs was elevated three-fold by the EVs (n=3, P<0.01) through a four-fold downregulation of PTEN expression (n=9, P<0.01).

Conclusion
This study suggests that EVs derived from MSCs have the potential to recover dysfunctional stem-cells derived from patient with diabetes; thus, EVs could be a useful approach to increase the efficacy of dAT-MSCs for chronic wound in diabetes patients.
Human keratinocytes cryopreservation protocol development for live skin equivalents

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Introduction
Living skin equivalents are known as a treatment of burns and trophic ulcers. These patients need to be treated immediately we have to create an optimal cryopreservation protocol for the storage of living skin equivalent cell components. To avoid an animal viral contamination it is necessary to find an optimal serum-free cryopreservation medium.

Materials & Methods
Skin equivalents have been developed from synthetic scaffold (collagen/hyaluronic acid), culture of human keratinocytes and mesenchymal stem cells. We examined different types of serum-free media (DKSFM (Gibco), EpiLife (Gibco), Cnt07 (CellnTec)). Serum substitute Panexin NTA (PAN-Biotech GmbH) was added to the most efficient variant in different concentrations (10%, 15%, 20%) and compared with DMEM/F-12 FBS (10%). Cell suspensions of keratinocytes were freezed at different speeds on the controlled rate freezer Planer 550/16. Cell viability immediately after thawing was measured with trypan blue exclusion test, metabolic activity was evaluated with MTT-test three times. To avoid cell negative selection immunofluorescent analysis was performed with markers of keratinocytes (Cytokeratin 14) and fibroblasts (Vimentin). To determine apoptosis we evaluated Caspase 3 and 9. Statistical analysis was represented using SEM (Excel), one-way ANOVA followed by Fisher’s post hoc test with p<0.05 considered statistically significant (STATISTICA 7.0).

Results
After tests, we have found the most appropriate medium which consisted of DKSFM with 10% Panexin NTA. Cells stored in it showed the highest viability after thawing. We observed growth and proliferation of keratinocytes during one week and showed that after successful thawing only several cell cultures could form confluent cell layer. The most suitable for cell metabolic activity cryopreservation control speed lowering was between 1 and 5 °C/min till -70 °C with transfer of cells to liquid nitrogen. Immunofluorescent analysis confirmed the identity of cells as keratinocytes.

Conclusion
We developed the appropriate cryopreservation protocol for primary culture of human keratinocytes with the convenient serum-free cryomedium which supports metabolic activity of viable keratinocytes and their proliferation. The work was fulfilled for Research Project “Development of technology for manufacturing, storage and application of biomedical cellular products for wound healing” in accordance to grant agreement.
Assembly and activation of gp91phox and p47phox subunits of NADPH oxidase 2 (NOX2) in fetal myotubes from a mice model of gestational obesity.

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Introduction
Maternal obesity affects the homeostasis of different fetal organs with long-term consequences for offspring. The intake of a high-fat diet (HFD) can transmit an excess of fatty acid which may lead to the accumulation of triacylglycerides (TAGs) in lipid droplets in the fetal muscle stimulating the expression of proteins capable of generating lipoperoxidation and thereby damaging intracellular signaling, particularly on the insulin pathway. NADPH oxidase 2 (NOX2) is an enzyme that induce lipoperoxidation in response to the increase of accumulated TAGs in lipid droplets. NOX2 forms an active complex by the assembling of p47phox (sarcolemma subunit) with gp91phox (cytosolic subunit). Therefore, we hypothesize that an excessive transfer of fatty acid to the fetus from obese dams activates NOX2 in fetal muscle stimulating the lipoperoxidation and disrupting the insulin signaling.

Materials & Methods
C57BL/6J female mice were fed with a HFD or control diet for five weeks, mated and maintained with the same diet during gestation. At gestational day 17.5, dams were euthanatized and fetus were collected and weighed. Legs from two fetus of each litter were obtained to isolate and culture myoblasts for 3 days in growing media (DMEM+F12, 10% bovine serum and 2.5% fetal bovine serum) and 3 days in differentiation media (serum free). Gp91phox and p47phox were evaluated by indirect immunofluorescence and the number of lipid droplets by BODIPY 493/503 staining.

Results
Our preliminary data shows that the assembly of gp91phox and p47phox subunits of NOX2 is present in the sarcolemma of fetal myotubes in the offspring of obese dams. Also, a single experiment showed a higher number and size of neutral lipid droplets. More observations will be performed.

Conclusion
The assembly of NOX2 subunits suggests that fetal muscle is susceptible of lipoperoxidation mediated by this enzyme. It seems that gestational obesity can cause accumulation of TAGs in lipid droplets and then activate the NOX2.
The comparison of the cyclins’ influence on epithelial-mesenchymal transition in prostate cancer

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Introduction
Prostate cancer (PC) is the most common cancer in men worldwide with ever-growing death rate. Its progression pathways are connected with the function of androgen receptor (AR). Escalating level of AR intensifies proliferation and allows PC cells to grow in a low androgen environment. Alteration of E-cadherin protein level during epithelial-mesenchymal transition (EMT) plays vital role in PC metastasis. Malignant transformation is accompanied by E- to N-cadherin phenotypic switch, which leads to greater cancer invasiveness as major hallmarks of the EMT via increased expression of vimentin and transcription factors-Snail and Twist, inhibit E-cadherin. There are evidences, that in this whole pathway, for e.g. cyclin D1, regulator of a cell cycle, play an important role by influencing both AR and EMT in PC (Xiaoming Ju et al., Cancer Res. 2014). The aim of this work was to define the exact role of distinct cyclins in EMT and their importance in future treatment.

Materials & Methods
The study was carried out on human prostate cell lines (RWPE, WPMY, LNCaP, PC-3). The expression and activity of cyclins (A2,B1,D1,E1,H), AR, HMG-CoAR, MMPs, E-, N- cadherins, vimentin, Snail, Twist were analyzed at mRNA and protein level using Western Blot and RT-PCR techniques.

Results
All tested cyclins showed the vital influence on expression of EMT markers. Cyclin A2 demonstrated positive correlation with metastasis markers, but negative with EMT markers both in PC-3 and LNCaP line. The expression of Cyclin B1 in PC-3 line showed negative correlation with E-cadherin expression, as well as with AR. Cyclin D1 represented the most noticeable influence on EMT, differently in both androgen-dependent (LNCaP) and androgen-independent (PC-3) cell lines. Cyclins E1 and H higher expressions correlated positively with EMT markers.

Conclusion
This research shows the importance of cyclins’ expression (especially A2, B1 and D1) in EMT in PC cell lines. They also influence AR pathway thus affecting androgen dependency, which raises the possibility for cyclins to be a potential target for siRNA in PC therapy.
Effect of lidocaine on an in vitro blood-brain barrier model: cell biology and biophysical experiments


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Introduction
The negative surface charge of the brain endothelial cell plasma membrane derives from the lipid head groups and the luminal glycocalyx. This negative charge is a significant element of the defence system of the blood-brain barrier (BBB) and regulates the transport of molecules across the BBB. We hypothesized, that lidocaine, a cationic and lipophilic drug, can change the surface charge of brain endothelial cells, therefore the goal of our study was to measure the effects of lidocaine on the BBB for the first time.

Materials & Methods
In this study as in vitro BBB models the hCMEC/D3 human brain endothelial cell line and primary rat brain endothelial cells in co-culture with primary astrocytes and pericytes were used. The concentration and the duration of the lidocaine treatment were optimized by viability tests (MTT, LDH) as well as by real-time cell electronic sensing. The surface charge was quantified by zeta potential measurement. Changes in the barrier function of the brain endothelial cells were examined by transendothelial electric resistance (TEER) and permeability measurement of differently charged fluorescent markers (FITC-dextran, lucifer yellow and rhodamine123). Immunostaining was also performed for junctional proteins.

Results
Lidocaine changed the surface charge of brain endothelial cells to more positive. TEER of brain endothelial cells decreased slightly after a short term lidocaine treatment at a clinically relevant concentration (10 μM). Lidocaine did not alter the flux of the neutral FITC-dextran and the negatively charged lucifer yellow, but decreased the permeability of the positively charged rhodamine123. Since rhodamine is also an efflux pump ligand, we also confirmed that lidocaine does not act as a P-glycoprotein efflux pump blocker.

Conclusion
Lidocaine changed the surface charge of brain endothelial cells and slightly influenced the barrier integrity of the BBB. This study helps to understand the biophysical background of lidocaine action on biological membranes and indicates, that lidocaine might interact with cationic drug molecules at the level of brain microvessels.
Periodontitis model based on cytologic analysis of buccal epithelium

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Introduction
Diagnostics of chronic periodontitis build on clinical symptoms and visual examination which contain a part of subjectivity from the doctor and from the patient. Since there is no relevant decrement in morbidity, further studies in the diagnostics, treatment and prevention of the disease are obvious. This paper aims to form the diagnosis model of chronic periodontitis based on cytologic analysis of buccal epithelium; to identify the predictors of periodontitis and classified them according to the level of significance.

Materials & Methods
The study was conducted on 111 adults living in Yekaterinburg. Patients were divided into several groups: №1 - healthy periodontal patients; №2 - 36 patients with mild chronic generalized periodontitis; №3 - with chronic generalized periodontitis of medium severity. According to the results of the buccal epithelium cytologic analysis, discriminant analysis was carried out. As independent predictors were taken the cells with different levels of maturation (basal, intermediate and superficial) and nuclear malformations of buccal epithelial cells: protrusion, micronucleus, perinuclear vacuoles, binuclear cells, chromatin condensation, vacuolization of the nucleus, karyorhexis, karyolysis, karyopyknosis and apoptosis. Discriminant analysis was carried out on the statistical software package Statistica.

Results
The model we built predicted the correct diagnosis in 79.3% of cases. The presence of perinuclear vacuoles, chromatin condensation and micronuclei was the most relevant marker of inflammatory periodontal diseases (p <0.001).

Conclusion
The obtained model allowed to identify the most important indicators of buccal cytograms in severity score of chronic periodontitis. Take into account the relative simplicity and noninvasiveness of cytologic analysis it can become a reliable and affordable diagnostic tool in periodontology.
High throughput screening for anti-HBV drugs targeting NTCP using stem cell-derived hepatocytes

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Introduction
More than 350 million people were chronically infected with hepatitis B virus globally. Na+-taurocholate co-transporting polypeptide (NTCP), a co-transporter of Na+ and bile acids, acts as a functional HBV receptor through specifically binding to HBV-PreS1 to mediate HBV entry. Moreover, NTCP can modulate innate antiviral immunity by augmenting the bile-acid-mediated repression of interferon stimulate genes (ISGs). Recently, a promising cell model, human stem cell-derived hepatocyte-like cells (HLCs), has been developed and displayed characteristics close to primary human hepatocytes (PHHs). HLCs expresses endogenous NTCP, are susceptible to HBV, support productive HBV infection, and can be maintained with a long-lasting hepatocyte-specific phenotype. So, it will be a good cell culture model for screening anti-HBV drugs. In this study, we aimed to screen dual-function anti-HBV drugs that not only inhibit HBV entry, but also enhance the interferon response.

Materials & Methods
We directly differentiated human embryonic stem cells (hESCs) into HLCs in vitro. Firstly, we use these HLCs and HepG2-NTCP cells to screen the drugs which can enhance the expression of ISGs directly and inhibit HBV replication in HepG2.2.15. Secondly, we screen drugs which can enhance the innate immune response to observe if the candidates can inhibit taurocholate uptake in HLCs and HepG2-NTCP. Finally, we use the HBV infection model, HepG2-NTCP cell line, to identify the candidates inhibiting HBV infection. Data were analyzed by Student’s t-test. A P<0.05 was considered significant.

Results
We have developed a stable system of hESC differentiation and successfully apply it in screening anti-HBV drugs. We discovered 10 candidate drugs that can inhibit HBV replication by detecting HBeAg levels. Some candidates can increase the ISG expression Using HLCs. Our system of HBV infection on HepG2-NTCP cell line is applicable.

Conclusion
Briefly, we have successfully develop a high throughput screening system for anti-HBV drugs by using HLCs. In the future, we will select the most effective anti-HBV drugs from the candidates with a dual function.
Dentistry and Otorhinolaryngology

Chair
Gyuri B. Halmos MD PhD

Presenters
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Randomized Double-Blind Placebo-Controlled Trial of Propolis Oral Solution for Oral Mucositis in Patients Receiving Radiotherapy for Head and Neck Cancer

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Introduction
Oral mucositis (OM) is one of the most debilitating and troublesome acute side effects of radiotherapy. It profoundly affects quality of life (QoL) which increases morbidity and mortality and contributes to rising health care costs. The mucositis pain can be as severe, which requires hospitalization and use of parenteral opioid analgesics. It also causes the interruption of the planned cancer therapy. Propolis, known as “bee glue,” is a wax-like substance that is collected from local flora by honeybees contains substances which reported healing the stomatitis.

The aim of this clinical trial was to evaluate the efficacy and safety of propolis oral solution in prevention of radiation-induced oral mucositis.

Materials & Methods
In this double-blind placebo-controlled trial, 30 head and neck cancer patients were randomized to use 20 ml of propolis (0.8 mg/ml) or placebo oral solution three times a day, for 5 weeks during radiotherapy. Clinical OM, dysphagia, pain scores and analgesic use were assessed weekly by blinded investigators during the 5 weeks radiotherapy period, using validated scales.

Results
Thirty subjects were randomized to the propolis or the control group, which were similar with respect to oral hygiene, tumor location, radiation dose and concomitant chemotherapy. In both arms, mucositis and pain scores decreased over the course of radiotherapy. Data analysis of NCI-CTC criteria showed significant difference between two groups in severity of mucositis in the third (p=0.03), fourth (p=0.02) and fifth (p=0.02) week of treatment. However; WHO scale determined that the propolis significantly reduced the maximal mucositis grade at second (p=0.03) and third (p=0.03) week. There were no adverse events attributed to propolis use.

Conclusion
Propolis oral solution can be considered as an effective, safe and well tolerated medication for prevention of radiation-induced oral mucositis and alleviating its symptoms. Our results were similar to those of recent studies.
A prospective evaluation of bleeding after single tooth extraction in patients consuming direct thrombin inhibitors, aspirin, and clopidogrel

Ghafari, Z. (Zahrah); Karimi-Sari, H.; Yousefi-Malekshah, SH; Yazdanpanah, H.; Sadeghi-Ghahrody, M.

Introduction

Although many studies evaluated the anticoagulants effects on bleeding after tooth extraction, there is a controversy regarding interrupting coagulation therapy before tooth extraction. Interrupting these medications may increase the thrombosis risk in some patients. Most of the previous studies were retrospective studies containing many confounders. This study aimed to evaluate the risk of bleeding after tooth extraction in patients taking oral anticoagulants prospectively and tried to remove the confounders' effects.

Materials & Methods

In this prospective study, patients taking oral anticoagulants needing tooth extraction were considered as the sampling frame. Patients aged 18 to 60 without meeting our exclusion criteria were selected as the study population. Only one tooth extraction was done for each patient to adjust the confounder effect of the number of extracted teeth. All extractions performed by a single dentist and in the same conditions. Bleeding time and amount, hemostatic method, and needing additional intervention to stop bleeding were evaluated within the first 24 hours after extraction. Patients taking different anticoagulant medications were compared in the subgroups.

Results

One-hundred sixty patients with mean age of 47.1 ± 9.4 years were evaluated (40 patients taking direct thrombin inhibitors (DTI), 40 patients taking Aspirin, 40 patients taking Aspirin and clopidogrel, and 40 matched healthy controls). All bleedings were controlled with gauze (51.4%), hemostatic gel (18.6%), suture (10.7%), and suture plus hemostatic gel (2.9%) without any significant difference between the groups (P>0.05). The instant hemostasis was complete in 37.1%, partial in 57.9%, and uncontrolled in 5.0%. There was no case of uncontrolled bleeding in 30 minutes hemostasis. There were no significant differences between bleeding time between the groups (ANOVA overall P=0.121).

Conclusion

These anticoagulant medications caused no serious bleeding in our study subjects. Hence, one tooth extraction seems to be safe in patients taking DTI, Aspirin, and Aspirin plus clopidogrel. More studies with good adjustment for confounders are needed to approve above results. We recommend studies evaluating bleeding risk in more than one tooth extraction in such patients.
Is behavioral intervention as effective as fluoride varnish in the prevention of “Early Childhood Caries” in all socio-economic classes? A cluster-randomized community trial

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Introduction
Fluoride therapy is assumed as one of the most reliable preventive method of dental caries. Likewise, behavioral interventions could reduce the incidence. The aim of this study was to compare the effectiveness of a behavioral and theory-based method with applying fluoride varnish in dental caries status, dental plaque, and level of Streptococcus Mutans among young children in Tehran, Iran.

Materials & Methods
A stratified cluster random sample of 239 mothers and their 24-36 month-old children who enrolled in public health care centers recruited in this study. Public health care centers were randomly assigned to three groups: Group A received motivational interview plus a leaflet for oral health care of young children, group B received fluoride varnish, and group C had no intervention. All children and their mothers were followed three and six months after baseline. Data were analyzed using STATA 11 and SPSS 19.

Results
SES (socio-economic status) were classified as five levels (from low to high) using Principal Component Analysis. Children in group A showed less dental plaque and S. mutans CFU than two other groups at six-month follow up. Children in groups A and B had less new dental caries than children in group C (P < 0.05). Marginal regression model showed that children in group C had 1.36 and 1.59 times higher chance of experiencing new dental caries than A and B groups, respectively (Adjusted OR=1.36, CI 95%=0.7-2.61; Adjusted OR=1.59, CI95%=0.8-3.14). Number Need Treatent (NNT) was calculated for each intervention to determine the effectiveness. NNT for behavioral method was 3.1 and 2.9 for fluoride varnish, respectively. NNT was also calculated for children in different SES classes. Whereas NNT for applying fluoride varnish was lower for middle class SES, NNT for behavioral method was lower in extremes of SES classes (the lowest and the highest).

Conclusion
There is not one effective prevention method for all SES classes due to cost-effectiveness and long-term effectiveness. In the middle class of SES, it is better to apply fluoride varnish. However in the lowest and highest classes of SES, it is more effective to use behavioral intervention.
Efficacy of nonsurgical periodontal therapy on oral cavity protozoan parasites in Iranian patients with periodontitis (A Cross-sectional Study)

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Introduction
Nowadays, periodontitis is well-known as one of the most common oral diseases. Trichomonas tenax and Entamoeba gingivalis are protozoan parasite resides in the oral cavity. Recently studies have shown the pathogenic potential of these parasites with oral diseases such as periodontitis. This study was designed to assess the efficacy of nonsurgical periodontal treatment on the frequency of these protozoa in saliva and plaque samples.

Materials & Methods
In this investigation, the saliva and dental plaque samples were collected from 54 patients with moderate to severe chronic periodontitis before and after periodontal therapy. The samples were assessed for the frequency of parasites. The collected samples were smeared on a glass slide, and then stained using Giemsa stain. A prepared questionnaire considering a number of data such as age, gender, use of toothbrush, etc. were provided by each patient.

Results
The obtained results demonstrated that the prevalence of E. gingivalis was significantly decreased in saliva (p<0.01) and plaque (p<0.05) after the treatment. Furthermore, the prevalence of T. tenax also significantly decreased in saliva (p=0.023) and plaque (p=0.016) after the treatment. Although there was no significant association between age, gender, education, residence, smoking and the prevalence of E. gingivalis and T. tenax; however a significant correlation was observed between the prevalence of these parasites and mouthwash and teeth brushing (p<0.05).

Conclusion
Our findings demonstrated that nonsurgical periodontal treatment might be decreased the prevalence of T. tenax and E. gingivalis in the oral cavity of patients with periodontitis.
Characterization of the odor-cued N400 effect in healthy, young participants

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Introduction
The physiological basis of odor naming still remains poorly understood. Evoked Potentials (EPs) are a suitable method to investigate such cross-modal cognitive processes, most notably the N400 component, whose amplitude reflects the difficulty of semantic integration of a stimulus (target) in a previous context (cue). However, the characterization of the odor-cued N400 effect (difference in the EP of trials with semantically matching versus nonmatching targets) is inconsistent in literature. In this work we aim to investigate the properties of the odor-cued N400 effect using different sensory target modalities, starting by the replication of an EP experiment from Olofsson et al. (2014).

Materials & Methods
24 young, healthy participants (14 women) were tested in an EP experiment using a semantic priming paradigm with picture and olfactory cues. As targets, matching and nonmatching written words were delivered. EEG-recording was realized with ASA software, odor-stimuli were offered by a simple olfactometer and non-odor-stimuli by presentation software. Average of the EP waveform on the target word was realized with EEProbe. No statistical analysis was performed until now.

Results
First glances at the grand average of the EP waveform from all 24 participants show high morphological similarities to the results of Olofsson et al., especially with regard to the N400 effect in odor-cued versus picture-cued condition.

Conclusion
The results from Olofsson et al. characterizing the odor-cued N400 effect seem to be replicable. Statistical analyses of the results are going to be performed to make a definite statement. More experiments using other sensory target modalities are planned to further investigate the properties of this EP component and thus the process of odor-naming.
Stress effects on the body and the maxillofacial region: a study based on biomedical methods

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Introduction

Constant stress experienced by students over academic year can contribute to a decline in functioning of body systems. The development of a method for diagnosing stress at early stages is of high significance. We aimed to design a method for early detection of mental and physical stress.

Materials & Methods

30 students aged from 18 to 21 years were examined before and after classes with mental workload, and after physical relaxation. The tests used: electric pulp test (EPT), the Shtange test, the Sheikh-Zade formula, pH-metry and fluorescent diagnosis of saliva, gum thermometry and Spielberger test.

Results

1. EPT. After mental workload: increased by 46.5% (p<0.01). After physical relaxation: restored by 23.2% (p<0.05).
2. The saliva pH at the end of the first academic year – 6.41 ± 0.19; after summer vocation – 6.87 ± 0.11, in the middle of the second year – 6.63 ± 0.11.
3. Comparative analysis of thermometry indicators of periodontal tissues in the first and second years – increased by 0.62 °C (p<0.001).
4. The spectrum of luminescent saliva samples after classes in comparison with the initial state revealed a wavelength range of 600-650 nm, which indicates a high content of porphyrin compounds. The integral intensity after classes increased by 10-30 times and showed a 7-10 times fold decrease after a night’s sleep.
5. Stange Test. After mental workload: decreased by 31.5% (p<0.001). After physical relaxation – 19.3% (p<0.001) improvement.
6. Sheikh-Zade formula. After mental workload: increased by 57.2% (p<0.001). After physical relaxation – decreased by 18.6% (p<0.05).
7. Spielberger test. The average level of personal anxiety, the high level of reactive anxiety.

Conclusion

1. The dynamic research of results of an EPT, gum thermometry, saliva pH, Stange test and the Sheikh-Zade formula allow to reasonably diagnose the level of stress impact on the body.
2. The saliva sample optical spectroscopy using the method of fluorescent diagnosis provides a possibility for an express stress diagnosis.
3. Night rest contributes to considerable normalization of the body metabolic indicators in students.
Development of a diagnostic prediction model for burning mouth syndrome in primary care

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Introduction
Burning mouth syndrome (BMS) is a challenging condition in clinical practice. Patients typically visit numerous specialists such as dentists and neurologists before being properly diagnosed and treated.

Materials & Methods
In this study we developed a diagnostic prediction model to evaluate the risk of BMS in individual patients given clinical, demographic and social characteristics that can be easily collected in daily practice. Data were gathered retrospectively from a cross-sectional study conducted between 2013 and 2017, and involving the university dental care unit from Russia. Patients were considered eligible when they were aged more 18 years, residents of the Nizhny Novgorod city and the area, not infected with HIV, hepatitis B,C. We adopted logistic regression with Firth correction to develop a multivariable prediction model for BMS. Variables were included according to empirical knowledge. Prediction model performance was evaluated using bootstrap validation and quantified using concordance statistic and calibration slope. We used R software.

Results
In total, we examined 413 dental medical records. The mean age of the patients was 54.2 (SD 12.6) years; most individuals were females (N=363). Co-morbidities were reported in 85% of patients. According to the occupational status, 42% of participants was classified as a &quot;professional&quot;. The amount of missing data was less than 1%. The final model comprised one continuous variable (age), five dichotomous (sex, co-morbidities, history of dental prosthetics, urban/rural residency) as well as a categorical one (profession). Upon validation, the c-statistic was 0.82, the calibration slope was 1, the bootstrap corrected slope= 0.88. The full model equation was made available.

Conclusion
The developed prediction model shows reasonable performance and could help to facilitate decision making in patients presenting with BMS symptoms. Further research is, however, needed to assess whether predictions remain sufficiently accurate in new patients, and to assess whether implementation of the model improves patient care.
Sleep apnea is associated with ventricular arrhythmias in postmenopausal women with hypertension

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Introduction
Arterial hypertension (AH) holds leading position in the structure of cardiovascular morbidity. High risk of developing AH becomes clinically significant after a woman enters menopause. Many information is accumulating about the negative effect of sleep apnea on the cardiovascular system.

Materials & Methods
144 postmenopausal women with hypertension 1-2 degrees (mean age 66.6 ± 7.5 years) were examined. The first group included 96 patients with VA. The second group consisted of 48 women without VA. The groups were divided into subgroups: A - index of apnea / hypopnea (AHI) <5 per hour of sleep; B - AHI ≥ 5 per hour of sleep. Patients underwent holter monitoring of ECG (Cardiotechnics 04 -8 (m), Inkart, Russia) and respiratory monitoring (Somnocheck micro, Weinmann, Germany). To characterize the VA, the Lown and Wolf classification was used in the Ryan modification. VA 3 and higher gradations were taken to arrhythmias of high gradations. Statistical data processing was performed using the STATISTICA 6.0 software package.

Results
Patients with sleep apnea were found in the I (36.5%) and II (22.9%) groups, but in the group with VA of such patients there was a 13.6% increase (χ² with the Yates correction = 1.9 p&gt; 0.05). Patient didn’t significantly differ in the frequency of detection of VA I, III, IVA and V grades (p&gt; 0.05). Frequent ventricular extrasystole (VE) II gradation by 22.2% (p <0.01 in the Fisher test) was more often recorded in patients in the IA subgroup (29.9 and 5.7% accordingly). Polymorphic pair VE more often (by 20.8%; p <0.01 by Fisher test) was detected in women of the IB subgroup. In patients with IB subgroups, arrhythmias of high gradations (51.4%) were more frequent (21.9% χ² = 4.56 p &lt;0.05) compared with the IA subgroup. Using the method of calculating the odds ratio, it was found that the AHI ≥ 5 episodes per hour of sleep increases the chance of development of high-grade VA by 2.4 times (95% CI: 1.16 – 5.92; P criteria χ² <0.05).

Conclusion
Sleep apnea (AHI ≥ 5 per hour of sleep) is associated with high-gradation VA in women with hypertension.
Endocrinology

Chair
Prof. Cisca Wijmenga PhD

Presenters
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Husain, Y. (Yousif)
Katamu Benjamin, B (Botey)
Korniiko, L.K. (Liza)
Purwanta, Adelaida, M.L. (Made Lady)
Qin, QHL (Hailun)
Seifar, F.S (Fatemeh)
Yuwanto, Maulidyah, F. (Fatika)
Effects of Ranolazine on HbA1c in diabetic patients with ischemic heart disease in comparison with conventional therapy

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Introduction
This study was conducted to determine the potential of Ranolazine as an anti-anginal drug to reduce the amount of glycosylated hemoglobin in diabetic patients who received Metformin and Gliclazide. Also to determine if the addition of Ranolazine could control both angina frequency and glycemic level in these patients.

Materials & Methods
This study was a randomized prospective clinical trial of Ranolazine versus conventional therapy in the control group in patients with T2DM and stable angina. TERISA (Type 2 Diabetes Mellitus Evaluation of Ranolazine In Subjects with Chronic Stable Angina) method was employed to determine the effectiveness of Ranolazine in reducing the frequency of angina and consumption of sublingual Nitroglycerin (TNG) in diabetic patients that remain symptomatic while using up to 2 anti-anginal agents in comparison with placebo. We also investigated the ability of Ranolazine up to 1000 mg twice a day in reducing HbA1c % from baseline up to 2 months after receiving Ranolazine. HbA1c % was detected using high-pressure liquid chromatography.

Results
Ranolazine treatment resulted in an absolute HbA1c % reduction of up to 15% in diabetic patients with HbA1c % of more than 7 and was more effective for poorly controlled diabetic patients (HbA1c>&gt;8% and P= 0.017). Ranolazine was not associated with serious hypoglycemic events, and no significant changes were observed when used with concurrent anti-diabetic therapy (P= 0.560).

Conclusion
Concurrent use of Ranolazine and anti-diabetes treatment (Metformin and Gliclazide), reduced the amount of HbA1c % in patients with the cardiovascular disease such as stable angina and poorly controlled diabetes and was well-tolerated.
Ketogenic diet beneficial effects on the DM-induced deterioration in higher cognitive brain defects in mice

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Introduction
Long-term diabetes is associated with accelerated ageing of the brain as evidence by impairment of cognitive function as well as motor performance. Many report emerged recently about the beneficial effects of carbohydrate free diet on the brain functions in diabetes mellitus. The aim of this study was to investigate the effects of supplementary diet modulation (ketogenic diet free of carbohydrate Approximate energy from fat 66.7%, carbohydrate 0%, protein 33.3%) on the motor coordination and learning in diabetic mice.

Materials & Methods
BALB/C mice (20-25g) received 55mg/kg streptozotocin i.p. daily for 5 days. Diabetes was confirmed by measurement of random blood glucose. Diabetic mice were randomly assigned to one of the following two groups for 12 weeks duration: (1) DM with normal diet; (2) DM with ketogenic diet. The data to be compared with other two control groups one with normal diet and the other with ketogenic diet. At the end of 12 weeks blood glucose measurements were repeated and animals were assessed by the Morris Water Maze and the Rotarod for cognitive and motor performance respectively.

Results
Our results showed that the diabetic animals had defects in learning and memory functions measured in water maze. The animals needed significantly more time than the controls to locate a hidden platform in a swimming pool to escape swimming. The control animals learned the test significantly faster and better. Same results showed deterioration of motor coordination in diabetic animals when compared to the control. Preliminary data showed than the diabetic animals that were fed with ketogenic diet were performing better in the water maze, as well as in the rotarod test for motor coordination.

Conclusion
Ketogenic diet is beneficial for the cognitive brain function deterioration detected in streptozotocin-induced DM in mice.
The association between type 2 diabetes's duration and major adverse cardiac events after percutaneous coronary intervention.

Katamu Benjamin, B (Botey)

Introduction

Diabetes mellitus is considered as an independent risk factor for the development of coronary artery disease and portends adverse prognosis in diabetic patients undergoing percutaneous coronary intervention (PCI) compared to non-diabetic patients. Few studies are currently available regarding the relationship between diabetes duration and major adverse cardiac events (MACEs). The aim of this study was to assess the association between diabetes duration and major adverse cardiac events after PCI and transluminal coronary angioplasty (PTCA).

Materials & Methods

We prospectively studied 151 cases of diabetic patients undergoing an elective PCI with drug-eluting stent (DES) deployment and or PTCA using a drug-coated balloon (DCB). Based on the duration of diabetes we divided patients into three groups: &lt;5 years' group (n=81), 5–10 years' group (n=35), and ≥10 years' group (n=34). Angiographic and clinical follow-up for assessment of angina recurrence, myocardial infarction, in-stent-restenosis, and cardiac death were conducted 6 months after the procedure for all the patients and at any given time if needed.

Results

A significantly higher rate of myocardial infarction was observed in diabetic patients with the most extended diabetes duration (5.8% vs 0% and 0%, P=0.048) compared with groups with shorter duration. The recurrence of angina was found to be significantly higher in the &gt;10 year's group than it was in the groups with shorter duration of diabetes (8.8% vs 1.2% and 0%, P=0.053). However, in-stent restenosis and cardiac death were not significantly different within groups.

Conclusion

Diabetes duration was associated with significant differences in major adverse cardiac events after percutaneous coronary intervention; the most extended diabetes duration portended the higher rates of MACEs than others groups at 6 months' follow-up.
Dexamethasone induces aggregation of Alzheimer’s disease key pathology protein in Tau-BiFC cells

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Introduction
According WHO, around 50 million people worldwide have dementia nowadays; in 2030 this number is projected to reach 82. Big contribution in molecular pathology of this state is given to specific misfolded proteins accumulation with loss of its function. In particular, accumulation of hyperphosphorylated and aggregated tau in brain leads to Alzheimer’s disease (AD). Nowadays, special attention in AD field studies devoted to hypotese of «dementia-diabetes» connection. Metabolic pathways of glucocorticoid dexamethasone are numerous, but important in this context one - it is well-known in vitro insulin resistance inducer. Thus, we investigated effect of dexamethasone on tau in Tau-BiFC cell line.

Materials & Methods
HEK293 cells expressing Tau-BiFC were plated on 384-well plate and treated next day with dexamethasone at 30uM and 100uM concentration. After 24 and 48h incubation plate was imaged automatically by using Operetta (PerkinElmer, Waltham, USA), 1 hour before treated by Hoechst 2 mg/ml. High resolution images were acquired by using a Nikon Eclipse inverted microscope (Ti, Nikon) at 1000×magnification. BiFC fluorescence images, acquired by using Operetta, were analyzed using the Harmony 3.1 software (PerkinElmer). The means and standard deviations of BiFC fluorescence intensities were plotted using Prism software 7 (GraphPad). Quantification data was analyzed by Student’s t-test.

Results
Tau-BiFC cells treated by dexamethasone (DT) showed significant increase in BiFC fluorescence by 4 fold (p<0.001) and its intensity by 4,5 fold (p<0.001) in comparison with control - not treated cells (NT) after 24h treatment. Same results after 48h: increase in DT BiFC fluorescence by 2,5 fold (p<0.05) and its intensity by 5 fold (p=0.1) comparing with NT. Important to notice, dexamethasone treatment deteriorated cell viability: general number of cells comparing to NT decreased in 2 times after 24h and in 3,9 times after 48h treatment.

Conclusion
Tau-BiFC cells treatment by dexamethasone showed significant tau aggregation, its severity was also confirmed by BiFC intensity. Decreased cell number upon dexamethasone treatment may be possible cell toxicity consequence. This data may suggest about dexamethasone involvement in tau pathology as possible insulin resistance inducer same as by some other mechanisms. Next studies are needed to suggest exact dexamethasone pathways and its role in discussed protein aggregation.
Introduction
Gut microbiota has been an intensely growing research of biomedicine especially for its role in metabolic diseases. Studies on its mechanism and profiling of species are on going, however very few of these data came from Indonesia. This study aims to learn the newly discovered bacteria Akkermansia muciniphila in the diabetic and non-diabetic Balinese population.

Materials & Methods
We conducted an analytic cross-sectional study involving participants from public health centers in Denpasar, Bali during the period of March-July 2017. From 109 participants 14.7% were diabetic without treatment, 22% were on treatment, 21.1% were pre-diabetic and 42.2% were non-diabetic as diagnosed by the health centers’ general practitioners. The treatment group was 33.3% on metformin, while 66.7% were on metformin-combined dual therapy. Determinants measured were demographic information, anthropometry, capillary blood glucose level and diabetes treatment. All were analysed for their correlation with A.muciniphila in the faecal material from which qPCR was conducted for quantification. Furthermore, all groups were tested for difference in each parameter.

Results
Treatment group showed the highest number of A.muciniphila with mean log copy number of 6.18/gram of feces followed by pre-diabetic (5.61/gram of feces), non-diabetic (5.31/gram of feces) and diabetic without treatment group (5.28/gram of feces) respectively. We found a correlation between waist circumference and the amount of A.muciniphila in general r= -0.40 (p=0.04), however no correlation found in each group. Further analysis showed diabetes treatment group had significant higher proportion of A.muciniphila compared to non-diabetes treatment group (p=0.01) and interestingly, non-diabetic group (p=0.02). Difference test based on types of diabetes treatment also proved no significant difference of A.muciniphila between those with metformin on single therapy and combined therapy.

Conclusion
Our results indicate that the number of A.muciniphila is rather related with diabetes treatment than abdominal adiposity. This supports the hypothesis of metformin as a potential gut modulator through enrichment of mucin-degrading bacteria. Our data also show better profile of A.muciniphila with diabetes therapy than non-diabetic group, suggesting the strong effect of metformin in providing better gut microbiota profile. This mechanism however, needs to be investigated further in the future study for its influence on clinical effects of diabetes therapy.
Triglyceride to high density lipoprotein cholesterol ratio is an independent predictor for type 2 diabetes mellitus in male: a retrospective study in a cohort of Chinese population

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Introduction
Dyslipidemia is commonly present in type 2 diabetes mellitus (T2DM). As a novel parameter of lipid abnormality in recent years, triglyceride to high density lipoprotein cholesterol (TG/HDL-C) ratio has been admitted as an independent predictor for T2DM. However, the association between TG/HDL-C ratio and T2DM among Chinese and how this correlation is impacted by gender are rarely studied. The present study examined the relationship between TG/HDL-C ratio and T2DM among the Chinese population by different gender.

Materials & Methods
116,855 participants (from the public database provided by Chen Y et al) who were free of diabetes at baseline were enrolled in the study. We divided the participants into two groups by the median (0.8163) of TG/HDL-C ratio and further analyzed by gender. We used cumulative incidence and person-years incidence to express incidence rates. The cox regression proportional hazard model was applied to estimate the predictive value of TG/HDL-C ratio to T2DM.

Results
The mean age of participants was 44.1±12.9 years, and 53% (n=62868) were male. During a median follow-up of 3.1 years, a total of 2,685 incident T2DM happened. The cumulative incidences were 2.30% (2.21-2.38%), 3.01% (2.87-3.14%), 1.47% (1.37-1.57%) for total incident diabetes, male’s and female’s. After adjusting for multivariate factors, the multivariate cox regression analysis found that elevated TG/HDL-C ratio was an independent predictive factor for T2DM in male (HR=1.55,95%CI 1.19-2.02), but not in female (HR=0.89,95%CI 0.56-1.42).

Conclusion
Among the Chinese population, the TG/HDL-C ratio was an independent predictor for T2DM in male.
The effect of reproductive factors on pituitary gland size in women at reproductive ages

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Introduction
The brain imaging of pituitary gland in females have shown a change in pituitary size and volume in female’s
population. It has been proven that pituitary gland is being affected by pregnancy, giving birth and hormone-related factors. Therefore, this study aimed to evaluate the factors which may have an impact on pituitary size in females at reproductive age and compare the mean pituitary size in females who have had a history of pregnancy, females at postpartum period and in who have not.

Materials & Methods
This population-based cross-sectional study was conducted on two hundred eight healthy women aged 12-55 years old. Participants underwent cranial Magnetic resonance imaging (MRI) and pituitary diameters (craniocaudal, anteroposterior and transverse) and volume were measured in each subject. The correlation of age, gravity, parity, lactation and intake of oral contraceptives with pituitary size were analyzed.

Results
During eighteen months of study, 180 females met the criteria of participation. The pituitary volume correlated negatively with hormone-related factors. The gravity and parity both had a significant negative effect on pituitary volume (r= -0.35, p<0.001, r= -0.35, p<0.001, respectively). The use of oral contraceptives and lactation were also in negative correlation with pituitary volume (r= -0.20, p=0.006, r=-0.56, p<0.001, respectively). The craniocaudal diameter was also affected by gravity (r= -0.62, p<0.001), parity (r= -0.57,p<0.001), intake of contraceptives (r= -0.32, p<0.001) and lactation (r=-0.70, p<0.001).

The anteroposterior diameter of pituitary gland associated significantly with gravity (r = -0.19, p=0.009), parity (r= -0.20, p=0.007) and lactation (r = -0.25, p=0.001). The transverse diameter of the pituitary gland also related negatively with reproductive-factors. The correlation between transverse diameter and the evaluated factors were: gravity (r=-0.15, p=0.04), parity (r= -0.17, p=0.02) and lactation (r=-0.17, p=0.02). Nullipara females had the greatest size of gland than the other females. Recent pregnancy led to increased craniocaudal and anteroposterior diameters, but not a meaningful change in volume or transverse diameter.

Conclusion
In this study, we found a negative effect of pregnancy, giving birth, and intake of oral contraceptives on pituitary size. Nullipara females found with the greatest pituitaries, even greater than the females at postpartum period.
Javanese Turmeric (Curcuma xanthorrhiza roxb.) Extract as Topical Therapy Increases Fibroblast Number and Blood Vessel Formation in Streptozotocin Induced Diabetic Rat

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Introduction
Diabetes Mellitus is one of many metabolic disease which can lead to macrovascular and microvascular complication. Hyperglycemia which is the hallmark of diabetes mellitus could interfere healing process marked by prolonged inflammation process, declining fibroblast proliferative capacity and disturbed angogenesis process. Javanese Turmeric (Curcuma xanthorrhiza roxb.) (JT) has a relatively complete efficacy as antimicrobial, anti inflammation, antioxidant, and wound healing agent. This study aimed to observe the effect of Javanese Turmeric extract in increasing fibroblast number and blood vessel formation in streptozotocin induced diabetic rat.

Materials & Methods
In this experimental study, diabetes was induced in 25 male Wistar rats by using Streptozotocin (STZ) 40 mg/kg intraperitoneally. Rats were divided into 5 groups (n=5) consisted of Negative Control (NC) group and Positive Control (PC) group which was treated with vaseline topically, JT 15% ointment treated rats (E1), JT 20% ointment treated rats (E2), JT 25% ointment treated rats (E3). After performed incision about 1,5 cm2 wound at the back of the rats, the animal obtained wound care once daily for 14 days. Microscopic examination was performed using OLYMPUS series XC10 equipped with software OlyVia with the magnification of 400x at each field of view. Each slide was measured in 5 field of view. Fibroblast number and blood vessel formation were analyzed statistically with parametric test, One-Way ANOVA using SPSS software (ver.21). P-value &lt;0,05 was determined as statistically significant.

Results
According to the examination result, increase fibroblast number difference between negative control group (NC), positive control group (PC), treatment groups with the dose of 15% (E1), 20% (E2), and 25% (E3) was E3&gt;E2&gt;E1&gt;NC&gt;PC, statistically significant (p&lt;0,05). Blood vessel formation difference between negative control group (NC), positive control group (PC), treatment groups with the dose of 15% (E1), 20% (E2), and 25% (E3) was E3&gt;E2&gt;E1&gt;NC&gt;PC statistically significant (p&lt;0,05).

Conclusion
Based on this study result, it was shown that Javanese Turmeric extract could improve wound healing activity by enhancing fibroblast number and blood vessel formation in rat with diabetic wound. This study concludes that Javanese Turmeric extract has the potency as topical therapy in diabetic wound.
Gastrointestinal Medicine

Chair
Aad P. van den Berg MD PhD

Presenters
García, V (Victor Manuel)
Guo, Y. (Yuanning)
Hone Lopez, S.
Karimi-Sari, H. (Hamidreza)
Theardy, MS (Madelaine Skolastika)
Toennaer, J.G.J. (Jurgen)
Zhu, G.X.
Cannabinoid agonists as inducers of cell death in gastric and rectum cancer cells

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Introduction
It has been reported in several studies that the endocannabinoid system can reduce the proliferation of tumor cells in different in-vivo and in-vitro models. In gastrointestinal cancer little has been described. Previously we tested cannabinoid agonists in a gastric and rectum cell lines, observing events of death at the 24 hours, so in this study it is to describe the types of death that appear during the treatment with different cannabinoids agonists, to provide new knowledge of the use of these agents in gastrointestinal cancer.

Materials & Methods
The human cancer cell lines AGS (stomach) and SW837(rectum) were cultured in DMEM-F12 medium supplemented with 10% fetal bovine serum (FBS) and then plated in 24-well plates to be treated with cannabinoid agonists (AEA, Meth-AEA and CP 55,940) at different concentrations, and their controls (without treatment and staurosporine as positive control of cell death) at 24 hours. Morphological evaluation, DNA laddering assay, cell viability and flow cytometry were used in this study to evaluate cell death. In addition, an immunoblot was performed to confirm the presence of the cannabinoids receptors. Data were analyzed by two-way analysis of variance (ANOVA), followed by post hoc Tukey’s test. Values of P < 0.05 were considered of statistical significance.

Results
In the presence of cannabinoids and the positive death control, changes in the cell morphology were observed with respect to the control without treatment. DNA degradation pattern was observed in presence of the cannabinoids and positive death control. Loss viability was evaluated with respect to the control without treatment and there were significant changes (P < 0.05). The dot plots in flow cytometry shown cell death in AGS and SW837 cell lines after exposure to 5 μM. Finally, the presence of cannabinoid receptors was demonstrated by immunoblot. All the experiments were evaluated at 24 hours.

Conclusion
The three cannabinoids tested exhibited similar concentration-dependent effects in the induction of the cell death. Our results support and confirm the therapeutic potential that agonists exert in gastrointestinal cancer cells.
Non-autonomic Neural Involvement in Tumor Microenvironment is Associated with Poor Prognosis of Esophageal Squamous Cell Carcinoma

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Introduction
Neural invasion is reported as a poor prognostic factor in multiple cancers, and it also exists commonly in esophageal squamous cell carcinoma (ESCC). However, a detailed pathological analysis of morphological features of neural involvement in tumor-nerve niche of tumor microenvironment (TMB) and their contribution to the prognosis of ESCC remains to be determined.

Materials & Methods
To describe the severity of neural association or invasion of ESCC in more detail, Neural Invasion Severity Score (NISS) and Neural Invasion Index (NII) based on different pathological features of neural involvement (epineural association (ENA), perineurial invasion (PNI), and endoneural invasion (ENI)) were applied. Cancerous tissues of 105 ESCC patients from 2010 to 2011 were used for H&E and immunohistochemistry staining. We use S100 as a general marker for nerves. To show the subtype of nerves, we stained VAChT (Vesicular Acetylcholine Transporter) for cholinergic nerves and Tyrosine Hydroxylase (TH) for catecholeminergic nerves. Kaplan-Meier plot and log-rank test with overall survival (OS) were applied for survival analysis. Univariate and multivariate analysis of the prognostic factors were done by Cox regression.

Results
Neural involvement were found in 84.8% (89 of 105 cases) of all cases, of which 68.6% showed PNI or ENI and 41.0% showed ENI. By applying Kaplan-Meier analysis, both NISS and NII (high vs. low level defined by median) were associated with worse survival (log-rank P = 0.029 for NISS and P = 0.039 for NII). In addition, both NISS (HR = 1.95 (1.10-3.46), P = 0.022) and NII (HR = 2.22 (1.24-3.97), P = 0.007) were demonstrated as independent prognostic risk factors when each involved with other clinical factors in Cox regression. Nevertheless, only 13 cases were associated with catecholaminergic neural invasion (44 cases showed no TH positive innervation in TMB), and only 5 cases showed cholinergic neural invasion. The log-rank P value for TH positive neural involvement is 0.300 for NISS and 0.242 for NII.

Conclusion
Provided that there are very few autonomic nerves involved in TMB, neural association and invasion are mainly depend on non-autonomic nerves and are associated with poor ESCC prognosis. The distinct subtypes of cancer associated nerves of ESCC remain further detected.
Checkpoint inhibitor-induced colitis shares mucosal histopathological features with inflammatory bowel disease and graft-versus-host colitis.

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Introduction
Checkpoint inhibitor-induced colitis (CIC) is a severe side-effect of immune-checkpoint inhibitors (ICI). Its pathophysiology is poorly understood, impairing improvement of prevention and treatment strategies. CD4+ and CD8+ T-cells and CD68+ macrophages are thought to be critical in colitis development. Several studies suggest histopathological similarities between CIC, inflammatory bowel disease (IBD) and acute graft-versus-host disease (aGVHD) colitis. However, no study directly compared the histopathology of these colitis entities. We aimed to improve the knowledge on CIC by performing a direct immunohistochemical comparison of CIC, IBD and aGVHD.

Materials & Methods
Archival formalin fixed paraffin-embedded colon biopsies obtained during routine diagnostic procedures from treatment-naive patients with CIC, IBD and aGVHD (all n=20) were studied. Biopsies from patients without histopathological abnormalities served as controls (n=20). Immunohistochemical staining was performed for CD4+ T-cells, CD8+ T-cells and CD68+ macrophages. In each biopsy 3 mucosal areas with highest cell density were selected for cell counting. The number of cells/hotspot were classified as 0-10, 10-50, 50-100, 100-150 and >150. The distribution of these cells was studied and compared between patient groups.

Results
CIC showed higher CD4+ and CD8+ T-cell counts (100-150 cells/hotspot in most patients) than IBD, aGVHD and controls (50-100 cells/hotspot in most patients in each group). CIC, IBD, aGVHD and controls shared a similar CD68+ macrophage count. Cells infiltrated the superficial and deep layers of the mucosa following a scattered or patchy distribution. We recognized four distribution patterns: A) superficial diffuse, deep scattered/patchy; B) superficial scattered/patchy, deep diffuse; C) superficial and deep diffuse; D) superficial and deep scattered/patchy. CD4+ T-cells showed pattern D in most CIC patients (74%), pattern C in most IBD patients (47%), pattern B in most aGVHD patients (54%) and pattern A in most control patients (83%). CD8+ T cells showed pattern D in most CIC patients (45%), and pattern A in most IBD (85%), aGVHD (63%) and control (100%) patients. CD68+ macrophages showed pattern A in most patients of each group.

Conclusion
CIC has a distinct immunohistopathological pattern that shares key elements with IBD and aGVHD.
Effect of interferon-free treatment regimens on mood, sleep quality and quality of life in hepatitis C patients

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Introduction
Some neurocognitive disorders have been known in hepatitis C virus (HCV) infected patients. These disorders may be due to direct virus effect or the effect of other manifestations on the central nervous system (CNS). According to the previous studies, mood and sleep disorders, and decreased quality of life (QOL) are prevalent among HCV infected patients. The food and drug administration (FDA) approved the first interferon-free treatment regimen for HCV infection in 2014. This study aimed to evaluate the effect of eradicating HCV infection on the patients’ sleep quality, mood, and QOL.

Materials & Methods
In this study, patients receiving one of the interferon-free treatment regimens for HCV infection in HepCC-2 trial (NCT03061032) were enrolled prospectively. Patients were assessed by the Pittsburgh Sleep Quality Index (PSQI), Beck’s depression inventory, and SF-36 QOL questionnaires before the treatment. Patients were treated by a combination of Sofosbuvir plus Ledipasvir or Daclatasvir (12 or 24 weeks) according to the Iran Hepatitis Network guideline. Patients were evaluated by the mentioned questionnaires at the end of treatment and 24 weeks after the treatment.

Results
One-hundred fifty patients with a mean age of 38.31 ± 12.1 years were evaluated (107 males and 43 females). All the patients achieved sustained virological response after the treatment and no case of relapse was observed at 24 weeks after the treatment. The PSQI global score showed a significant decrease at the end of treatment (-4.46, P<0.001) and 24 weeks after the treatment (-6.40, P<0.001). Beck’s score was significantly decreased by 9.33 and 14.61 units at the end of treatment and 24 weeks after the treatment, respectively (P<0.001). Patients’ QOL was also increased 15.90 scores after the treatment and 12.45 scores 24 weeks after the treatment. There were no significant effects for the treatment regimen, patients’ gender and age, HCV genotype, and the existence of other comorbidities on these improvements (P>0.05).

Conclusion
Our study showed that HCV eradicating by direct-acting antivirals could improve the patients’ sleep quality, mood, and the QOL just after the treatment and 24 weeks after the treatment. Approving these results needs more follow-up periods and considering all other confounders affecting QOL, sleep quality, and mood.
Amniotic Epithelial Exosomes Result In Reversal of Epithelial to Mesenchymal Transition in Hepatocellular Carcinoma Cell Lines

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Introduction
Mesenchymal type hepatocellular carcinoma (HCC) with epithelial to mesenchymal transition (EMT) constitutes the most aggressive HCC. Our work has shown that exosomes from amniotic epithelial cells (AECs), an intriguing cell from the epiblast which can switch between epithelial and mesenchymal phenotype, contain a myriad of growth and signaling factors that regulate cell differentiation and has immunomodulatory and antiproliferative properties. We hypothesize that modulation of HCC differentiation into more differentiated epithelial phenotype via amniotic epithelial cell exosomes will abrogate aggressive biology.

Materials & Methods
Size exclusion chromatography via the use of qEV columns was used to separate AEC media into exosome (less than 100 nm) and non-exosome fractions (more than 100 nm). Using the MACSplex exosome kit, we showed the abundant expression of CD63, CD9 and CD81 in these AEC exosomes. HUH-7, SK Hep-1 and HLF cell lines were seeded into plates treated with exosomes, non-exosome fractions and control daily. Proliferation and migration were assessed over 72 hours by Alamar blue, Glo and wound healing assays. Immunofluorescence for vimentin, E cadherin, KDR and EPCAM were performed to assess for epithelial to mesenchymal transition (EMT).

Results
The proliferation of all three cell lines were significantly reduced in the exosome and non-exosome arms compared with control, on both Alamar Blue stain and Glo assay (all p<0.05). Wound healing was reduced significantly in the exosome arm vs control in Sk-Hep1 and HLF (p=0.016 and 0.004 respectively), but not in HUH-7 (p=0.156). On immunofluorescence, there was upregulation of the epithelial marker E cadherin in the exosome and non-exosome arms in SK-Hep1 and HUH7, but it was not expressed in the control arm. E cadherin was upregulated in the cells treated with exosomes compared to non-exosomes in SK-Hep1 and HUH7. There was downregulation of the mesenchymal marker vimentin in the HLF cells treated with exosomes and non-exosomes as compared to control.

Conclusion
Exosomes have the ability to modulate HCC tumour biology, possibly by pushing HCC cell lines into mesenchymal epithelial transition to become less proliferative and motile.
Prognostic factors for survival in duodenal adenocarcinoma and intestinal type papilla of Vater adenocarcinoma

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Introduction
Duodenal adenocarcinoma and intestinal type papilla of Vater adenocarcinoma are both rare gastrointestinal malignancies. Due to this rarity, survival per disease stage remains unclear. This study aims to analyse current OS for DA; defining survival per disease stage, treatment modality and investigate influencing prognostic factors. Systemic chemotherapy remains a topic of discussion and this study will examine the use and effect on survival in adjuvant and palliative setting. Furthermore, new treatment strategies for advanced disease are currently being explored, including curative treatment of oligometastasis.

Materials & Methods
All patients diagnosed with duodenal adenocarcinoma (DA) and intestinal type papilla of Vater adenocarcinoma (IPVA) in the VUmc and AMC, during the period from 2000 to 2017, were included. Diagnosis was histologically confirmed by biopsy or resection and patients were identified using the PALGA database. Clinical relevant data was collected and correlated to overall survival for tumour stage and treatment modality using the Kaplan-Meier survival analysis, Log-rank test and Cox-regression analysis.

Results
The median overall survival (OS) of patients diagnosed with intestinal type adenocarcinoma in the duodenal area (n = 155) was 49 months. For stage 0-IIB disease median OS was 121 months, for stage IIIA - IIIB disease 50 months and for stage IV disease 14 months (Log rank p-value < 0.001). Median OS for DA and IPVA per disease stage did not differ significantly (Log-rank p-value = 0.73). Resection of the primary tumour was the only treatment option for curation. Survival of patients diagnosed with positive lymph nodes (stage III) who were treated with adjuvant chemotherapy (n = 20) did not differ from the wait-and-see group (n = 38, Log-rank p-value = 0.12). Six patients with stage IV disease were treated through resection of the primary tumour including resection of liver metastases, of whom four still alive.

Conclusion
Survival per disease stage for DA corresponds to IPVA and is decreased in more advanced stages. Small sample size and short follow-up in sub-group analyses is a limitation for this cohort. A large scale prospective study will help draw final conclusions regarding the benefit of systemic therapy and surgical resection of liver metastasis and adjuvant treatment.
SMYD3 controls a Wnt-responsive epigenetic switch for ASCL2 activation and cancer stem cell maintenance.


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Introduction
Tumor growth is fueled by subset of cells with stem cell properties. While persistent activation of Wnt/β-catenin signaling confers CSC properties, it remains unclear how epigenetic modifications regulate Wnt target genes to dictate their self-renewal. Here, we report a novel Wnt-responsive epigenetic switch for CSC maintenance through activating the stem cell transcription factor ASCL2 in gastric carcinoma (GC).

Materials & Methods
Cells were treated by Wnt3a to activate the Wnt signaling (Wnt on). WB or qPCR was applied to detect the level of protein or mRNA, respectively. The protein-DNA interaction was measured by ChIP assay. Appropriate cell function tests were used for evaluating the CSC property. Data were analyzed by t-test and Kaplan-Meier method etc.

Results
We characterize ASCL2-expressing (ASCL2+) GC cells as a subset of Wnt-responsive CSCs that depend on ASCL2 for self-renewal. High-throughput RNAi screening uncovers that the histone methyltransferase SMYD3 determines H3K4me3 status at the ASCL2 locus to promote ASCL2 expression. Moreover, SMYD3 may be transcriptionally activated by the β-catenin/TCF4 complex, indicating that the SMYD3-ASCL2 axis may be an integral component of Wnt signaling. Consistently, SMYD3 maintains self-renewal and tumorigenicity of ASCL2+ CSCs largely through inducing ASCL2. Clinically, overexpression of SMYD3 and ASCL2 are associated with malignant progression and poor patient outcomes in GC.

Conclusion
Together, these findings define a Wnt-responsive CSC pathway that could be exploited to identify essential regulators of the signaling output, and reveal SMYD3 as an epigenetic target for eliminating CSCs in human cancers.
Gynaecology

Chair
Ayten Elvan MD PhD

Presenters
Alkaff, Mr (Firas Farisi)
Fuentes, G (Gonzalo)
Gowani, SG (Shahnoor)
Litvinova, K. (Kateryna)
Moaveni, A.K (Amir Kavian)
Nagy, R.A. (Ruxandra)
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Comparison of Serum Calcium and 25-Hydroxy Vitamin D Level Between Normal Pregnancy and Early-Onset Pre-eclamptic Pregnancy in Indonesia

Alkaff, Mr (Firas Farisi)

Introduction
Preeclampsia is one of the most common cause of maternal and fetal morbidity and mortality worldwide. This disorder is categorized into early-onset preeclampsia (EOPE) and late-onset preeclampsia (LOPE). EOPE are usually accompanied by severe complications for both the mother and perinatal, while LOPE is accompanied by maternal mild complications. Although the pathogenesis of EOPE is not yet fully elucidated. Recent studies indicate that serum calcium and 25(OH)D (25 Hydroxy Vitamin D) levels may plays a role in this disorder’s pathogenesis. The aim of this study was to compare the calcium and 25(OH)D serum levels between pregnant women with normal pregnancy and with EOPE in Indonesia.

Materials & Methods
This study was a case-control study, conducted in Dr. Soetomo General Hospital from July to October 2017. 36 women with EOPE and 64 women with normal pregnancy were included in this study. Inclusion criteria was pregnant women in 2nd or 3rd semester with BMI &gt; 18 Kg/m2. Blood sample analysis were done to measure serum calcium and 25(OH)D level. Data was expressed as Mean ± Standard Deviation. Data distribution was analyzed using Shappiro-Wilk test. Comparison of serum calcium and 25(OH)D level between two groups was analyzed using Independent t-test. Correlation between serum calcium and 25(OH)D level was analyzed using Pearson correlation test. P-value of &lt; 0.05 was considered as statistically significant.

Results
There was a significant difference in serum calcium level between case and control group (8.294 ± 0.725 vs 8.670 ± 0.405 mg/dl; p = 0.006). In 25(OH)D level, there was no difference between both groups (16.128 ± 7.5463 vs 17.325 ± 6.4992 ng/dl; p = 0.406). No correlation was found between calcium and 25(OH)D level (r= 0.165; p = 0.101).

Conclusion
Calcium deficiency plays a role in the incidence of EOPE among pregnant women in Indonesia. The actual role of calcium deficiency in EOPE needs further investigation.
Adenosine transport is reduced by alkaline intracellular pH in human umbilical vein endothelial cells from gestational diabetes mellitus

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Introduction

Human umbilical vein endothelial cells (HUVECs) from gestational diabetes mellitus (GDM) pregnancies show reduced transport of the endogenous vasodilator nucleoside adenosine via the human equilibrative nucleoside transporters 1 and 2 (hENT1/2) and activation of the endothelial nitric oxide (NO) synthase. Increased NO generation is seen in an alkaline medium and elevated NO reduced the hENT1/2 expression and activity in HUVECs. We evaluated whether HUVECs from GDM show an altered intracellular pH (pHi) and its consequences on the hENT1/2 transport activity.

Materials & Methods

HUVECs were isolated (collagenase digestion) from full term normal (n = 11) or GDM (n = 8) pregnancies collected at the Clinical Hospital CHRISTUS-UC (Chile), and conformed to the principles outlined in the Declaration of Helsinki. HUVECs were cultured in medium 199 plus sera (20%) up to passage 2. The pHi was measured in cells loaded with the fluorescent pH-sensitive probe BCECF-AM (12 µM, 10 min) and exposed to NH4Cl (20 mM). Basal and pHi recovery rate (dpHi/dt) were estimated (up to 360 s) in cells exposed to 5 µM 5-N,N-hexamethylene-amiloride (HMA, Na+/H+ exchangers (NHE) general inhibitor), 0.1 µM zoniporide (Zn, NHE1 inhibitor), 0.1 µM concanamycin A (V-ATPases inhibitor), or 10 µM Schering (H+/K+-ATPase inhibitor).

Results

HUVECs from GDM show higher basal pH compared with cells from normal pregnancies (pHi = 7.5 ± 0.1 vs. 7.1 ± 0.1, respectively) (values are mean ± S.E.M., compared by unpaired ANOVA, P<0.04). Incubation of cells with Zn and HMA caused a reduction in the basal pH (pHi = 7.3 ± 0.2 and 7.2 ± 0.3, respectively) in cells from GDM. The dpHi/dt in GDM was higher (2.1 ± 0.3 fold) than in normal pregnancies. Zn and HMA reversed the GDM-increased dpHi/dt to values in normal pregnancies. The GDM-reduced hENT1/2-mediated adenosine maximal transport capacity at basal pH was reversed by Zn and HMA-induced intracellular acidification to values in cells from normal pregnancies.

Conclusion

HUVECs from GDM pregnancies show NHE-1–mediated alkaline pH leading to inactivation of hENT1/2 mediated transport (support: FONDECYT 1190316, GF holds an MSc fellowship from the Universidad de Antofagasta (Chile)).
Evaluation of Clinical efficacy of Uterine Relaxants in prevention of Preterm labor: A Prospective study at Tertiary Care Teaching Hospital.

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Introduction
Uterine relaxants are the drugs used to suppress premature uterine contractions. Babies born alive and delivered between 28 to 37 completed weeks of gestation are referred to as preterm babies. PTL is associated with poor neonatal outcomes like- respiratory distress syndrome, Jaundice, Anemia, etc. We conducted this study to assess the effectiveness of oral as well as vaginal progesterone in prolonging the threatened PTL for ≥ 48 hours and to analyze the maternal and fetal outcomes associated with it.

Materials & Methods
This comparative clinical study was carried out from April 2018 to July 2018 after obtaining permission from institutional review board and informed consent was provided by all the participants. A total of 78 patients diagnosed with threatened PTL and aged between 19 to 35 years with gestational age between 28 and 37 weeks from LMP and cervix no more than 4 cm dilated were included. The selected patients who refused treatment were allocated to Control group (n= 29). Rest were divided into Group 1 (n= 21) & Group 2 (n= 28) by using lottery method. Data was analyzed with statistical analysis program (SPSS version 23). Numerical variables were presented in the form of mean ±SD. Fischer’s exact test was applied to evaluate primary outcome. Student’s unpaired t- test was applied to analyze quantitative variables. P-value equal or less than 0.05 was considered as statistically significant.

Results
Maternal age ranged from 19 to 35 years with mean age of 23 ± 3.2 years. Out of a total 78 patients, primary outcome was achieved in 39 patients (50%). PTL was prevented by ≥ 48 hours in 20.6%, 52.3% and 78.5% of patients in control, group 1 and group 2 respectively. Post Partum hemorrhage(15), followed by anemia(13) and vaginal infection(10) was the most common adverse maternal outcomes. Only 10.2% of the neonates delivered in our study had birth weight ≥ 2.5 kg. Thus, low birth weight was the most common adverse neonatal outcome. Mean birth weight of the neonates was 1.72 ± 0.5 Kg. More than half of the neonates (58.9%) required admission in NICU. The number of days of NICU stay varied between 2 to 8 days, mean ± SD = 2 ± 1.9 days. Respiratory distress was the next most common finding; hence, 28.2% neonates in our study needed the use of surfactant. Other less common outcomes were anemia (7.6%) and infection (7.6%)

Conclusion
Although the sample size is small, findings of our study support the use of natural micronized progesterone in prolonging threatened preterm labour.
Probable impact of hostile intrauterine environment on DNA methylation reprogramming in early embryos

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Introduction
Missed abortion (MA) often indicates reduced reproductive capacity. Modified epigenetic profile (in response to infection, diet, stress, etc.) may derange intrauterine environment in women with liable MHC set. The preimplantation embryo is less protected from environment than the germline and, thus, is particularly susceptible to epigenetic alterations. Probably aberrant genome-wide DNA methylation reprogramming in embryos is linked to adverse intrauterine events and, if extreme methylation values attributable to epimutations in developmentally important genes exceed threshold, bring along embryo loss.

Materials & Methods
In order to shed a light on link between uterine environment and epigenetic alterations at imprinted loci followed by pregnancy loss, our study scrutinized 56 cases of MA in the first trimester with regard to H19 hypermethylation and biallelic IGF2 expression. 21.4% (12) women found to harbor methylation abnormalities of these genes were selected to the 1st group. Then their intrauterine washings profile at the 8th postovulatory day (isoprostane F2-IsoPs as oxidative stress marker, glycodelin GdA crucial for implantation due to immunosuppressive activity, IL6, TNFα, IL1β) was compared with profile of other 44 women who had shown no methylation abnormalities (2nd group), 29 women after unsuccessful IVF cycle (3rd) and 15 reproductive-age females who had had uncomplicated pregnancy 2-4 years ago (control). Because indispensable precondition for progesterone-regulated GdA production in endometrium is functioning ovaries, next ovulatory cycle follicular fluid was tested for F2-IsoPs.

Results
Our study revealed significantly higher levels of all proinflammatory cytokines and F2-IsoPs in 1st and 3rd subsets comparatively to 2nd and control groups, and opposite situation regarding GdA: much lower value in 1st and 3rd groups. The highest value of follicular fluid F2-IsoPs was detected in the 1st group and just slightly lower in the 3rd, 2nd group matched very low control F2-IsoPs.

Conclusion
Both excessive F2-IsoPs in growing follicle and impaired uterine susceptibility affect ovarian-uterine cooperation in GdA production that implies reduced protection of embryo against maternal immunity. Methylation abnormalities of imprinted genes may serve as an indicator for more profound epigenetic defects caused probably by hostile uterine environment. Followed gaps in regulation of embryo DNA methylation reprogramming beget conflict between paternal and maternal genomes on egg growth.
Evaluation of the effects of taking Evening Primrose Oil (EPO) capsules from 38th week of pregnancy in nulliparous women (labor / induction / outcomes)

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Introduction
Evening Primrose (Oenthera Biennis) is a medical plant from North America. Evening Primrose Oil (EPO) contains Gamma-Linolenic Acid (GLA) that stimulates the production of prostaglandins in body. It is believed initiate cervical ripening due to EPO. The aim of this study was to evaluate the effects of taking EPO from 38th week of pregnancy in nulliparous women on the type of delivery, induction need, duration of induction, labor duration, neonatal outcomes, quality of labor and maternal complications.

Materials & Methods
In double-blind randomized controlled trial performed in Sanandaj Besat Hospital, 440 nulliparous pregnant women in 38th week of pregnancy and with bishop score of <6 were divided randomly in to two groups (220 in each). First group took EPO 1g Q12h and next group took placebo. In the other part of the study women that did not enter to labor phase until 40th week of pregnancy from both groups, were evaluated during the induction by oxytocin to check the effects of EPO on induction and outcomes.

Results
Normal labor (vaginal or cesarean delivery) without needed of induction was occurred in 134(60.9%) women of EPO group (15 C/S (11.19%) and 119 NVD (88.80%)) and 122(55.45%) women of placebo group (21 C/S (17.21%) and 101 NVD (82.78%)). Frequency of cesarean section deliveries decreased significantly in EPO group compared with placebo group. 86(39.09%) women from EPO group and 98(44.54%) women from placebo group needed induction (oxytocin) for delivery, that the rate of successful vaginal delivery was significantly higher in EPO group and duration of active phase, second stage and third stage of labor were shorter in EPO group. No significant difference of neonatal factors and outcomes (such as 1st and 5th min apgar score / need for NICU admission ..) were found between the EPO and placebo groups.

Conclusion
Research showed significant positive results of taking EPO capsules from 38th week of pregnancy in nulliparous women, on the type of delivery (decrease cesarean section), length of labor, need for induction, duration of induction and success rate.
The origin of ovarian follicular bile acids in humans

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Introduction
Bile acids (BA) are present in follicular fluid (FF), the natural environment of the oocyte, and have been linked to embryo development. However, information on the source of ovarian BA is scarce. Therefore, we aimed to study local ovarian synthesis and BA transport from blood into FF.

Materials & Methods
Total BA levels were determined in matching FF and blood samples from women who underwent modified natural cycle-in vitro fertilization. In vitro BA production by human mural (MCG) and cumulus granulosa cells (CGC) was measured by mass spectrometry. Gene expression and protein production were quantified in human MCG and CGC and in human ovarian tissue by quantitative PCR and Western blot and immunohistochemistry, respectively.

Results
There was a significant correlation between the levels of BA in blood and FF (rs=0.186, P=0.027). Moreover, levels of FF BA were almost double those in blood (OR 58.01, 95% confidence interval: 31.05-108.40, P<0.001), indicating that, in addition to passive diffusion, other sources of ovarian BA might exist. The key BA synthesis enzyme CYP7A1 was absent in MGC and CGC, and there was no evidence of BA production in vitro. Therefore, local ovarian BA production is unlikely. However, common BA importers (Na+/Taurocholate Cotransporting Polypeptide, Apical Sodium-Dependent Bile Acid Transporter) and an exporter (ATP Binding Cassette Subfamily C Member 3) were identified in GC, theca cells and the oocyte.

Conclusion
In summary, these results indicate that passive and active transport of BA from blood into FF constitute the main sources of ovarian BA.
Atosiban versus Nifedipine for Inhibition of Preterm Labor: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

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Introduction
Preterm labor (PTL) is associated with high rates of newborns death and serious adverse events. The choice of 1st line therapy lies mainly between two different tocolytic classes, atosiban, and nifedipine. Therefore, our study aimed to compare the clinical efficacy and safety of atosiban versus nifedipine for treatment of PTL.

Materials & Methods
PubMed, Scopus, Web of Science, and Cochrane CENTRAL were searched for randomized controlled trials (RCTs) comparing nifedipine with atosiban in women with PTL. Records were screened for eligibility and data were extracted and analyzed using RevMan 5.2 with a random effect model to pool the safety and efficacy data as relative risk (RR), with their 95% confidence interval (CI).

Results
Six RCTs with a total of 992 patients were included. There was no significant difference between atosiban and nifedipine regarding efficacy or effectiveness either in pregnancy prolongation ≥ 48 hours (RR = 1.06, 95% CI [0.92, 1.22], p = 0.44, RR = 0.93, 95% CI [0.84, 1.03], p = 0.18, respectively), or in pregnancy prolongation ≥ seven days (RR = 1.04, 95% CI [0.89, 1.21], p = 0.65, RR = 0.91, 95% CI [0.79, 1.05], p = 0.18, respectively). Atosiban was associated with less adverse events than nifedipine, with statistical significant difference in headache and tachycardia (RR = 0.47, p = 0.05, RR = 0.20, p = 0.02, respectively); while there was no significant difference regarding palpitation, hypotension, vomiting, and nausea (RR = 0.37, RR = 0.30, RR = 1.55, RR = 2.44, respectively). Risk of neonates’ adverse events with atosiban was similar to nifedipine.

Conclusion
In PTL women, our findings suggested that atosiban is better than nifedipine regarding maternal adverse events with no difference in pregnancy prolongation ≥ 48 hours or ≥ 7 days, or in neonates’ adverse events. However, further studies with increased sample size are needed.
Diagnostic value of signal peptide-CUB-EGF domain-containing protein 1 as an early and late biochemical marker in the ovarian torsion rat model.

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Introduction
Ovarian torsion is a gynecological emergency that may affect infertility. Most of the cases are diagnosed during operation. Signal peptide-CUB-EGF (epidermal growth factor-like protein) domain-containing protein 1 (SCUBE1) is an experimental marker of ischemia that has been previously studied both in rat models and humans. In this study, we aimed to measure the SCUBE1 values as a biochemical marker for early diagnosis and to determine the early and late changes of the SCUBE1 values in the ovarian torsion and to determine whether SCUBE1 could be a marker for diagnosis in the acute phase of torsion.

Materials & Methods
A total of 18 Sprague-Dawley rats were equally divided into three groups. Group 1 (n = 6) was the Sham group and was only given a laparotomy procedure. Group 2 (n = 6) underwent bilateral ovarian torsion and ovarian ischemia lasting 8 h. Group 3 (n = 6) was subjected to bilateral ovarian torsion and ischemia lasting 24 h. Blood samples were collected from all three groups after the operations, and SCUBE1 levels were studied. Ovarian samples were collected, and microscopic evaluation was performed. The correlation of SCUBE1 levels and histopathological findings were investigated.

Results
The mean SCUBE1 level of group 3 was statistically higher than other groups (P < 0.01). Follicular degeneration and infiltration of inflammatory cells were, respectively, statistically significant in groups 2 and 3 (P = 0.002 and P = 0.045, respectively).

Conclusion
The SCUBE1 is practical biochemical marker which can be useful for the diagnosis of the ovarian torsion in the first 24 hours, but more randomized controlled studies are necessary in order to implement it in clinical settings.
Immunology and Infectious Disease I

Chair

Wouter F.W. Bierman MD PhD

Presenters

Barazesh, A. (Afshin)
López, M.C. (Maria)
Marin, M.J.M (Maria Jose)
Paneva, S. (Sofija)
Ushakova, E.I. (Ekaterina)
Waheed, Y.W (Yasir)
Zasadziński, K. Z. (Konrad)
Antileishmanial activity of mannosylated meglumine antimonate-loaded albumin nanoparticles for treatment of cutaneous leishmaniasis: An in vitro evaluation

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Introduction
Cutaneous Leishmaniasis (CL) is one of the six important diseases in tropical and subtropical regions which is caused by an intra-macrophage protozoan parasite called Leishmania. Selective drugs for treatment is pentavalent antimony compounds, but because of side effects and resistance to parasites, the use of new formulations seems to be necessary. Therefore, by choosing macrophages as a drug target, many of the problems associated with these drugs can be solved. In this study, we encapsulated the Meglumine Antimonate into the Albumin as a drug carrier (MA-Alb-NPs) and mannosylated it with Mannose ligands (MA-Alb.Mann-NPs). Then, evaluated in vitro anti-leishmanial activity of these nanodrugs on Leishmania major.

Materials & Methods
The precipitation method and Millard reaction were used to encapsulate and mannosylated the drugs. After assessing the quality of nanodrugs, their cytotoxicity and anti-leishmanial effects were evaluated on L.major promastigotes in in vitro conditions.

Results
Both designed nanodrugs had the lowest cytotoxicity against macrophages in comparison with glucantime as a control drug. The IC50 values of MA-Alb-NPs and MA-Alb.Mann-NPs were calculated 8.35 ± 0.92 and 9.59 ± 0.98, respectively, which is very significant compared to the IC50 obtained for the control drug (26.67 ± 1.42).

Conclusion
Given that both designed nano-formulations exhibited significantly more antileishmanial effects than their simple form (Glucantime) and they can improve the effects of this old drug, so, they can be good alternatives and it is suggested that further studies should be done in vivo in this regard.
Human Pegivirus-1 and Hepatitis C virus infection in Colombian patients with diagnosis of lymphoma

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Introduction
Lymphoma disease is a malignant pathology. It is occasioned by alterations in the development and differentiation of lymphocytes. The disease could be classified in Hodgkin and Non-Hodking (NHL) lymphoma. On the other hand, Human Pegivirus-1 (HPgV-1) and Hepatitis C virus (HCV) belong to Flaviriviridae family, genus Pegivirus and Hepacivirus, respectively. Their genome organization, as well as RNA sequence, have many similarities. Several reports have demonstrated a strong evidence of HCV infection and Non-Hodgkin lymphoma (NHL), while scarce epidemiological data suggest that HPgV-1 could be associated with Non-Hodgkin lymphoma (NHL). The aim of this study was to describe molecular markers of HPgV-1 and HCV infection in samples from patients with diagnosis of lymphoma in Colombia.

Materials & Methods
Blood samples were collected from 28 patients with diagnosis of lymphoma attending the oncology unit of Manuel Uribe Angel Hospital (Northeast, Colombia). Viral RNA was purified from plasma and peripheral blood mononuclear cells by QIAamp Viral RNA Kit and TRIZOL, respectively. Detection of HCV (5′UTR) and HPgV-1 (5′UTR and NS5A) regions were tested by three nested RT-PCR protocols previously reported. HCV and HPgV-1 positive samples were sequenced by automated dideoxy method (Macrogen). HCV viral genotype was analyzed using GenBank prototypes. Phylogenetic inference and tree reconstruction were performed with MEGA 7.0, BioEdit, MrBayes, Tracer v1.6, and FigTree v.1.4.6 software.

Results
Viral genomes were detected in 9 out of 28 samples. HPgV in four cases and HCV in five. None of the samples were positive for both viral genomes. Eight samples corresponded to patients with diagnosis of NHL, while one case (HCV genome positive) to Hodgkin lymphoma. Regarding HCV phylogenic analysis, all sequences grouped into the genotype 2 cluster with sequences from Colombia, Venezuela, Mexico, Uruguay, and Japan, including the reference sequence of genotype 2 from Japan.

Conclusion
Viral genomes were present in the samples recruited (9/28). All HCV isolates belong to genotype 2 and the phylogenetic analysis to determine HPgV genotype is in construction. This study is the first molecular analysis of HPgV-1 and HCV infection in Colombia patients with lymphoma.
Antimicrobial Use in Acute Care Hospitals in Colombia: A Multicenter Point Prevalence Study

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Introduction

Pointprevalence surveys of antimicrobial prescribing provide a useful insight into the appropriate use. The aim of the study was to estimate the point prevalence of antibiotic (ATB) and antifungal (ATF) use and prescription characteristics in patients hospitalized in acute care hospitals in Colombia.

Materials & Methods

Six acute care hospitals were included in a singleday point prevalence survey (August 27, 2015). A sample of 700 patients was estimated, stratified random sampling according to hospital and admission service was applied. Hospitalized patients aged ≥14 years were included. An electronic data collection form was used to record demographic information, active infection, antimicrobial use, microbiological culture, appropriate antimicrobial coverage.

Results

Seven hundred patients were included with a median age of 54 years (IQR: 31 70), the prevalence of infection was 38%, including 20% from nosocomial infection. Three hundred and thirty (47%) patients received antibiotics, with a total of 477 prescriptions for 44 different antibiotics, 55.7% and 45.6% of patients in the intensive care unit and hospital, respectively, received antibiotics. Beta lactams and quinolones were the most commonly used antibiotics groups; the most common antibiotics were Ampicillin/Sulbactam 16.7%, Cefazolin 13.9% and Vancomycin 13.3%; 34% of patients received more than one antibiotic, and the median duration was 4 days (IQR: 28). The main indication was the treatment of community acquired infections, antibiotic prophylaxis 9%, and 13% was unjustified prescription; 52% of the isolates were Enterobacteriaceae and four patients in which at least one bacterium was isolated had an inappropriate antibiotic coverage, 4% (4/101). The prevalence of antifungal use was 3.6%, of which Fluconazole (40%) and Caspofungin (24%) were the most frequent and had a median duration of 5 days (IQR: 2 8); 3% and 7% of hospitalized patients and those in intensive care units, respectively, received antifungals.

Conclusion

The high frequency of antibiotic use in acute care hospitals requires strategies of rational use of antibiotics to optimize their use.
The binding epitopes and molecular mechanisms of LGI1-autoantibodies

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Introduction
Leucine-rich glioma-inactivated 1 (LGI1), a secreted neuronal protein, connects pre- and postsynaptic a-disintegrin-and-metalloproteinase (ADAM) 23 and ADAM22, and regulates Kv1.1 voltage-gated potassium channel and AMPA-receptor-mediated synaptic transmission, mainly in the hippocampus. Autoantibodies against LGI1 are found in patients with limbic encephalitis (LE), and patients exhibiting isolated seizures, Morvan's syndrome, pain, and neuromyotonia. Polyclonality and pathogenicity of LGI1-antibodies has been demonstrated recently, but little is known about their pathogenic molecular mechanisms and epitopes.

Materials & Methods
Serum LGI1-antibodies were obtained from 30 clinically-characterized LE patients, while monoclonal antibodies (mAb) were cloned from peripheral patient B-cells by collaborators.

Full-length LGI1, its leucine-rich-repeat (LRR) and its epitempin (EPTP) domains were independently cloned into the mammalian expression vector pcDNA3.1, together with a transmembrane domain and EGFP. Constructs were expressed in HEK293T-cells and cell-surface binding of antibodies was studied with live cell-based assays and fluorescence microscopy. For functional studies, secreted full-length LGI1 was expressed in HEK293T-cell medium and applied to ADAM22/23 expressing HEK293T-cells.

Results
Serum LGI1-antibodies were reactive for the full-length LGI1, as well as both the LRR- and EPTP-domain, with titers that were mutually correlated and variable over time. By contrast, previous work by the group had shown that LGI1-mAbs preferentially bound either the LRR-domain or EPTP-domain, with little cross-reactivity. The two mAb classes exhibited distinct molecular mechanisms. EPTP-mAbs blocked interaction of LGI1 with its receptors ADAM22/23 in a dose-dependent manner. On the other hand, LRR-mAbs bound LGI1 docked on ADAM22/23 and mediated internalization of the complex.

Conclusion
The results demonstrate that LGI1-mAbs exhibit distinct, dichotomous molecular mechanisms in vitro, reminiscent of their distinct binding epitopes. This suggests the two mAb classes may have different pathophysiological effects in vivo. In support of this, patient sera contained both mAb classes, with titers that varied over time, suggesting the relative mAb ratios may have clinical implications and predict disease phenotype. Future experiments should focus on finer epitope mapping for design of better-targeted individualized therapies, as well as on the downstream neurophysiological effects of the antibodies in neuronal cultures for improved understanding of disease mechanisms Although this study looked at LE, the experimental strategy can be extended to studying other antibody-mediated diseases.
CD4+ and CD8+ T lymphocytes protect mice treated with TLR4 agonist after resection of the primary tumor from metastatic 4T1 breast cancer

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Introduction
The 4T1 mammary carcinoma is a transplantable tumor cell line that is very aggressive and highly tumorigenic. We used subcutaneously cancer implantation and injection of TLR4 agonist to evaluate the hypothesis that primary tumor resection and treatment with immunotherapy drug improve survival in metastatic breast cancer by reducing overall tumor burden and increasing anti-tumor immune response. Also, we used ELISpot assays to measure key cellular functions of immune system cells.

Materials & Methods
Murine mammary adenocarcinoma 4T1 cells (15x10^5) were implanted subcutaneously into the right side of each 60 BALB/c mice. Tumor growth was monitored daily starting at the day when tumors became palpable. Mean tumor dimension was calculated as V= (L x W x W)/2, where V is tumor volume, W is tumor width, L is tumor length. Surgical resection was performed on day 11 after inoculation of 4T1 tumor cells. Kaplan-Meier analysis with a log-rank test was performed to calculate the survival curves. CD4+ and CD8+ T lymphocytes we sorted on FACS Aria II from the tumor and conducted ELISpot to measure production of IFNy. Cytolytic activity of CD8+ T cells we studied in immune cell killing assay for measurements of tumor cell death.

Results
Resection of primary tumor extended survival of non-treated mice by 20 days, but still after that time all mice die very quickly from metastases. The treatment of the TLR4 agonist (Immunomax *) contributes to survival extension by 40 days and completely cured 20% of the mice of metastatic breast cancer. On day 149, we re-inoculated the tumor cells in the surviving mice. In 2 mice treated with the TLR4 agonist, the tumor did not grow. CD4 + T cells produce a lot of IFNy in response to cancer cells. CD8 + T lymphocytes from the tumor completely kill 4T1 cancer cells compared to other T cells from naive mice.

Conclusion
Decreasing overall tumor burden and treatment with the TLR4 agonist activated immune cells and improved mice survival. Furthermore, survivors mice had immunological memory after repeated inoculation of the tumor cells with the treatment of TLR4 agonist.
Cloning, sequencing and in vitro analysis of Hepatitis C virus polymerase gene from Pakistani patient samples.

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Introduction
Hepatitis C virus is a global health problem. Pakistan has the 2nd highest rate of HCV in the world. The HCV NS5B gene makes the RNA dependent RNA polymerase of the virus. HCV polymerase is one the best target to design antiviral drugs.

Materials & Methods
Hepatitis C virus Polymerase gene (NS5B) was amplified, cloned and sequenced from Pakistani isolates. Nucleotide and amino acid sequence comparison of important domain of HCV polymerase gene was done with already reported sequence available in NCBI. Phylogenetic analysis was performed by using CLC work bench software. Polymerase gene was expressed in both Prokaryotic and Eukaryotic Cells. Polymerase gene was further studied in different HCV replication assays.

Results
We compared the sequences of 6 different motifs of HCV NS5B gene name from A-F and a beta hairpin loop. The motif A sequences remained high conserved especially the divalent cation binding motif. There are certain nucleotide changes in motif B, which did not affect the respective amino acids. The residues which takes part in sugar section remains highly conserved. Motif C, which forms the active site of enzyme, remains highly conserved. High amino acids variation is observed in motif D and motif E. While motif F remains conserved. Phylogenetic analysis revealed that our reported sequences are clustered with sequences from India. We also analyzed the effect of different drugs on the HCV NS5B gene is biochemical and cell based assay.

Conclusion
The important residues taking part in polymerization remains highly conserved. NS5B gene showed very good activity in biochemical and cell based replications assays.
Herpes zoster in children

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Introduction
Herpes zoster (HZ) is an infectious disease caused by reactivation of latent varicella-zoster virus infection. It manifests with vesicular eruption in an affected dermatome. It is usually a disease of adult/elderly persons but may also occur in children. The main risk factor for HZ is immunodeficiency.

Materials & Methods
Medical charts of all children with HZ diagnosed in Department of Children’s Infectious Diseases (Pediatric Ward of Infectious Diseases Hospital in Warsaw) between 1.06.2013 and 31.08.2017 were analyzed. There were 101 immunocompetent patients (Group A) and 32 immunocompromised (Group B). Age, history of varicella, time interval between varicella and HZ, underlying diseases, immunosuppressive therapy, dermatome involvement and HZ complications were studied in both groups.

Results
The median age in Group A and Group B was 9 years 5 months. Group B consisted mainly of patients with oncologic disorders (21/32). The mean time interval between varicella and HZ was similar: 4 years 10 months in the Group A and 4 years 11 months in the Group B. In two children from the Group B recurrent HZ was reported. In both groups thoracic dermatomes were affected the most frequently (59,4% and 44%, p=0,12). There were not statistically significant differences between involvement of cervical, lumbar dermatomes and of regions nerved by trigeminal nerve in both groups, but dermatomes S1-S2 were affected in 5 patients from the Group B and in no patient from the Group A (p<0,005). In both groups there were single cases of herpes zoster duplex (with involvement of noncontiguous dermatomes). Complications occured in 27/101 (27%) patients from the Group A and in 8/32 (25%) from the Group B. In both groups bacterial infections (including sepsis) and disseminated HZ were diagnosed but neurologic complications were observed only in the Group A.

Conclusion
Herpes zoster occurs in both immunocompetent and immunocompromised children. Clinical manifestations usually are similar. Serious complications, although uncommon, affect not only immunocompromised patients but also otherwise healthy children.
Medical Microbiology

Chair
Janette K. Burgess PhD

Presenters
Brushett, S.N. (Siobhan)
Das, S. (Srijan)
Ghosh, S. (Saptarshi)
Mishra, S. (Smita)
Onwubiko, CEU (Chinyere)
Shang, W. (Weilong)
Thapa, S. Thapa (Sandeep)
vander Ham, I. T. (Iris)
A novel mechanism of Staphylococcus aureus transition from colonization to infection

Brushett, S.N. (Siobhan); Chlebowicz, M (Monica) Dr.; García-Cobos, S (Silvia) Dr.; Raangs, E.C. (Erwin C.); Bosma, F (Fenna); Friedrich, A.W. (Alex W.) Prof. Dr.; Rossen, J.W. (John) Prof. Dr.; Monge Gomes do Couto, N. (Natacha) Dr.

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Introduction
Staphylococcus aureus is one of the most causative pathogens of bloodstream infections (BSIs) and the most important cause of BSI-associated death. Though it has previously been described that S. aureus infection strains are clonally identical to some endogenous carriage strains, the mechanism of transition from S. aureus colonization to infection is not yet clearly understood. In this study, we hypothesized that some S. aureus colonization strains acquire single-nucleotide polymorphisms (SNPs) associated with infection at the colonization site, which facilitate these strains in establishing an infection when breaching the mechanical barrier of the skin or mucosa.

Materials & Methods
With the aim of identifying potentially novel and distinct genetic markers associated with infection and colonization, 144 S. aureus infection isolates and 74 colonization isolates, of various genotypes, were whole genome sequenced (WGS) and analyzed using several bioinformatics tools.

Results
Using a WGS approach, we demonstrated that non-synonymous SNPs associated with infection were significantly (FDR<0.05) present in S. aureus bloodstream infection (SAB) isolates, but were also consistently present in a subset of colonization isolates. Interestingly, these colonization isolates were different to those that contained SNPs significantly (FDR<0.05) associated with colonization.

Conclusion
These results, therefore, provide evidence towards our hypothesis and further facilitate our understanding of S. aureus pathogenesis. Moreover, these findings could ultimately and potentially be used in the clinical setting as an indication of SAB risk, thereby allowing for the optimal management and possible circumvention of SABs in at-risk patients. Should this approach be successful, this could also possibly aid in decreasing the incidence rate of SABs, and, in turn, also possibly decrease the associated morbidity and mortality rates.
Phenotypic characterization of Enterococcal infection with special reference to Vancomycin resistance

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Introduction
Enterococci are the second leading cause of hospital-acquired infections in eastern India. Though not highly virulent, their intrinsic resistance to broad-spectrum antibiotics allows them to cause super-infections with fatal outcomes.

The objective of the study is to find out the prevalence of enterococcal infections in a tertiary care hospital of eastern India and thus perform phenotypic characterization along with testing of antibiotic sensitivity patterns of isolates. Medical College Hospital, Kolkata, West Bengal was the hospital chosen for the purpose.

Materials & Methods
A total 2349 non-repetitive, consecutive isolates were collected from different clinical samples namely pus, blood, urine and sputum over a period of six months. Direct smear examination and culture for isolation of the organism was done. Phenotypic based scheme included Gram staining, Esculin hydrolysis and PYR testing to identify genus Enterococcus. Species-level identification was done by API (KB005: high strep identification kit) and few supplementary biochemical examinations. PYR- positive isolates were further characterised into VRE (Vancomycin Resistant Enterococci) and non-VRE depending upon vancomycin (30 mcg) disc inhibition zone size. E-test was further done to determine Minimum Inhibitory Concentration (MIC) of the VRE group. Finally, isolates were classified into groups depending on their MIC values.

Results
Out of the 2349 isolates, 141 were identified as genus Enterococcus. E. faecalis 33%, E. faecium 15%, E durans 24%, E. dispar 15%, E. casseliflavus 7%, E. mundtii 5% and E. gallerinerium 2% . Resistance to different antibiotics was seen and 52 out of 140 isolates were found to be resistant to Vancomycin (by Kirby-Bauer Disc Diffusion Method) VRE confirmation was done by E-test.

Conclusion
The study reveals the problem of multidrug-resistant Enterococcus and emergence of VRE in eastern Indian clinics. Clinicians should thus consider this and treat accordingly as soon as possible to restrict the spread of such infections which is a threat to the entire community.
Methicillin Resistant Staphylococcus aureus: A Real Concern in Healthcare Set Up

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Introduction
Staphylococcus aureus is notorious in developing resistance against many antimicrobials. It develops Methicillin resistance by altering PBP2 receptors and such isolates are commonly found in healthcare setups creating a great therapeutic problem. Very few as well as costly therapeutic options are left, patient’s morbidity is increased and bed turnover rate is decreased. Mortality is also increased.

The objective of our study was to identify and characterize genotypically by demonstrating the mecA gene in the isolates of Staphylococcus aureus in clinical samples in a tertiary care hospital to get an idea about the methicillin resistance.

Materials & Methods
A total 2349 non-repetitive, consecutive isolates were collected from different clinical samples namely pus, blood, urine and sputum over a period of six months. Standard laboratory procedures were followed for phenotypic identification of methicillin-resistant Staphylococcus aureus (MRSA) using Cephoxitin disc. Vitek 2 automation confirmed MRSA strains through MIC value. Isolates were confirmed as MRSA by demonstration of the mecA gene by PCR.

Results
402 isolates out of 1152 (34.89%) were phenotypically identified as MRSA and rests were MSSA. Genotypic identification demonstrated the presence of mecA gene in phenotypically positive isolates. Among 402 isolates 285 were pus samples, 72 were blood, 35 were urine and 10 were sputum samples. Majority of MRSA were isolated from pus samples. No isolate was resistant to vancomycin or linezolid.

Conclusion
Our study revealed that the prevalence of MRSA (34.89%) is quite high in our healthcare set up. This is a warning to be conveyed to our infection control committee to develop proper antibiotic policy.

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Introduction
The rapid evolution of microorganisms with the advancement of medicines makes the amelioration of various kinds of disease difficult. Prolonged interaction of microorganisms with the administered drugs via human immune system gives rise to various resistant strains against a wide range of drugs. Their parallel evolution due to rapid mutation is one of the reasons for unavailability of sophisticated treatment. Several drug regimen has already been designed which, today, are of no use. This situation creates a kind of global threat and shows the need for major research boost. Justicia adhatoda, an Indian medicinal plant, is known to cure a wide range of diseases like respiratory ailments like bronchitis, asthma, cough, cold, influenza, tuberculosis, and diabetes to some extent. The medicinal properties of the plant have extensively been discussed in ancient scriptures. Hence, the whole plant extracts of Justicia adhatoda was studied to assess its anti-diabetic, anti-microbial and anti-inflammatory activities by series of biochemical assays.

Materials & Methods
J.adhatoda plant was acquired verified by NISCAIR (NISCAIR/RHMD/Consult/2015/2907/100). The whole plant extracts were prepared in four solvents viz; Ethanol(EtOH), Ethyl Acetate(EA), Chloroform(CH) and Dichloromethane (DCM) by mixing powdered whole plant of J.adhatoda followed by overnight incubation at 37°C. The mixture was filtered and concentrated for further use. The Assessment of various properties of plant extracts was done by performing various biochemical tests viz, - Reducing power assay, DPPH assay, Alpha-amylase enzyme inhibition assay, for anti-oxidant and anti-diabetic activity, Micro-broth dilution assay for anti-bacterial activity & Cell lysis inhibition and Protease inhibition assays for Anti-inflammatory activity. Standard protocols were followed for all assays.

Results
Ethanol extract showed highest anti-diabetic activity closely followed by Ethyl acetate, while DCM extract showed the highest anti-inflammatory activity. All three extracts came out to be excellent anti-microbial, while Chloroform and Ethyl acetate extract showed slightly higher anti-microbial action than other extracts.

Conclusion
Although all extracts were found to possess the aforementioned activities, Ethanol extract came out to be the best one. The bioactive compound analysis is ongoing, however, impression for alkaloids and steroids to be an important factor were made on the basis of phytochemical analysis. Further exploration is needed for definitive results.
THE STUDY OF THE THERAPEUTIC ACTIVITY OF THE EXTRACTS OF GNETUM AFRICANUM LEAVES AGAINST IN-HOSPITAL BACTERIAL STRAINS

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Introduction
The rediscovery and reintroduction of antimicrobial agents into conventional medicine is the purpose of this work, since the newest, linezolid oxazolidinones were introduced in 2000. The therapeutic potential of Gnetum africanum extracts were obtained in methanol, hexane and chloroform solvents at different concentrations, and tested on different in-hospital antibiotic-resistant bacterial strains.

Materials & Methods
The cleaned, dried leaves were ground into a fine powder from which 10 g each was extracted with 100 ml of 95% methanol (methanol extract), 100 mL of hexane (hexane extract) and 100 mL of chloroform (chloroform extract) under magnetic stirring in the dark at room temperature for 24 hours. The extracts were tested on 5 bacterial strains isolated from the in-hospital patients - Staphylococcus aureus, Bacillus cereus, Escherichia coli, Klebsiella spp., Enterobacter aerogenes.

Results
At 265.50 mg/mL and 31.85 mg/mL conc. of the methanol extract, the inhibition rate (IR) of 3 mm was seen on S. aureus and E. Aerogenes and 2mm IR observed against B. cereus, E. coli and Klebsiella spp. Hexane extract showed IR ranging from 2mm to 4mm on the B. cereus strain at 132.75 mg/mL, 15.92 mg/mL, 22.10 mg/mL conc. On S. aureus strain, the hexane extract exhibited intermediate antibacterial activity only at 132.75 mg/mL conc., with little or no effects on the other bacterial strains tested. Chloroform extract of G. africanum at 66.37 mg/mL, 7.96 mg/mL and 11.05 mg/mL conc. showed no significant antibacterial activity.

Conclusion
Our results showed that the extracts of Gnetum africanum have an antibacterial effect, which is depending on the type of solvent used for the extraction, the concentration tested and the bacterial strain of concern.
β-Lactam Antibiotics Stimulate the Pathogenicity of Methicillin-resistant Staphylococcus aureus Via SarA-controlled Tandem Lipoprotein Expression

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Introduction
Methicillin-resistant Staphylococcus aureus (MRSA) is a leading cause of nosocomial infections worldwide. MRSA resists nearly all β-lactam antibiotics that have a bactericidal activity and a signal inducer effect. β-lactams are not only widely used in practice to treat infectious diseases, but also stimulates MRSA pathogenicity and worse outcome of bacterial infections. However, whether the inducer effect of empirically used β-lactams stimulates MRSA pathogenicity in vivo remains unclear.

Materials & Methods
Tlpps mutant strains were constructed to determine whether Tlpps contribute to innate immune stimulation. Recombinant Tlpp1-his protein was purified to determine whether MRSA Tlpps exhibit immune modulatory effects on primary macrophages. BALB/c mouse infection models were used to investigate the β-lactam-stimulated Tlpps contribute to the pathogenesis of MRSA. EMSA experiments were used to revealed the direct regulation of SarA on Tlpps expression.

Results
We demonstrated that a new cluster of tandem lipoprotein genes (tlpps) was upregulated in MRSA in response to the subinhibitory concentrations of β-lactams. The increased Tlpps significantly enhanced the production of interleukin-6 and tumor necrosis factor-a in RAW264.7 macrophages (P < 0.01). The tlpps deletion mutant (N315Δtlpps) significantly decreased the proinflammatory cytokine levels in vitro and in vivo (P < 0.01). Purified lipidated Tlpp1-his could trigger a TLR2-dependent immune response. The bacterial loads of N315Δtlpps in the mouse kidney were lower than those of the wild-type N315. The β-lactam-treated MRSA exacerbated cutaneous infections in both BALB/c mice and C57BL/6 mice, presenting increased lesion size, destroyed skin structure, and easily promoted abscess formation compared with those of the untreated MRSA did. This phenomenon was diminished in the C57BL/6 TLR2-/- mice. We also demonstrated the β-lactams that promoted the MRSA pathogenicity were SarA dependent, and the increasing expression of Tlpps after β-lactam treatment was directly controlled by the global regulator SarA.

Conclusion
β-lactam-stimulated MRSA tlpp expression is directly controlled by the global regulator SarA. The increased Tlpps in MRSA significantly promotes TLR2-dependent signaling pathway activation and results in promoting exuberant, systemic inflammation responses, thereby facilitating MRSA colonization and infection. Our findings suggested that β-lactams must be used carefully because they might aggravate the outcome of MRSA infection.
Assessment and diagnosis of Entamoeba hystolytica, E. dispar and E. moshkovskii in stool sample from rural community of Nepal

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Introduction
Nepal is a developing country which has many health problems. Amebiasis is one of the infectious diseases that is highly seen in rural area of Nepal caused by Entamoeba species. Recent reports show that open defecation, drinking untreated water, unsanitary habits and lack of basic health knowledge cause higher mortality and morbidity in our country. E. histolytica is an anaerobic pathogenic parasitic. However, E. dispar and E. moshkovskii exits as non-pathogenic. Likewise, E. histolytica, E. dispar and E. moshkovskii are morphologically identical but genetically distinct species.

Materials & Methods
A total of 270 faecal sample were collected from south eastern terai region of Nepal after the informed consent form. The samples were processed by direct wet smear and formalin ethyl acetate concentration technique. Eventually, microscopic examination were performed for the detection of Entamoeba species along with other intestinal parasites. Furthermore, enzyme immunoassay were executed to detect antigens of E. histolytica through ELISA. Additionally, microscopically positive samples for Entamoeba species cysts were further characterized using a Nested- PCR targeting 16S-like ribosomal RNA gene. The PCR generate amplicons of 174 bp for E. dispar, 439 bp for E. histolytica and 553 bp for E. moshkovskii which under subjected to 2% agarose gels electrophoresis and visualized under UV transilluminator.

Results
8.52% of the total collected samples were microscopically positive for Entamoeba cysts either singly or in combination with other intestinal parasites. Likewise, among 270 stool sample, viral diarrheal was most significant form of diarrhoea found in 76.67% of patients. Among different organisms, As. Lumbricoids and E. histolytica, G. lambia and H. nana were identified in most of the patients accounting for 11.11%, 8.52%, 2.59% and 1.11% respectively. However, Lumbricoids, G. lambia, Tenia solium and E. histolytica were present in an individual patient while two patient was found with both As. Lumbricoids and G. lambia. Among several symptoms, diarrhoea seems to be the common symptoms infecting all of the patients which is followed by fever and vomiting which accounts for 55.1 % and 46.2% correspondingly. Whereas, nausea appears to be the least common symptoms infecting only 14.4% of patients. Subsequently, 56 cases were PCR positive, 51 cases were ELISA positive whereas 47 were found to be positive by microscopy.

Conclusion
Molecular techniques are indeed promising tools for epidemiological studies, particularly in discriminating the pathogenic from the non-pathogenic species of the Entamoeba species. This study reports a new nested multiplex PCR strategy for detection and differentiation of E. histolytica, E. dispar and E. moshkovskii which is highly rapid, specific and sensitive which is useful for proper diagnosis, immunological assay and drug testing.
Topographical substrates stimulate vasculo- and angiogenesis in vitro

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Introduction
Continuous scientific advances in tissue engineering and regenerative medicine have resulted in novel implications and opportunities in improving or replacing biological tissue. By understanding and subsequently mimicking the cell’s natural environment, regenerative processes have been manipulated. One of the many applications of strategies based on regenerative medicine is the engineering of facial, skeletal muscle to treat patients with longstanding facial paralysis. Several methods are being developed to promote skeletal muscle repair and functional regeneration. One of the major challenges of engineered tissue, however, is integrating the grafts into the host’s vasculature. Tissues exceeding a thickness of 150-200 µm require a vascular network to maintain exchange of gases, nutrients and metabolic by-products after implantation. Consequently, developing vascular networks in constructed tissue is of critical importance for progression of the field of tissue engineering and regenerative medicine.

Materials & Methods
Endothelial cell behaviour is known to be influenced by many factors including substrate chemistry, stiffness and topography. This study aims to use directional topographical substrates to study vasculo- and angiogenesis in vitro to vascularize engineered facial, skeletal muscle. Described substrate topography is believed to mimic the cells’ natural environment and stimulate alignment and proliferation of endothelial cells. Culturing two endothelial cell types, Human Pulmonary Microvascular Endothelial Cell (HPMEC) and Human Umbilical Vein Endothelial Cell (HUVEC), on directional topographical substrates, allows for the study and comparison of effects of topographical cues on vascular network formation. HPMEC and HUVEC cultures stabilized with addition of Adipose Stem Cells, a cell type known for its pericytic behaviour, were monitored on polydimethylsiloxane (PDMS) surfaces with directional, wavy topographical features created by surface oxidation using air plasma treatment.

Results
Qualitative assessment of vascular network formation substantiated by gene expression analysis and YAP localisation using immunohistochemistry support the believe that linear topographical substrates stimulate vasculo- and angiogenesis in vitro. Culturing HPMECs and HUVECs on directional topography promotes proliferation and sprouting of endothelial cells.

Conclusion
Substrate topography can direct endothelial cell types into proliferative or differentiative phenotypes and stimulate vasculo- and angiogenesis in vitro.
Neurology I

Chair
Prof. H.P.H. (Berry) Kremer MD PhD

Presenters
Bamberg, H (Helena)
Dehghankhalili (Maryam)
Majd, A. (Alireza)
Olluri, E.O. (Elton)
Ren, Ren SC (Shuancheng)
Rodrigues Santana, P.H. (Pedro Henrique)
Shiravand, S.S.H (Sepideh)
Tent, S (Sanne)
The effect of different components of enriched environment on adult hippocampal neurogenesis and white matter plasticity

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Introduction
The environment we experience can induce plasticity processes in our brain and thereby shape it depending on the challenges we encounter. This capacity to adapt is crucial for learning, development, and personality formation. The enriched environment paradigm (ENR) aims to create a complex surrounding for the laboratory animal by generating new sensory, physical and social stimuli. This is achieved by the availability of toys, larger group sizes to increase social interaction and enhancing physical activity by using bigger cages and thereby more space to roam and explore. Numerous studies have shown remarkable effects of ENR on brain plasticity, including a positive influence on the generation of new neurons in the hippocampus, a unique form of plasticity, as well as on myelination in the white matter. Furthermore, a great potential of the paradigm as an endogenous approach in therapy and prevention of neurological and psychiatric diseases has been demonstrated. Nevertheless, many of the mechanisms and effects of ENR remain unknown, which raises the necessity of further investigation to optimize this environmental intervention. Our objective is therefore, to further analyze enrichment-induced plasticity. We aim to identify the role of the different aspects of ENR in inducing previously described effects on adult hippocampal neurogenesis and white matter microstructure.

Materials & Methods
To this end, 80 female C57BL6/Jrj mice are randomly allocated into five groups and housed in different environments for two months. Each housing condition differs in the complexity of enrichment, either including all three components (large group, spacious cage and toys), only some of it, or none. Adult neurogenesis in the hippocampus and myelination, oligodendrocyte precursor cells and microglia in the corpus callosum are then stereologically assessed.

Results
We assume that each component is capable of inducing some effects on neurogenesis and white matter. Yet, we expect that the effect of ENR is multifactorial and that exposing the animals to a single factor does not lead to the same impact as the complex paradigm.

Conclusion
This research contributes to understanding the underlying mechanisms of ENR as well as to improving its setup and thus to be able to use the full potential of this exceptional endogenous therapy.
MicroRNA Expression Profiles, Target Genes and Pathways in Intervertebral Disc Degeneration; A Meta-analysis of Three Microarray Studies

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Introduction
Determining the expression profile and target genes of miRNA would assist in determining the pathophysiologic pathways in various diseases. The pathogenesis of IDD is multifactorial and is a matter of debate which requires further basic research. The aim of this study was to determine the expression profile of microRNAs (miRNAs) in degenerated intervertebral disc compared to normal healthy intervertebral disc and also to determine the target genes and proposed pathways involved in IDD.

Materials & Methods
We conducted a meta-analysis of 3 available miRNA expression datasets to identify a panel of co-deregulated miRNA genes and overlapping biological processes in IDD. Degenerated intervertebral disc were compared to normal healthy discs. We selected 35 miRNA features common to all three platforms. Then, we calculated differential expression p-values from our unpaired data using metaMA package in R statistical software according to the moderated t-test method (Llima). Based on the P-values (where the threshold was less than 0.05), a list of differentially expressed miRNAs was identified.

Results
After normalization and selection of common miRNA features across all three platforms, we found a total of 5 differentially expressed miRNAs among which miR-574-3p, miR-199a-5p, miR-483-5p were not identified in any individual studies. Our results revealed that miR-199a-5p, miR-574-3p, miR-551a and miR-640 are commonly upregulated in IDD compared to control while miR-483 is commonly downregulated. Pathway analysis of identified dysregulated miRNAs indicated the involvement of “ECM-receptor interaction”, “adherens junction” and “TGF-beta signaling pathway” in the pathogenesis of IDD. Moreover, the network of predicted targets for these miRNAs identified most affected target genes as ‘erbb4’ and ‘cltc’.

Conclusion
We found that the identified miRNAs through meta-analysis are candidate predictive markers for IDD through different pathways.
Autonomic dysfunction and white matter microstructural changes in drug-naïve patients with Parkinson’s disease

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Introduction
Autonomic dysfunction (AD) is one of the non-motor features of Parkinson’s disease (PD). Some symptoms tend to occur in the early stages of PD. AD also has a great impact on patient’s quality of life. In this study, we aimed to discover the association between AD (Scales for Outcomes in Parkinson’s disease-Autonomic, SCOPA-AUT) and microstructural changes in white matter tracts in drug-naïve early PD patients to elucidate the central effects of autonomic nervous system impairments.

Materials & Methods
In total, this study included 85 subjects with PD recruited from the Parkinson’s Progression Markers Initiative (PPMI) database. Among the 85 PD patients, 38 were in Hoehn & Yahr stage 1 (HY1PD) and 47 were in stage 2 (HY2PD). Diffusion magnetic resonance imaging (DMRI) data were reconstructed in the MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function. The spin distribution function (SDF) values were used in DMRI connectometry analysis. We investigated through diffusion MRI connectometry the structural correlates of white matter tracts with SCOPA-AUT subscores and total score.

Results
Connectometry analysis also revealed positive association with white matter density in bilateral corticospinal tract in HY1PD patients and negative association in genu of corpus callosum (CC) and, bilateral cingulum in both groups. In addition, there were associations between gastrointestinal, sexual, thermoregulatory and urinary items and structural brain connectivity in PD.

Conclusion
Our study reveals positive correlation, suggesting neural compensations in early PD. Cingulum and CC tracts have well-known roles in PD pathology, compatible with our findings that bring new insights to specific areas of AD and its role in central nervous system (CNS) neurodegeneration, paving the way for using prodromal makers in the diagnosis and treatment of PD.
Early seizures after ischemic and hemorrhagic stroke

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Introduction
Despite the common occurrence of early seizures (ES) after stroke, the relationship between risk factors and this complication of stroke is not well established. In this study we have examined the frequency of ES after stroke in patients with ischemic and hemorrhagic stroke and the relationship between clinical measures on admission.

Materials & Methods
We included 1073 patients (mean age 69 ± 12, 51.6% females) with ischemic and hemorrhagic stroke. The frequency of seizure occurrence within 2 weeks of stroke was determined. We used a logistic regression model to analyse the effect of blood pressure on admission and other clinical factors (age, gender, diabetes, atrial fibrillation and dyslipidemia) on the occurrence of ES after stroke.

Results
ES occurred after 4.1% and 4.0% of ischemic and hemorrhagic strokes respectively. Compared to patients with high blood pressure on admission, those with low and normal blood pressure had a higher risk of ES after stroke (2.9% vs. 7.5% vs. 7.6%, p=0.001). Also the mean age of patients with post-stroke ES was lower (62.5 vs. 69.3, p<0.001). In a logistic regression analysis, low/normal blood pressure remained independently associated with ES after stroke with OR of 2.46 (95% CI 1.38-4.63, p=0.006).

Conclusion
ES after stroke was equally frequent in patients with ischemic and hemorrhagic stroke. Low/normal blood pressure on admission and younger patient age were risk factors for ES after stroke.
The paraventricular thalamus is a critical thalamic area for wakefulness

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Introduction
Patients with localized injury to the paramedian thalamus show disturbance of consciousness ranging from hypersomnolence to even sleep-like coma when injuries are bilateral, indicating that the paramedian thalamus is a critical node for the controlling wakefulness. The paramedian thalamus consists of a large number of nuclei with distinct input and output connections and participate in various brain functions. However, the specific nucleus and circuitry controlling wakefulness have not yet been identified.

Materials & Methods
In the present study, fiber photometry and multichannel electrophysiological recording combined with EEG/EMG recordings were used for monitoring neuronal activities; Chemogenetic and optogenetic method were used for cell-type specific manipulation; Channelrhodopsin-2-assisted circuit mapping, rabies mediated retrograde monosynaptic tracing, and immunohistochemistry were also adopted.

Results
By generating the unbiased maps of cFos-positive neurons in the whole paramedian thalamus, we observed an especially high level of cFos expression in the paraventricular thalamus (PVT) after a period of wakefulness. Fiber photometry and multichannel electrophysiological recording combined with EEG/EMG recordings revealed that the activities of PVT glutamatergic neurons were tightly coupled with wakefulness. Chemogenetic inhibition or lesion of PVT glutamatergic neurons caused a reduction of wakefulness, whereas optogenetic activation of the PVT not only induced a transition from sleep to wakefulness but also accelerated emergence from general anesthesia. By using channelrhodopsin-2-assisted circuit mapping, we found that the PVT glutamatergic sent dense projections to nucleus accumbens and this pathway mediated the wakefulness-controlling effects of the PVT. Moreover, we found that PVT glutamatergic neurons receive direct inputs from hypocretin neurons in the lateral hypothalamus using rabies mediated retrograde monosynaptic tracing. Chemogenetic or optogenetic manipulations demonstrated that hypocretin neuron to the PVT projections is the effector pathway for wakefulness control.

Conclusion
Taken together, these results demonstrate that the PVT is both necessary and sufficient for wakefulness. Moreover, the control of wakefulness by PVT preferentially require an output projection to nucleus accumbens and an input pathway from hypocretin neurons in the lateral hypothalamus.
Dementia and occupation, a neuropathological study

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Introduction
Cognitive reserve (CR) is defined by the capacity of resisting to neuropathological insults associated with dementia without manifesting clinical symptoms. Several factors are associated with cognitive reserve, such as education and being exposed to mentally challenging activities. Among CR proxies, occupation is one of the least studied in the literature, especially considering neuropathological analyses. We aimed to perform a neuropathological study of cognitive reserve in a population with high levels of unskilled occupations.

Materials & Methods
In this cross-section study, we described clinical and neuropathological variables from participants of the Human Brain Bank of the Biobank for Aging Studies from the University of São Paulo Medical School. Cognitive function was assessed by the Clinical Dementia Rating (CDR) scale, and the occupation during the lifetime was codded as skilled, semiskilled and unskilled according to the complexity of the work performed. Associations of dementia, neuropathological insults and occupation during the lifetime were first assessed by chi-square and ANOVA analyses, followed by multivariate logistic regression models.

Results
Among 1048 participants (mean age 74 ± 11.8 years old, 49% men, 69% white, median education of 4 years), 91(8.6%) had skilled occupations, 528 (50.3%) were semiskilled, and 429 (40.9%) were unskilled. Cognitive impairment was present in 50.4% of the subjects divided as CDR=0.5 (30.6%), CDR= 1 (22.6%), CDR= 2 (15.9%), and CDR =3 (30.9%). In the univariate analyses, occupation was associated with dementia (OR= 1.88; 95%CI=1.15- 3.04; p 0.0002). However, after adjusting for age, sex, education and the neuropathological lesions, the association was not significant (OR 1.36 ; 95% CI= 0.75-2.47; p=0.30).

Conclusion
We did not find an association between occupation during the lifetime and dementia. Similar studies have found such association to be positive; however we were the first to do an analyses including an extensive set of neuropathological lesions in a context of high frequencies of unskilled occupations.
Intranasal insulin administration attenuates maximal electroshock-induced seizure responses in rats

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Introduction
Insulin has recently gained a great deal of attention for its central nervous system functions. Brain insulin apart from its role in both peripheral and central glucose metabolism, has been shown to regulate neurotransmission, learning, memory and exert neuroprotection. Therefore insulin may constitute a promising therapy against various neurological disorders and neurodegenerative contexts. The present study aimed to investigate the potential therapeutic effect of insulin against maximal electroshock (MES)-induced seizures.

Materials & Methods
In this study two groups of male Wistar rats, weighing 250-300 g were used (N=7). In one group animals were treated with intranasal insulin at the dose of 0.5 IU per day and in the other group were treated similarly with normal saline for 12 days. Both groups were subjected to seizure induction by three sessions of MES (50 Hz, 60 mA and 1 sec) at 2 h intervals on days 1, 4, 8 and 12 of experiments. All the MES inductions were made two hours after insulin or vehicle treatments. Then duration of seizure responses was measured after each trial of MES.

Results
Obtained results revealed insulin treatment shortens duration of MES-induced seizure. However, this protective effect was only significant at the days 8 and 12 of experiments.

Conclusion
Based on the results of this experiment, intranasal insulin treatment via high central bioavailability protects against seizure. Further mechanistic studies on using insulin or provoking its signaling pathways would help identifying innovative strategies to prevent or reduce seizure activity.
Do treatment-naive the novo Parkinson’s Disease patients have an increased intestinal wall permeability?

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Introduction

Parkinson’s disease (PD) is characterized most of the time as a disease with motor deficits. However, non-motor symptoms occur often earlier than motor symptoms, which can present up to 20 years before diagnosis. Emerging evidence suggests gut microbiota have a notable impact on modifying the neuroinflammation in PD. By modulating the integrity of the intestinal mucosal barrier, the microbiota can have an impact on local intestinal as well as systemic inflammation. A prerequisite is that the intestinal epithelial barrier should be porous enough for neurotropic pathogens to traverse. Several studies have found increased intestinal wall permeability in PD, however almost all performed studies done were on PD patients already receiving medication. What the intestinal wall permeability of treatment-naïve de novo Parkinson patients is, is not known so far to our knowledge. Therefore, the aim is to assess whether treatment-naïve the novo PD patients have an increased intestinal wall permeability as well.

Materials & Methods

The research is part of the Dutch Parkinson Cohort (DUPARC) study. The DUPARC cohort study concerns de novo PD patients who are treatment naïve at baseline. Aimed is to assess the gut permeability of 20 de novo PD patients compared to 20 age- and sex-matched controls with the use of biomarkers in the fecal samples (Zonulin and Calprotectin), markers in the blood plasma (Zonulin and LPS) and the conduction of a sugar test (Sucrose/Lactulose).

Results

No results have been established up until now, however in previous research it was suggested that there is an increased intestinal wall permeability in PD patients already receiving medication. Since this research is performed with treatment receiving PD patients, deviant findings or variations can be found for treatment naïve patients.

Conclusion

This is the first study to investigate the intestinal wall permeability of treatment naïve the novo PD patients. Results of this study can therefore support the identification of early and predictive markers of Parkinson’s disease and be of help to understand the disease process better.
Nuclear Medicine and Imaging Techniques

Chair
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3D Imaging of Cellular Processes in ECM Hydrogels

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Introduction

Cell behaviour is subject to the local microenvironment with regards to biochemical-, topographical- and mechanical stimuli, among others. The vascularization progress in tissue is well-studied, but research in this field remains hampered by the limited depth of view of the currently available inverted microscopes, due to the impossibility of visualizing a three-dimensional (3D) structure in detail. This lack of visualization techniques prevents the current studies from characterizing the environmental cues that trigger the vascularization in different surroundings. The aim of this study is to provide insight into de novo development of microvasculature in a 3D scaffold by application of different diagnostic imaging techniques such as microCT and microMRI, after which the results are processed into a 3D image.

Materials & Methods

By means of gel matrices that consist of a gelatin methacryloyl/Geltrex™ mixture in which fluorescent labelled Human Pulmonary Microvascular Endothelial Cells (HPMEC) and immortalized Adipose-Derived Stem Cells (iADSC) were embedded, a 3D environment based on the properties of the extracellular matrix, is mimicked. These gel-based scaffolds are imaged using different techniques, among which microCT and microMRI.

Results

Each scanning technique shows to have its own pros and cons concerning the imaging of scaffolds. Despite the fact that the maximum spatial resolution is lower (approximately 25 µm), the uMRI appears to give a more clear visualization of the embedded cells due to its relatively high soft tissue contrast, whereas microCT imaging requires a contrast agent to highlight the presence of the cell structures. In this experiment, coated core-loaded nanoparticles are used in order to give better microCT results on which the microvasculature could be distinguished. At the time of writing, results do not allow for an appropriate conclusion as yet.

Conclusion

By visualizing and 3D imaging gel-based scaffolds in which pro-vasculogenic cells are embedded, the vascularization progress can be examined in more detail comprising the localization and curved development of the cell aggregates. This knowledge could be of great interest with respect to the pre-vascularization of organoids, but can also provide insight into the vascularization process during diabetes, tissue damage and repair.
The Impact of Electromagnetic Field on Memory

Dondoladze, K. (Khatuna) Memory and EMF

Introduction
The electromagnetic field is considered as an important physical factor capable changing the cognitive and non-cognitive behavior. Some researchers note that the mobile frequency EMF, which is usually generated from a mobile phone, causes memory loss; while other studies confirmed that the EMF leads to improving memory. Ghrelin is neurohormone which participates in memory consolidation, hippocampus receptor expression, its artificial introduction leads to the strengthening of learning and improving memory processes; Attention and concentration can greatly influence memory encoding, storage, and recall.

Materials & Methods
Animals: In the study, we used 110-120g 8-week Wistar male rats: EMF-exposure (experimental) group rats (n = 20) that we placed under EMF, and sham control group rats (n = 20) in identical conditions, but without EMF. In both groups, we studied memory associated with attention and concentration changes. EMF was generated with GSM system mobile phone. Memory tests: Two feeder test was performed after the 20th day of starting the study. 5-Choice Serial Reaction Time Test (5-CSRTT) was used to study rodents memory, attention and concentration. Laboratory examination: We have determined the Ghrelin concentration using the Enzyme-Linked Immunosorbent Assay (ELISA).

Results
The study has shown that EMF affects memory encoding and information recall also, memory tests gave the clinical picture of memory loss; mainly related to the impact of electromagnetic fields on the difficulty of paying attention and decreased concentration, which was also confirmed by Ghrelin’s concentration increasing under EMF action.

Conclusion
Considering the results, it seems that under EMF action conditioned-reflex memory encoding, memory tracks consolidation and recall occurs with delay - which mainly are related to decreased attention and concentration. This results was also confirmed by the increase in the concentration of hormone ghrelin (participating in memory process), under influence of household frequency EMF.
An evaluation of normal cartilage thickness in MRI study of different knee compartments among subjects with different ages and genders

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Introduction
Age and gender-dependent changes in knee joint cartilages among healthy individuals are issues considered in differentiating pathologic and non-pathologic diversities in general population. The purpose of this study was to determine the normal cartilage thickness in different compartments of knee joint among subjects with different ages and genders by MRI.

Materials & Methods
Subjects were included in the study after a preliminary knee examination and evaluation of their MR images by two expert radiologists to have no pathologic features. A total of 113 subjects categorized into three age groups; group 1 (n=52) aged 15 to 30 years, group 2 (n=41) aged 31 to 45 years and group 3 (n=20) aged 45 years and above were included in our study. All the participants underwent knee MRI as a part of the cross-sectional study. Knee cartilage thickness was measured manually within 11 sites as follow: Medial Posterior Femoral (m.p.F), Medial Anterior Femoral (m.a.F), Medial Median Femoral (m.m.F), Lateral Posterior Femoral (l.p.F), Lateral Anterior Femoral (l.a.F), Lateral Median Femoral (l.m.F), Medial Patellar (m.P), Median ridge Patellar (m.r.P), Lateral Patellar (l.P), Medial Tibial (m.T) and Lateral Tibial (l.T). The anthropometric parameters were also collected at the time of the MRI study. Normal thickness range for each region of interest (ROI) and their association with age and gender were reported. Also the correlation of weight and each cartilage thickness was assessed as a potential confounding factor.

Results
Age was significantly in negative correlation with Patellar cartilage thickness in all ROIs only among females: m.P (r=-0.38, P=0.01), m.r.P (r=-0.39, P=0.00) and l.P (r=-0.37, P=0.01). Gender was a significant associated factor in cartilage thickness of different ROIs within each age group: group 1: l.a.F (P=0.02), m.a.F (P=0.02), m.m.F (P=0.02), and m.T (P=0.03), group 2: m.P (P=0.01), group 3: m.P (P=0.00), m.r.P (P=0.00) and l.P (P=0.00). In all mentioned ROIs, males had thicker cartilages than females.

Conclusion
Our findings indicated that the gender-dependency of cartilage thickness differed by age category. As in younger ages, the difference was prominent in Femorotibial sites and as age increases, this difference is notable in Patellar sites. However, age inversely correlated only with Patellar cartilage thickness in females.
Synthesis and Radiolabeling of a Novel Radiopharmaceutical (Technetium-99m)-(DOTA-NHS-ester)-Methionine as a SPECT-CT Tumor Imaging Candidate for Breast Cancer Detection

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Introduction
Introduction: Nowadays, Breast cancer is the most common and deadliest cancer among women, and can easily be cured by early detection. Molecular imaging plays a very important role in the detection of abnormalities, especially, cancers. SPECT/CT, a kind of imaging technique is able to reveal crucial information due to radiopharmaceuticals used.

Materials & Methods
In this study, Technetium-99m-(DOTA-NHS-ester)-Methionine radiopharmaceutical was synthesized using conjugation between DOTA-HNS ester (chelator) and Methionine (marker). Then it was labeled with Technetium-99m. The synthesized Radio drug performed in breast cancer diagnosis using SPECT/CT imaging technique. LC-mass, HNMR and FTIR applied to confirm conjugation between DOTA-HNS ester chelator and Methionine. Technetium-99m is the most efficient radioactive element which constituted basic element among radio drugs. DOTA-NHS ester is used in this research to increase Technetium-99m conjugating with Methionine. For the final radiopharmaceutical, MTT assay was done for cellular toxicity and radiochemical purity was evaluated by TLC. Biodistribution and cellular uptake were other studies that were done.

Results
Results: LC-mass, HNMR and FTIR confirmed conjugation between DOTA-HNS ester and Methionine. Radiochemical purity of final radiopharmaceutical obtained 94%, which is high. Cellular uptake indicates higher percentage with the use of Methionine as marker. Cellular toxicity was observed to be low in Human embryonic kidney cells 293 (HEK-293). Radiopharmaceutical biodistribution study 90 min after injection, revealed distribution in Tumor was about 5 times more than brain and muscle.

Conclusion
Although mammography is one of the most common diagnostic method for breast cancer nowadays, there could be inefficiencies for smaller cancerous tissues distinction that can be improved by more high-tech technologies such as SPECT/CT imaging technique. it leads to earlier diagnosis and certainly earlier treatment.
Valuation of Four-Quadrant Location Method in Diagnosis and Differential Diagnosis of the Orbital Tumor by Comparison Study Combining CT and MRI with Pathology

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Introduction
To valuate four-quadrant location method in diagnosis and differential diagnosis of the orbital tumor by comparison study combining CT and MRI with pathology.

Materials & Methods
Data of 87 patients (44 female and 43 males), aged 1 to 84 years were recruited in this study, including the computed tomography (CT), Magnetic resonance imaging (MRI), and histopathology diagnosis. All orbital tumors were verified radiologically and pathologically in the First Affiliated Hospital, the Second Affiliated Hospital of Anhui Medical University and the Anhui Provinical Hospital from Sep-2008 to April-2016. 49 patients underwent CT scanning (31 Conventional CT and 18 dynamic contrast enhancements CT) and 38 patients underwent MR Imaging (35 dynamic contrast enhancement MRI and 3 conventional MRI). The clinical data were retrieved from the medical record. We classified the orbital region according to four-quadrant and eight-space (FQES) division and traditional muscleconal division with center point of optic nerve. survival rate at 1 and 5 years after initial treatment).

Results
Among the 87 cases of the orbital tumors, 70 cases (80.45%) were orbital benign tumors and 17 cases (19.54%) were malignant tumors. Regarding the location of the orbit, 41 lesions (47.12 %) were in superolateral, 18 lesions (20.68%) were in inferolateral, 16 lesions (18.39%) were in inferomedial, 8 lesions (9.19%) were in superomedial, 3 lesions (3.44%) were in globe, 1 lesion (1.14%) was in optic nerve. Benign tumor was diagnosed in 70 patients, of them 34 were male and 36 were female, and the mean age was 45.19 years. Malignant tumor was diagnosed in 17 patients; of them 10 and 7 were male and female respectively, mean age was 57.71 years. There was no significant difference in the age of patients with benign versus malignant tumors (P=0.505). No significant difference was observed in patient’s gender when we compared patients with benign versus malignant tumors (P=0.448). In comparative study of four quadrant spatial distribution was show significant difference between hemangioma and pleomorphic adenoma (P=0.027) but there was no significant difference seen in other tumors.

Conclusion
The four-quadrant and eight-space (FQES) division of the orbit in CT and MRI plays an important role in determining the location, origin and nature of orbital tumor, which may have supplementary role to traditional muscleconal division in the assessment of the orbital tumors. The orbital tumors were well justified by combining methods of the four-quadrant and eight-space (FQES) division with traditional muscleconal division, which useful quailitively diagnosis and differential diagnosis of the orbital tumors.
Microstructural characterization and validation of a 3D printed phantom for diffusion MRI

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Introduction
Diffusion MRI has the potential to quantify histological features of the brain at a micrometre scale. However, there is no “ground truth” to validate its techniques. We have recently proposed a novel phantom produced using fused deposition modeling (FDM) 3D printing with a composite material consisting of rubber-elastomeric polymer and a PVA component (PORO-LAY). When immersed in water, the PVA dissolves, leaving behind small pores that can mimic diffusion characteristics of axons. Different printing parameters such as print-head temperature can have an effect on the microstructural properties of the phantom. In this study, we investigate how diffusion tensor MRI (DTI) derived metrics of the phantom vary with different print-head temperatures.

Materials & Methods
3 phantoms were created by printing 11 mm radius cylinders with 100 μm thick layers of parallel lines to mimic linear fibres. The phantoms were produced at three different print temperatures: 215°C (low), 225°C (nominal), and 235°C (high). The phantoms were immersed in water for 168 hrs and stacked in a test tube with distilled water for imaging. Diffusion MRI was implemented at 9.4 T using 120, 60, and 20 directions at b=2000, b=1000, and b=0 s/mm² respectively, TE/TR=37/2500 ms, FOV=200x200 mm², 0.7 mm isotropic in-plane resolution, 6 axial slices (3 mm, one per phantom), and scan time 8.5 min per each scan. MRtrix was used to compute DTI-derived metrics (axial diffusivity, AD; radial diffusivity, RD; fractional anisotropy, FA). To investigate phantom stability, an identical scan and analysis was performed 11 days later.

Results
AD and RD had a strong observed dependence on print temperature. RD had an almost linear relationship with the printing temperature. The repeated scan showed phantom stability within optimal and high temperatures.

Conclusion
The strong dependence of diffusion properties of the phantoms on print-head temperature suggests that customization of diffusion properties on this phantom may be possible. The observed results from the scan performed 11 days later illustrates the strong stability of the phantoms in water over time for optimal and high temperatures. Future work should investigate the effect of other printing parameters and experiment with more complex brain-mimetic geometries.
Improving of the sleep quality under the influence of the extremely low frequency electromagnetic field

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Introduction
We have the master circadian clock is contained within the suprachiasmatic nucleus, which located in a small region of the brain, hypothalamus. The master circadian clock controls the «slave circadian clock», which generate their own near-24-hour rhythms in local tissue. It helps the organism to anticipate daily environmental changes corresponding with the day-night cycle and adapt to them. Periodic variations of natural weak extremely low frequency electromagnetic field (ELF-EMF) along with illumination can serve for entrainment of circadian rhythms. So the aim of our study was to assess the impact of weak ELFEMF on different characteristics of diurnal and nocturnal sleep.

Materials & Methods
In our experiments we use an ELF-EMF generator "Smart Sleep"(author’s design) formed rectangular current pulses supplied to the magnetic field emitter. The device has 7 modes of pulse frequency: 2, 4, 8, 16, 20, 32, 40 Hz. At a distance of 70–200 cm from the device field intensity was less than 0.2 μT, which is significantly less than the permissible hygienic standards. 30 healthy volunteers (both sexes, aged 18–23) took part in the study and self-assessed the night’s sleep: sleep quality, sleep latency, wellbeing on awakening, sleep fragmentation, quality of dreams, emotions in dreams, dreams' memorability, awareness in dreams. There are two parts of the experiment: with and without stimulation.

Results
The Kruskall-Wallis single-factor rank analysis was used. Significant improvements under ELF-EMF influence were found: p < 0.05 for the: wellbeing on awakening (4 Hz, 20 Hz), sleep fragmentation (8 Hz) and latency (20 Hz), the dream memorability (4 Hz), quality (2 Hz, 16 Hz), emotions (8 Hz) and awareness (20 Hz); p < 0.01 for the: sleep latency (32 Hz), the dream memorability (2 Hz), quality (4 Hz) and emotions (2 Hz) in our nocturnal experiment. Our diurnal data still being processed.

Conclusion
Therefore the non-pharmacological remote physiotherapy exposure to ELF-EMF can be used to correct the sleep disorders and the normalization of circadian rhythms of sleep.
Oncology I

Chair

Prof. Barbara L. van Leeuwen MD PhD

Presenters

Chan, SK (Sik Kwan)
Gonzalez, M.I (Martha)
Huang, Q (Qin)
Li, SZ (Shaozhong)
Li, Z.W.L (zuwei)
Liu, L.P (pei)
Niu, NX (Xia)
Yuan, YMH (MingHeng)
Half-life of Plasma Epstein-Barr virus (EBV) DNA clearance at midcourse of radiotherapy predicts distant metastasis in non-metastatic nasopharyngeal carcinoma

Chan, SK (Sik Kwan) MPhil, Lee, VHF (Victor Ho Fun) MD

Introduction
Plasma Epstein-Barr virus (EBV) DNA have been used to monitor treatment response and provide prognostic information on survival for nasopharyngeal carcinoma (NPC). However, prognostic role of half-life of EBV DNA clearance to detect distant metastasis (DM) remains uncertain under the era of intensity-modulated radiotherapy and implementation of 8th edition of American Joint Committee on Cancer Cancer Staging Manual. We aimed to test the hypothesis that prognostication of treatment outcome is feasible by half-life of EBV DNA clearance at midcourse of chemoradiotherapy/ radiotherapy.

Materials & Methods
Forty-four patients with non-metastastic NPC were prospectively recruited and treated in Queen Mary Hospital, Hong Kong. All patients had blood checked for plasma EBV DNA titres at weekly intervals until it was undetectable. Concentrations and half-life of plasma viral clearance were determined by real-time quantitative polymerase chain reaction.

Results
Overall stage distribution was: stage II in 9 (20.4%); stage III in 21 (47.7%); stage IVA in 14 (31.8%). After a median follow-up of 18.4 months (range 3.4-57.1 months), 9.1% experienced distant metastases. Two-year distant metastasis-free survival (DMFS) was 87.8%. Mean half-life of plasma EBV DNA clearance was 9.82 days. Patients were stratified into two groups on the basis of their half-life. Patients who had 15 or fewer days of half-life enjoyed longer DMFS (94.7% v. 60.0%, P<0.002). Prognostic significance of half-life of 15 days and survival endpoints were further evaluated in Cox regression models with age, gender, T- and N-classification, overall stage, and gross tumour volume of the primary tumour and the positive neck nodes. Only 15-day half-life was prognostic of DMFS (P=0.02; HR=14.945; 95% CI=1.545 to 144.604). Area under ROC curve for half-life of plasma EBV DNA clearance to predict DM was 0.809 (95% CI, 0.638 to 0.980). Comparing to other cut-off points, half-life of 15 days was chosen as a stratifying factor (sensitivity and specificity: 75% and 87.5%)

Conclusion
15-day half-life of EBV DNA clearance was prognostic of 2-year DMFS in patients with non-metastatic NPC. Prognostication could be shifted from post-therapy time to midcourse of treatment. Imaging screening for DM and intensified therapy at midcourse of CRT phase should be considered for high-risk patients (half-life < 15 days).
In silico identification of microRNAs regulating the expression of HPV E6/E7 targets and microRNAs availability on cervical exfoliates samples

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Introduction
Cervical cancer occupies the first place in mortality in populations with low human development index where 80% of the 570,000 cases and the 311,000 deaths estimated at 2018 worldwide occurred. Only the persistent infections with oncogenic high-risk HPV genotypes could lead to cancer. Despite current cervical cancer screening methods have high sensitivity and specificity (Pap smear and HPV test, respectively) to detect High-Grade Squamous Intraepithelial Lesion (HSIL), are not able to distinguish oncogenic from non-oncogenic HPV infections. MicroRNAs are small RNAs of 18 to 25 nucleotides that regulate gene expression and had shown differential profiles in cervical intraepithelial lesions. Our hypothesis is that microRNAs regulating HPVE6/E7 targets have the potential to become diagnostic biomarkers for HSIL.

Materials & Methods
EntrezID-NCBI Codes of 19 HPV E6/E7 target proteins were used for microRNAs prediction in miRWalk2.0 software, validation of microRNA-target RNA interactions was done through miRWalk2.0 software, the microRNA selection was done manually based on literature reports, only upregulated microRNAs in HSIL/cervical cancer and HPV infected keratinocytes were selected. The quantity of microRNAs was measured on 40 cervical exfoliates samples using High Pure miRNAs isolation kit (Roche) and Qubit™ miRNA kit (Invitrogen™).

Results
Our in silico approach identifies 13 microRNAs upregulated in HSIL and cervical cancer, those microRNAs were also found upregulated on the papers regarding HPV infected keratinocytes. All the microRNAs negatively regulate the expression of the transcripts derived from tumor suppressors as TP53 (p53), CDKN1A (p21) and CDN1B (p27). In our experimental approach, we obtain an average of 210ng of microRNAs starting from 50µl of cervical exfoliates samples.

Conclusion
Our in silico approach together with the published reports on the HPV infected keratinocytes identifies the overexpression of some microRNAs on HSIL and cervical cancer that potentially could work as diagnostic biomarkers, those microRNAs are directly related with the function of HPV E6/E7 oncoproteins. The quantification assay showed that cervical exfoliates are a suitable source of microRNAs.
Construction and Validation of Nomograms for Predicting Prognosis in Non-Metastatic Inflammatory Breast Cancer: A Population-based Study

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Introduction
As the most aggressive breast cancer, non-metastatic inflammatory breast cancer (IBC) has a poor prognosis. However, analysis of features related to prognosis is challenging due to the rarity of this disease. This study aimed to identify prognostic factors of non-metastatic IBC and establish a survival estimation tool to assist clinicians with prognosis assessment and treatment regimen selection.

Materials & Methods
We extracted 893 non-metastatic IBC patients diagnosed between 2010 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. All patients received surgery, radiation therapy and chemotherapy. These patients were randomly divided into training (n=625) and validation (n=268) cohorts. In the training cohort, prognostic factors identified by the Cox proportional-hazards model and the competing risk model were utilized to construct nomograms for predicting 3- and 5-year overall survival (OS) and breast cancer specify-survival (BCSS). In the internal validation of the training cohort and the external validation of the validation cohort, concordance indexes (C-indexes), time-dependent receiver operating characteristic (ROC) curves and calibration curves were generated to verify the performance of nomograms. Moreover, patients were stratified into risk groups based on the risk score calculated from the OS nomogram.

Results
Independent prognostic factors identified by the Cox proportional-hazards model and the competing risk model were integrated to construct the nomograms. In the training cohort, C-indexes for predicting OS and BCSS were 0.746 (95% CI, 0.703-0.789) and 0.76 (95% CI, 0.673-0.847) respectively. Calibration curves demonstrated an acceptable agreement between the nomogram prediction and actual survival. Areas under ROC curves (AUC) for predicting 3- and 5-year OS and BCSS were 0.751, 0.755, 0.756 and 0.755, respectively. Higher risk scores were significantly associated with worse OS in all molecular subtypes. The external validation of the validation cohort also showed a great performance of nomograms.

Conclusion
We unveiled the impact of clinicopathological features on the survival of non-metastatic IBC and formulated nomograms, in which the likelihood of individual survival can be easily calculated.
Notch1 promote chemoresistance via trans-activating the expression of Ecto-5′-nucleotidase (NT5E or CD73) in breast cancer.

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Introduction
Breast cancer is the most prevalent cancer in women all around the world in terms of the highest cancer incidence and mortality rate. Chemotherapy can be used as complementary therapy in addition to surgery. Standard chemotherapy such as doxorubicin, taxanes, or platinum compounds as salvage treatment are commonly used in clinical therapy. However, chemotherapy resistance is an important obstacle to favorable prognosis in breast cancer patients. Chemotherapy resistance remains a substantial problem in the treatment of advanced or metastatic breast cancer, especially for triple-negative breast cancer (TNBC), in which standard systemic therapy are currently limited to chemotherapeutic agents. Our study aims to understand better the molecular mechanism that lead to failure of chemotherapy in TNBC.

Materials & Methods
1. The cisplatin-resistant MDA-MB-231DDPR cells were obtained by exposure to cisplatin for 6 months, from 0.1 µg/L to 1 µg/L. Finally, the MDA-MB-231DDPR cells were maintained in 1 µg/L cisplatin concentration.
2. Western blot analysis and RT-PCR was examined the protein and mRNA expression of Notch1 and NT5E in the multiple breast cancer cell lines.
3. CCK assay was examined the cell activity.
4. Immunofluorescence assay was examined location and quantitative of protein.
5. ChIP assay was examined Whether Notch1 binds to NT5E promoter.
6. Luciferase assay was examined Whether Notch1 can regulate NT5E promoter activity.

Results
Our result revealed that the expression of Notch1 and NT5E were elevated in cisplatin resistant MDA-MB-231 DDPR cells than the parental counterpart. We also demonstrated that, in cisplatin resistant and parental MDA-MB-231 cells, Notch1 could positively regulate the expression of NT5E both in mRNA and protein levels. Additionally, Notch1 was capable of binding to CBF-1 on the promoter of NT5E to drive NT5E transcription, resulting in higher expressions of NT5E. and over expressing NT5E can reverse the recovery sensitivity to cisplatin caused by deficient Notch1.

Conclusion
In summary, our study demonstrates that Notch1 signaling activation was positively correlated with chemoresistance in MDA-MB-231DDPR cells by partially promoting NT5E expression.
Oncogene miR-187-5p is associated with cellular proliferation, migration, invasion, apoptosis and an increased risk of recurrence in bladder cancer

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Introduction
Bladder cancer, the ninth-most-common malignancy worldwide with an estimated 356,000 new cases and 145,000 deaths annually, has a propensity to relapse, requiring lifelong monitoring after diagnosis. 75% patients diagnosed with BC are non-muscle invasive BC and over 50% of them experience recurrences within 6–12 years of initial diagnosis. miRNA are small, noncoding RNA and shown to be oncogenes or antioncogenes in bladder cancer, contributing to numerous BC cell processes, including cell proliferation, differentiation, migration and apoptosis.

Materials & Methods
RT-qPCR were performed to detect the expression of miR-187-5p in tissues and cell lines, After which, clinicopathological variables and the prognostic value of altered miR-187-5p expression in BC was analyzed with the 48 formalin-fixed paraffin-embedded BC samples. Moreover, Cell functional assays (wound healing assay, CCK-8 assay, transwell assay and flow cytometry assay) were performed to explore the relationship between miR-187-5p expression and cell proliferation, migration, invasion and apoptosis in BC.

Results
Up-regulation of miR-187-5p was observed in BC tissues and BC cell lines. Cox proportional hazard regression analysis demonstrated that the patients with low expression of miR-187-5p experience lower risks of recurrence in the univariate and multivariate analysis. The Kaplan-Meier recurrence-free curves suggested that the patients with low expression of miR-187-5p experience lower risks of recurrence. Up-regulation of miR-187-5p promotes cell proliferation and mobility and inhibits the apoptosis of 5637 and UM-UC-3 cell, while downregulation of miR-187-5p reverses these effects.

Conclusion
The results of our study demonstrated that oncogene miR-187-5p is associated with cellular proliferation, migration, invasion, apoptosis and an increased risk of recurrence in bladder cancer.
L1CAM/CD24/Heparanase axis can promote glioma tumorigenesis by a positive-feedback loop and predict poor prognosis in glioblastoma

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Introduction
Glioblastoma is the most common central nervous system tumor which has poorest prognosis in the solid tumors. The previous studies indicated that the highly expression levels of L1CAM, CD24, and heparanase in glioblastoma, suggesting that the expression levels of these proteins might be associated with the malignancy and prognosis in the patients with glioblastoma. We have found that L1CAM, CD24, and heparanase might compose the complex, indicating that L1CAM/CD24/heparanase axis might play an important role in glioma tumorigenesis and invasion, which may be associated with the poor prognosis of the patients with glioblastoma.

Materials & Methods
We performed immunofluorescence, Co-IP, GST pull-down, colony-formation, transwell, Immunohistochemistry, as well as animal model to investigate the molecular mechanisms of the functions of L1CAM/CD24/heparanase axis in glioma tumorigenesis. Statistical analyses were performed using the Prism version 6.0 Software (GraphPad). The data were processed using SPSS statistical Software version 21.0 (Chicago IL). All experiments were repeated at least three times with similar results.

Results
CD24 and heparanase are consistently upregulated by L1CAM, whereas L1CAM gene silencing was associated with decreased CD24 and heparanase expression. This finding was further substantiated by a similar pattern of heparanase, CD24, and L1CAM immunostaining in glioma patients (Pearson’s correlation; R=0.66, p=0.00001). Notably, upregulation of these three proteins stimulated glioma cell migration, invasion, colony formation in soft agar, and tumor growth in mice, suggesting that L1CAM/CD24/heparanase axis promotes glioma tumorigenesis by a positive-feedback loop. In addition, the anti-CD24 neutralizing monoclonal antibody or peptides attenuated their interaction and inhibited glioma tumor growth in U87-transplanted mice. Furthermore, pathological analysis demonstrated that either their expression level or interaction was closely associated with the poor prognosis in the patients with glioblastoma, suggesting that L1CAM/CD24/heparanase axis might be a potential target for the treatment of the patients with glioblastoma.

Conclusion
L1CAM co-localizes with CD24 and heparanase. L1 can bind with CD24 and heparanase and enhance the expression of CD24, heparanase. Inhibition of L1CAM/CD24/heparanase axis significantly suppresses glioma proliferation and invasion. Our results thus reveal a novel L1CAM/CD24/heparanase axis that plays a significant role in glioma tumorigenesis.
Study on the methylation of promoter of Notch3 gene in breast cancer

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Introduction
Breast cancer is a leading cause of cancer-related death in women. In our previous study, we found that Notch3 can inhibit EMT a tumor suppressor via regulating Kibra involved in Hippo-Yap signaling pathway in breast cancer. And the expression of Notch3 is hardly detected in triple negative breast cancer (TNBC) cells. In recent decades, many Epigenetic modification such as DNA methylation or histone methylation has been reported as a key cause to regulate gene expression. Once the DNA containing CpG island is methylated, the expression of the target gene will be decreased. In this study we assumed that the low expression of Notch3 may be caused by DNA methylation.

Materials & Methods
1. Analysising the promoter of Notch3 by prediction software and designing MSP and BSP.
2. Treating MDA-MB-231 cells with RG108 or 5-Aza and detecting whether the methylation can be reversed by RT-PCR and Western blotting.
3. Analyzing and comparing the methylation efficiency in Triple negative and Luminal subtype breast cancer cells by bisulfate sequencing.
4. Elucidating which DNA methyltransferase affect the methylation of Notch3 promoter by knocking down every DNA methyltransferase family molecule one by one, such as DNMT1 and DNMT3B and DNMT3L.

Results
1. We found a large CpG island in the promoter of Notch3 gene by prediction software, and PCR results with MSP showed that the promoter of Notch3 existed higher methylation level in Triple negative breast cancer cells than that in the Luminal subtype.
2. After RG108 or 5-Aza treatment, the expression level of Notch3 was restored significantly.
3. Higher methylation efficiency was confirmed in Triple negative breast cancer cells by bisulfate sequencing. It was main found in the Non-CpG methylation of notch3. Especially, methylated in CpT locus.
4. Once knocking down DNMT family molecules including DNMT1, DNMT3b as well as EZH2, Notch3 can obviously be upregulated.

Conclusion
Collectively, these results indicate that the promoter of Notch3 gene is methylated in breast cancer cells, and the methylation efficiency is higher in TNBC than that in luminal subtype. Furthermore, this methylation of Notch3 promoter is controlled by double inhibition system, namely DNA methylation and Histone methylation mediated by PRC complex.
Notch3 inhibits epithelial-mesenchymal transition in breast cancer cells via up-regulating STAT5A

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Introduction
Breast cancer was commonly diagnosed and was identified as leading causes of cancer death in women, of which tumor invasion and metastasis is the key cause of death. Previous studies have demonstrated that epithelial mesenchymal transition (EMT) was the important step in tumor metastatic. Our study aimed to explore the function of STAT5A in breast cancer. Here, we found that Notch3 could up-regulates STAT5A at the mRNA level. We focused on the CSL binding site on the promoter of STAT5A and verified that Notch3 could bind and active STAT5A promoter, resulting in inhibition of the EMT of breast cancer.

Materials & Methods
1. RT-PCR and Western blotting was examined the mRNA and protein level.
2. ChIP assays was examined Whether Notch3 binds to STAT5A promoter.
3. Luciferase assays was examined Whether Notch3 could regulate STAT5A promoter activity.
4. Wound healing assays and the Transwell invasion assays was examined the cell activity
5. Kaplan-Meier Plots was used to explore the relationship between Notch3, STAT5A and patients prognosis.

Results
Our study demonstrated that Notch3 could bind and positive active STAT5A promoter, resulting in inhibiting the EMT of breast cancer cells. Moreover, we found that patients with Notch3 and STAT5A overexpression had higher recurrence-free survival rates.

Conclusion
Notch3 can inhibit epithelial-mesenchymal transition in breast cancer via up-regulating STAT5A, which provides novel insights into the complex regulation of EMT and provides a basis for further delineation of the Notch3/STAT5A pathway as a promising candidate of prognostic indicator and/or therapeutic avenue for breast cancers.
Orthopaedics and Rheumatology

Chair

A. L. (Lex) Boerboom MD

Presenters

Agrawal, A.
Agrawal, S.P (Siddharth)
Chen, Z.M. (Ziming)
Elena, C.E. (Costea)
Farokh Payam, M.F.P (Mandana)
Shrestha, D (Deepak)
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What Is the Normal Trajectory of Interleukin-6 and C-reactive Protein in the Hours and Days Immediately After TKA?

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Introduction
Periprosthetic joint infection (PJI) can be treated successfully if detected early enough. Although C-Reactive Protein (CRP) and Interleukin 6 (IL-6) are elevated in late infection, little is known about their levels and trends immediately after an arthroplasty. A deviation of biomarkers from their normal trajectory, may help detect PJI earlier.

Materials & Methods
We studied serum IL-6 and CRP levels in 50 patients undergoing primary Total Knee Arthroplasty (TKA) at following time points: Preoperatively 12 hours and postoperatively at 12 hours, 48 hours, 4 days, and 2 weeks. The same surgeon, approach, postoperative management and laboratory methods were used for each patient. Repeated-measures analysis was done using Friedman’s (non-parametric) test.

Results
No patient showed any clinical sign of infection. Mean Follow-Up was 1 year. IL-6 showed a sharp rise from a preoperative median value of 6pg/mL to a peak of median value of 133pg/mL at 12 hours postoperatively, decreasing to a median value of 7pg/ml at 2 weeks. This was not different from the baseline median value with the numbers available (p=0.455). CRP showed a gradual rise from a preoperative median value of 2mg/L which peaked at 48 hours to a median value of 125mg/L, decreasing to median value of 12mg/L at 2 weeks. This was still higher than the baseline median value with available numbers (p&lt;0.001).

Conclusion
We found that after uncomplicated TKA, IL-6 showed a sharp rise to peak at 12 hours, then fell rapidly to near baseline levels by 4 days and returned to the baseline level at 2 weeks. CRP showed a gradual rise to peak at 48 hours, then fell gradually, remaining elevated at 4 days and higher than baseline level at 2 weeks. Future studies can help define more definitive thresholds for IL-6 and CRP; ideally, these should derive from large, multi-center studies. With such data, any deviation from a known normal trajectory can facilitate a quicker decision to perform knee aspiration to diagnose early PJI more promptly.
Preference of Calcium supplements over Bisphosphonates in post-menopausal Osteoporosis and Quality of Life of such women: a cross sectional study.

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Introduction
Osteoporosis is a silently progressing metabolic bone disease resulting in the loss of mineralized bone. In postmenopausal females, the deficiency of estrogen causes exaggerated loss in bone mass leading to fractures after minor trauma. Osteoporosis decreases self-esteem and changes perception of body image, leading to psychological consequences. By evaluating the prevailing prescription pattern and measuring the quality of life, we aim to create a platform for developing better treatment protocols for osteoporosis.

Materials & Methods
An analytical cross-sectional study was done on 91 post menopausal women who were diagnosed with osteoporosis. Drug Utilization Pattern and General History were recorded in the Case Record Form. Pre-validated QUALEFFO-31 QoL questionnaire was administered to each enrolled patient. Depending on the treatment received, patients were divided in 2 groups. Group -1 (n=60) who received only calcium and vitamin D3 and Group-2 (n=31) who additionally received Bisphosphonates.

Results
All the patients received calcium, vitamin D3 supplementation and analgesics. Nearly 1/3rd of the patients received Bisphosphonates. Risedronate was most prescribed Bisphosphonate (21%), followed by alendronate (5.4%), ibandronate (4.3%) and zoledronate (2.1%). Overall pain domain was affected the most with a function score of 62.84. Higher pain domain was reported in group-2 as compared to group-1 (p<0.05). Both the groups faced similar severity of problems in daily life however 6.7% patients in group-1 and 29% in group-2 found it almost impossible to lift weight (p<0.05). Climbing stairs was severely impaired in 25% patients in group-1 and 42% patients in group-2 (p<0.05). Mental domain function score was 44.4. Patients in both groups felt tired, lonely, less energetic, downhearted and felt low spirited.

Conclusion
Bisphosphonates are first choice of drugs for osteoporosis, yet in India, Calcium and Vitamin D supplements with relatively lesser efficacy are preferred due to their easy availability and low economic burden. Every prescription contained NSAIDs to relieve pain. Osteoporosis causes pain and physical debilitation that compromises the ability to carry out daily tasks at a normal efficiency and has detrimental effect on mental health as evident on patient’s perceived QoL score.
An analysis of the correlation between the postoperative effect of total knee arthroplasty and angles of axial alignments of the lower extremity

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Introduction
An appropriate angle of implantation in total knee arthroplasty (TKA) plays a pivotal role in the survival rate of implants and the clinical outcomes. In previous studies, the hip–knee–ankle angle (HKA) was used to predict the surgical efficacy; however, the correlation between HKA and clinical function was questioned. We aim to investigate whether HKA can be utilized to evaluate the postoperative efficacy of TKA, and to explore the correlation between the postoperative outcomes of TKA and the angles of multiple axial alignments of the lower extremity.

Materials & Methods
In this retrospective study, clinical data of patients who underwent primary TKA between April 2013 and April 2017 were analyzed. Femoral posterior condylar offset (FCO) and the angles of axial alignments of the lower extremity, including HKA, femoral interior angle (FIA), distal femoral valgus resection (DFVR), coronal tibiofemoral angle (CTA), sagittal tibial angle (STA), sagittal femoral angle (SFA), coronal femoral angle (CFA), mechanical lateral distal femoral angle (mLDFA), mechanical medial proximal tibial angle (mMPTA), and ankle angle (AA), were measured on postoperative X-ray images. Each of them was linear regression analysed along with postoperative knee function which was assessed by KSS, OKS and WOMAC. The standardized regression coefficients were compared.

Results
Seventy patients, aged (66.03±9.80) years on average, who underwent 101 primary TKAs were included. The HKA was 0°±3° in 58 cases (57.43%), and 0°±1° in 17 cases (16.83%). Correlation analysis demonstrated that FIA, DFVR, HKA and mLDFA were all significantly correlated with postoperative function. The absolute values of correlation coefficients after normalization were statistically compared and it was found that the sequence of correlation coefficients was mLDFA (0.344) &gt; DFVR (0.334) &gt; FIA (0.292) &gt; HKA (0.288).

Conclusion
HKA can be utilized as one of the multiple parameters for evaluating the surgical quality of TKA. FIA, DFVR, HKA, and mLDFA have been found to be associated with postoperative function; and they can be used to predict the postoperative efficacy. mLDFA is the most intimately correlated with postoperative function, and it is a reliable parameter to predict the postoperative outcomes. Intensive attention should be paid to the angle of femoral implants in the coronal plane.
The quality of life in patients with knee osteoarthritis assessed with EQ-5D-5L

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Introduction
Osteoarthritis (OA) is one of the most common joint disorders that has a significant burden on the health and well-being of patients. The impact of knee OA on patients' lives has not been well studied in the Republic of Moldova.

Objective: to determinate the quality of life (QoL) in patients with knee osteoarthritis.

Materials & Methods
Patients fulfilling ACR criteria were eligible for participation in this trial if they had experienced clinical symptoms of knee OA at least 3 months before inclusion into the study. We assessed patient's QoL using the EQ-5D questionnaire with its five dimensions (EQ-5D-5L): mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Results
There were 30 patients integrated in the study including 23 females, mean age 61,2 ±11,65 (range 30 to 82 years), with disease duration 14,83 ±7,03 years (range 2 to 27 years). The EQ-5D-5L results showed that on average 67% of patients reported problems in all five dimensions, 96% had difficulties with mobility, 71,4% with self-care and 92,6% with usual activities. In 96,4% of cases, patients suffered pain/discomfort, the mean level of pain being 72,2 ±11,9. The problem of mental health, anxiety and depression, was identified in 89,2% cases. The QoL was lower for females, but significantly on mobility and self-care domains (p<0,05). There was significant correlation between QoL and age (p<0,05) and moderate correlation with the pain level.

Conclusion
Osteoarthritis can profoundly affect many aspects of the life, including physical and mental well-being; women seem to be more susceptible than men.
Effect of Capsaicin Cream on Chronic Low Back Pain in Patients With Inter-Vertebral Disc Herniation

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Introduction
Low back pain is one of the most common debilitating disorders worldwide, and the third cause of visit a doctor. One of the most common causes of the low back pain is spinal disc herniation. No general agreement exists on the most effective treatment for it, yet. This study aimed to determine the effect of Capsaicin cream on the low back pain in patients with inter-vertebral disc herniation in Ahvaz.

Materials & Methods
The present study is a double blind clinical trial in which 43 patients with chronic low back pain, according to the characteristics of the subjects were randomly divided into two groups of treatment (n=23) and control (n=20) groups. Data collection instrument included demographic specifications and Visual Analogue Scale (VAS) questionnaire that were completed on arrival and at the first, second and third weeks after intervention. The treatment and placebo group used the ointment for three weeks and three times a day as a thin layer on the painful position. After collecting, the data were entered into SPSS (version 18) and analyzed using the analytical – descriptive statistics.

Results
The findings showed a significant difference in the average pain intensity between the groups of the study pre-and post-intervention (p=0.0001) and the rate of using analgesics in the treatment group has been significantly decreased (p=0.008). Also in studying patients' satisfaction was significant difference existed between the two groups using the ointment (p=0.0001)

Conclusion
The results showed that Capsaicin cream has beneficial effects on pain relieving and reducing of analgesic use in patients with inter-vertebral disc herniation. Therefore to use the ointment in treatment of low back pain caused by inter-vertebral disc herniation can be recommended.
Miniplate Augmented Cervical Open Door Laminoplasty provide better Hinge gutter union and Prevent Hinge fracture displacement. A Retrospective analysis of 73 cases.

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Introduction
Expansive open door laminoplasty is the widely accepted procedure for the treatment of multilevel cervical spondylotic myelopathy nowadays. Among the various fixation procedures to secure the open Lamina, miniplate fixation provides better clinical and radiological outcomes and has been accepted worldwide. However, the effects on hinge fracture union and hinge fracture displacement following miniplate fixation has not been proven till now. We elucidate the status of hinge gutter union and hinge fracture displacement postoperatively.

Materials & Methods
A retrospective clinical study with total of 73 adult men and women, underwent cervical open door laminoplasty between August 2015 to November 2017 in Tianjin Hospital were included in the study. Thirty patients (140 laminae) underwent laminoplasty with miniplate fixation whereas 43 patients (160 laminae) underwent laminoplasty with Anchor suture fixation. Patients following open-door laminoplasty with available postoperative CT scans were enrolled in this study. Hinge fractures were identified intraoperatively by obvious instability or click sounds during lamina opening or by post-operative computer tomography (CT) images. Hinge gutter union and hinge fracture displacement were evaluated with CT scan. Clinical outcomes was assessed by the Japanese Orthopedic Association (JOA) scores, Nurick scores and Neck Disability Index (NDI) scores pre and postoperatively with questionnaires. Statistical analysis was done using SPSS and analyzed by independent samples t-test, Chi-square test. RadiAnt DICOM viewer was used to measure the hinge fracture displacement.

Results
Both the fixation secured the open laminae effectively immediately after surgery. Third postoperative day CT scan revealed 17 (12.14%) and 24(15.62%) hinge fractures in group A and B respectively. Two-year post-operative CT scan showed 4(2.85%) and 11(6.87%) anterior displaced hinge fracture, 5(3.57%) and 13(8.12%) posterior displaced hinge fracture and 2 (1.42%) and 5(3.12%) hinge fractures showed non-union in miniplate and anchor suture group respectively but none of them had any neurological symptoms. Miniplate group showed higher hinge fracture union than anchor suture group, although the difference was not statistically significant(p=0.58).

Conclusion
Laminoplasty by Titanium miniplate fixation holds the laminae securely, prevent hinge fracture displacement and promotes hinge gutter union for a long-term follow-up compared to Anchor suture fixation. However surgical and clinical precautions should be considered for successful surgical outcomes.
**Longitudinal circular osteotomy as surgical method of treatment of nonunion fractures: in vivo and clinical cases**

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**Introduction**

Successful treatment of nonunion, delayed union and malunion fractures of long bones remains a major clinical challenge. The purpose of this study was to find if longitudinal circular osteotomy can stimulate bone regeneration in nonunion and delayed union fractures to reduce later surgeries required to augment the healing process and to accelerate the time to healing.

**Materials & Methods**

In vivo four-millimeter segmental defects were created in the midtibial diaphysis of 10 adult mongrel dogs and held distracted by external fixation. Four weeks later, nonunion fractures were operated by longitudinal circular osteotomy. Healing of the nonunion was evaluated radiographically, clinically 4, 12 weeks postsurgery.

Clinical cases. 21-year and 34-year males were presented to Regional Center of Traumatology and Orthopaedics with nonunion fractures of ulnar and femur, respectively. The patients had undergone a mean of three previous operations for nonunion which had been present for a mean of 15 months. They were examined clinically and radiographically to confirm diagnosis. Longitudinal circular osteotomy was carried out as surgical treatment. Results were evaluated radiographically, clinically after 1, 3, 6 months. Treatment was considered successful when the nonunion healed without additional procedures.

**Results**

Longitudinal circular osteotomy stimulated the callus formation and nonunion healing in dog's nonunion model as well as in human. All of the treatment group dogs reached clinically and radiographically observable bony union 12 weeks. In both patients nonunion healed with no need for further procedures. There were an improvement of the patients' quality of life (less pain, good range of motion).

**Conclusion**

These data suggest that longitudinal circular osteotomy may be a potential alternative that offers numerous advantages over standard techniques in the treatment of nonunion fractures. Further study is needed to confirm these findings in large clinical study.
Pharmacology I

Chair
Leo E. Deelman PhD

Presenters
Ebrahim Soltani, Z.E.S (Zahra)
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Kothari, A. (Arpit)
Mehrbakhsh, N.M (Negar)
Porkoláb, G.
Rahimi, N (Nastaran)
Shen, D.F (Daifei)
Possible involvement of nitric oxide in antipruritic effect of metformin on chloroquine-induced scratching in mice

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Introduction
Chloroquine has long been used in the treatment of rheumatoid arthritis, systemic lupus erythematosus and malaria. Pruritus (itch) is the main side effect associated with CQ therapy. A recent study has reported that metformin suppresses nonhistamine-mediated itch by inhibiting mTORC1 through AMPK pathway signaling in mice. AMPK is an anti-inflammatory signaling pathway so that pharmacological stimulation of AMPK prevents NO production. As the role of NO in itch with various mechanisms and signaling pathways, such association would represent metformin as a new anti-pruritic option in various pruritic disorders.

Materials & Methods
Here we investigated the involvement of nitric oxide (NO) pathway in antipruritic effect of metformin in CQ-induced scratching in mice. Metformin (5, 10, 100 and 200 mg/kg, i.p) was injected 4 h prior to CQ injection. A non-specific nitric oxide synthase (NOS) inhibitor, NG-nitro-L-arginine methyl ester (L-NAME; 1 and 10 mg/kg, i.p); or a nitric oxide precursor, L-arginine (10 and 100 mg/kg, i.p.) was administrated 30 min before injection of CQ (400 µg/site, i.d.). A neural NOS inhibitor, 7-nitroindazole (7NI; 1 and 10 nmol/site, i.d.) concurrently was administrated with 400 µg/site of CQ. The scratching behaviors were recorded following intradermal (i.d.) injection of CQ (200 and 400 µg/site).

Results
Our results show that metformin (100 and 200 mg/kg, i.p.) significantly reduces the CQ-induced scratching behavior in a dose-dependent manner. L-arginine inhibits the anti-pruritic effects of metformin. While, injection of L-NAME and 7-NI significantly potentiates the inhibitory effects of sub-effective doses of metformin on the scratching behavior.

Conclusion
We conclude that acute injection of metformin significantly inhibits CQ-induced scratching behavior. This effect mediating through inhibition of NO pathway; especially nNOS enzyme.
Hydroalcoholic extract of Arum orientale attenuates myocardial neutrophil recruitment and necrosis after myocardial infarction in rat.

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Introduction
Arum orientale is a medicinal plant which wildly grows in northwest of Iran. In the present study, the effects of hydro-alcoholic extract of A. orientale on isoproterenol-induced myocardial infarction (MI) were evaluated.

Materials & Methods
Thirty adult male wistar rats were used in this study. A subcutaneous injection of isoproterenol (150 mg/kg/day) for 2 consecutive days at an interval of 24 h was used for the induction of myocardial infarction in rats. Hydroalcoholic extract of Arum orientale was injected ip at doses of 40, 80, and 160 mg/kg/day 20 min before each isoproterenol injection. Then, histopathological changes, Myeloperoxidase (MPO) activity, lipid peroxidation, and creatine kinase activity were evaluated.

Results
Induction of MI significantly (P<0.001) increased necrosis, neutrophil infiltration and MPO activity in heart tissue, peripheral neutrophil percent and MDA level and CPK activity in the serum. While administration of A. orientale significantly reduced necrosis, neutrophil infiltration and MPO activity in the heart (at dose 160 mg/kg) (P<0.05, P<0.01 and P<0.05 respectively). Also treatment with A. orientale significantly (P<0.05, P<0.05 and P<0.001 respectively) decreased peripheral neutrophils in blood, MDA levels and CPK activity in serum.

Conclusion
Our results for the first time reported cardioprotective effects of A. orientale that partially can be through suppression of inflammatory responses and reduction of lipid peroxidation following MI. Our findings may lead to discover novel herbal-origin drugs in order to prevent and treat MI and various ischemic heart diseases.
Effect Of Vitamin D On Cardiovascular Risk Factors Among Adults With Obesity: A Meta-Analysis

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Introduction
The major public health problems today in both developed, as well as developing countries, are cardiovascular diseases. Vitamin D functions as a steroid hormone and well known for its role in calcium and bone homeostasis. In recent times, it has been recognized that a variety of processes and regulatory systems, including metabolic syndrome (obesity and diabetes), immunity, inflammation is modulated by Vitamin D. The relationship between Vitamin D status correction and cardiometabolic profile improvement in adults with obesity can help in starting public health initiatives in using Vitamin D supplementation for decreasing cardiovascular risk. The aim is to evaluate statistical evidence from existing randomized controlled trials about the efficacy of Vitamin D on the cardiovascular risk factors of otherwise healthy adults with obesity. A meta-analysis is the need of the hour in evaluating the effect of vitamin D on cardiovascular risk factors, particularly in obese individuals.

Materials & Methods
Fourteen studies containing 1580 patients were taken up for Meta-Analysis MedCalc Statistical software version 18.9 was utilized. Random and Fixed-effect models were applied to calculate the Standardized Mean Difference of change between groups. The principal summary measure was the Standardized Mean Difference (SMD) (at a 95% Confidence Interval). Funnel Plots and Forest Plots were plotted.

Results
The aim was to measure the effect of D Vitamin on cardiovascular risk factors including HDL-C, LDL-C, Triglycerides as well as Blood Pressure and Blood Glucose. We have found statistically significant results in efficacy of Vitamin D in increasing HDL-c (95% Confidence Interval(CI) 0.00918 to 0.454 (fixed), P= 0.041) and LDL-c levels(95% Confidence Interval(CI) 0.402 to 0.856 (fixed), P<&lt;0.001). Statistically non-significant reduction in Body Weight, BMI and Triglyceride levels were noted. Statistically significant decrease in Diastolic blood pressure (95% Confidence Interval(CI)-0.402 to -0.034(fixed), P= 0.020) and Blood Glucose levels (95% Confidence Interval(CI)0.0898 to 0.578(fixed) , P= 0.008) and Statistically non-significant decrease in Systolic blood pressure were noted.

Conclusion
Vitamin D appears to be cardioprotective from most of the results obtained but a statistically significant increase in LDL-c levels contraindicates the above statement. Large scale studies at pharmacologically relevant doses and for sufficient duration are warranted before definitive conclusions can be reached.
The role of tamoxifen (a selective estrogen receptor modulator) on neurological score, blood-brain barrier and brain edema after traumatic brain injury in male rat

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Introduction
Tamoxifen is an oral medication that is used for the treatment of breast cancer, and it acts on an estrogen receptor for agonist or antagonist effects due to its effects on the environment. The matrix metalloproteinase is an enzyme that is produced by endothelial cells, microglia and astrocytes, and When the expression of the matrix metalloproteinase-9 will be progressed by an increased mucosal-permeability, it will be resulted in edema and nerve damage Therefore, in this study, we evaluated the effects of tamoxifen neuronal protection after induction of traumatic brain injury in rats.

Materials & Methods
Wistar rats received different doses of tamoxifen (2.5, 5 and 10 mg / kg) intraperitoneally after induction of Tbi. Of course, animals were anesthetized and intubation before brain injury induction. A brain injury was made by marmarou method and drug will be injected half an hour after the brain injury. VCS of the animal was recorded at before TBI, at TBI moment, first, second and third day after the traumatic brain injury. Beam Walk and Beam Balance tests were taken from an animal at this time. The level of permeability of the blood-brain barrier was monitored by the Evans colored substance. After 72 hours, CSF collection is fixed in nitrogen to be used for ELISA tests.

Results
The results showed that traumatic brain injury reduced neurological scores, but tamoxifen 5 mg / kg on the third day after trauma caused minimal difference with Sham or Intact groups (p <0.001). The brain edema and Evans blue content were significantly lower in the tamoxifen 5 mg / kg group than in the group receiving tamoxifen (2.5 mg / kg) (P <0.001). Beam Walk (Traversal time) in the tamoxifen group 5 mg / kg did not have a significant difference with the Sham or Intact group on the second and third day after the trauma. In addition, tamoxifen injection (5 mg / kg) also reduces the secretion of matrix metalloproteinase-9.

Conclusion
According to the findings of this study, it can be concluded that prescription of tamoxifen (5 mg / kg) in the time of traumatic brain injury in rats can reduce the consequences of brain trauma.
Nanoparticles targeted with ligands of brain endothelial transporters increase cargo penetration across a culture model of the blood-brain barrier

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Introduction
Pharmaceutical treatment of most neurological diseases is hindered by the low permeability of drugs across the blood-brain barrier (BBB). Nanoparticles targeting nutrient transporters at the BBB are promising new candidates to increase the brain penetration of therapeutics. The aim of our study was to test the combination of two ligands of BBB nutrient transporters, alanine and glutathione, as targeting molecules for nanoparticles.

Materials & Methods
Vesicular nanoparticles, so-called niosomes, were prepared from non-ionic surfactants and cholesterol. The surface of niosomes were decorated either with alanine or glutathione for single ligand labelling, as well as their combination for dual ligand labelling. Serum albumin complexed with Evans blue (EBA, 67 kDa) was selected as a cargo of niosomes. A real-time, impedance-based cell analysis was performed on primary rat brain endothelial cells (RBECs) to determine nanoparticle toxicity. Cellular uptake of EBA in RBECs was quantified by fluorescent spectrophotometry and visualized by confocal microscopy. Permeability of the nanoparticle cargo across our BBB co-culture model, consisting of endothelial cells, pericytes and astrocytes, was measured by fluorescent spectrophotometry.

Results
Treatments with niosomes did not influence the viability of RBECs. The presence of targeting molecules on niosomes increased the cellular uptake of the cargo in brain endothelial cells and elevated the permeability of the cargo across the BBB model. Dual ligand labelling of nanoparticles was especially effective, resulting in a 2.5-fold higher cellular uptake (249.2% vs. 100%, P < 0.001) and an 8-fold higher permeability (2.26 × 10−6 cm/s vs. 0.28 × 10−6 cm/s, P < 0.01) of EBA compared to cargo encapsulated in non-targeted niosomes.

Conclusion
Our data indicate that single- and especially dual labelling with ligands of multiple nutrient transporters at the BBB can potentially be exploited for brain targeting of nanoparticles.
The involvement of opioidergic and nitrergic systems on seizure threshold induced by pentylenetetrazole in cholestatic mice

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Introduction
It is common knowledge that central neural transmission is affected by chronic liver diseases. Cholestasis results in some changes in behavior which include fatigue, cognitive dysfunction, mood disorders, and seizures. Alteration of endogenous opioids and nitric oxide (NO) levels are well recognized in patients who developed cholestatic liver diseases. Opioid antagonists have been documented in reversing cholestasis-induced pruritus. Endothelial NO synthase (NOS)-derived NO could be protective against liver diseases, whereas NO produced by inducible NOS (iNOS) is deleterious. Moreover, the role of both NO and opioid have been well documented in different models of seizures. The aim of this study, therefore, was to evaluate the contribution of opioidergic and nitrergic pathways in pentylenetetrazole (PTZ)-induced seizures following chronic irreversible cholestasis in mice.

Materials & Methods
Seizures were induced by intravenous injection of pentylenetetrazole on day 5 after bile duct ligation (BDL). Non-selective inhibitor of nitric oxide synthase, L-NAME; selective iNOS inhibitor, aminoguanidine; selective nNOS inhibitor, 7-nitroindazole; and antagonist of opioid receptors, naltrexone were administered intraperitoneally to animals 5 days after BDL. Data are expressed as the means ± SEM clonic seizure threshold for each experimental group. The one- or two-way analyses of variance (ANOVAs) followed by Post hoc Tukey’s tests were used to analyze the data of seizures. A P-value less than 0.05 was defined statistically significant. All statistical analysis was done by the 24th edition of SPSS software.

Results
Seizure threshold significantly reduced in cholestatic mice in comparison to the sham group (P < 0.001). One-way ANOVA revealed that administration of L-NAME (10 mg/kg), aminoguanidine (50 mg/kg), naltrexone (10 mg/kg) and co-administration of L-NAME (3 mg/kg) and naltrexone (10 mg/kg) significantly reversed the pro-convulsant effect of bile duct ligation (P < 0.001). But, 7-nitroindazole did not alter the seizures threshold of cholestatic mice.

Conclusion
Our results suggest that inducible nitric oxide synthase and opioid receptor may be involved in cholestasis pro-convulsive property in mice.
N-n-butyl haloperidol iodide attenuates liver fibrosis via inhibition of JAK2/STAT3 and TGF-β1/smad signaling pathway.

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Introduction
Liver fibrosis is one of the leading causes of morbidity and mortality worldwide with very limited therapeutic options. N-n-butyl haloperidol iodide (F2) is a calcium channel blocker that has been shown to inhibit fibrogenic mediators and have anti-proliferation effect in vascular smooth muscle cells. We investigated the therapeutic potential of F2 to hepatic fibrosis and its mechanism of the anti-fibrotic effect.

Materials & Methods
We used TGF-β1-activated LX-2 cells (a human HSC line) and mouse models of fibrosis induced by treatment with either carbon tetrachloride (CCl4) or thioacetamide (TAA). Serum hepatotoxicity markers were determined, and histopathological evaluation was performed. Hepatic fibrosis was assessed by measuring α-smooth muscle actin (α-SMA) and Collagen expression and collagen deposition by Masson's trichrome staining, Sirius red staining, and hydroxyproline content. The effects of F2 on the expression of smad2/3, JAK2, STAT3 were also assessed by Western blot.

Results
F2 significantly attenuated Hepatic fibrosis induced by CCl4 and TAA, as indicated by decreased α-SMA and Collagen expression and collagen deposition. F2 co-treatment significantly inhibited the protein levels of TGF-β1 and p-Smad2/3 in mouse model livers and activated LX-2 cells. F2 suppressed the expressions of p-JAK2 and p-STAT3, to restrain TGF-β1/Smad signaling.

Conclusion
F2 attenuated CCl4- and TAA-induced liver fibrosis in mice, inhibited TGF-β1-induced HSC activation in vitro. The anti-fibrotic mechanism of F2 against CCl4-and TAA-induced liver fibrosis in mice may have been due to inhibit the JAK2/STAT3 pathway and restrain TGF-β1/Smad signaling activation. F2 is a potential therapeutic agent that can be used to attenuate hepatic fibrosis in mice, it may provide an effective new strategy for anti-fibrotic therapy.
Public Health I

Chair

Sander K.R. van Zon PhD

Presenters

Alhamood, A.A.A (Abduljabbar)
Araya, A. (Alex)
Arshad, M.A.A (Muhammad Asharib)
Bagheri, M (Mohammad)
Chauhan, N. (Nupur)
Gapchup, Tejal.
Hamza, Mr (Ali)
Kurniawan, A.L (Adi Lukas)
The Usage of Virtual Reality to Deliver Diabetes Self-Management Education in Lieu of Face-to-Face Setting

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Introduction
According to the United States Census Bureau, the working adults’ average visit to the doctor decreased from 4.8 to 3.6 in 2015. Similar research from the United Kingdom states that one million patients a week cannot get a doctors appointment. Therefore, developing a way to close the gap between the doctors and patients was created through virtual reality. The purpose of creating a new platform was to identify patients’ experience of using virtual reality in lieu of face-to-face setting. Randomly selected patients who are diagnosed with diabetes are chosen to participate in this project for consistency. Diabetes was chosen because more than 9.4% of the U.S population, or 30.6 million, are diagnosed with diabetes.

Materials & Methods
Each participant was given all the necessary equipment to participate that include but not limited to laptops, wifi, headphones, mice, and blood glucose and heart monitor. Each participant was analyzed through four domains that include (1) the value of information gained, (2) cultivating diabetes self-management skills and reaction, (3) the value of interaction through virtual reality, and (4) the technological development through the use of virtual reality. Each participant receives a survey after each visit and the data was stored in REDcap program.

Results
The data of 280 participants in virtual reality and face-to-face were analyzed to show whether virtual reality is a fit program to increase and encourage the number of adults’ doctor visit annually. Patients under virtual reality show a healthier lifestyle and exercise 40 minutes more than face-to-face patients.

Conclusion
It can be concluded that the virtual reality can be used as a platform for busy adults that can not afford to waste time to go to a hospital for an appointment. The research will continue studying this through getting more participants to tweak the platform and perhaps apply it to different kinds of patients.
Incidence of diagnosed cancer in the public health system in the Coquimbo region, Chile. 2009 - 2013.

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Introduction
Cancer is the second leading cause of death in Chile, accounting for 25.6% of total deaths. The aging population has led to an increase in the prevalence of cancer diagnoses. Currently, there is no national registry of cancer, in Chile, that allows for accurate calculation of the real cancer incidence. We aimed to determine the incidence of different types of cancer diagnosed in the public health system of the Coquimbo Region, between 2009 and 2013. In addition, the relationship between incidence and mortality was explored.

Materials & Methods
A descriptive and retrospective study was conducted. A total of 6,841 biopsy reports where cancer was diagnosed were included. Incidence rates were calculated based on the estimated population according to the 2002 Census and the 2014 update. Excel was used for data tabulation. Regression analysis, t-Student and Chi-square tests were used. Level of significance was at $\alpha = 0.05$. The study was approved by the Thesis Evaluation Commission of Master in Public Health.

Results
The highest incidence was recorded in the urinary and male genital system, with 37.9% of the cases. These were followed by cancers of the digestive, skin and subcutaneous tissue, breast and female genital systems, with the remaining systems being represented at frequencies lower than 4%. By organ, the highest incidence was observed in prostate, with 26.1% of cases, followed by skin, female breast, stomach and large intestine. Incidence rate and mortality were not necessarily related.

Conclusion
According to estimates from the Ministry of Health of Chile, the most incidental cancers in the country were prostate and stomach cancers for men, breast and non-melanomas skin cancers for women. In this study, skin cancer for men and cervical cancer for women turned out to be the second most important on each gender. There was no relationship between Incidence and Mortality in the most common cancers. These results come from the population beneficiaries Public Health System which represents approximately 90% of the population of the Coquimbo Region, being a solid base for the development of later studies.
Perceptions and Practices regarding the Process of Informed Consent in Surgical Patients in a Tertiary Care Hospital in a Developing Country.

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Introduction
Informed consent before surgical procedures is an imperative aspect of surgery. Proper informed consent is essential for patients to have sound knowledge about the indication, risks and benefits of the procedure. Aim of the study was to assess perceptions of post-operative patients about the process of informed consent and to identify various factors that influence the process of informed consent in a tertiary care hospital.

Materials & Methods
Cross-sectional study was carried out at a tertiary care hospital of Lahore. After taking consent from patients and Institutional Review Board, interviews were conducted by principal investigators using a validated questionnaire from 101 patients who had undergone elective surgery. Statistical analysis was done using SPSS version 23.

Results
Informed consent did not influence the decision of 85 (84.2\%) patients to proceed with surgery. Majority 92 (91.1\%) patients considered it to be important. Satisfaction regarding provision of information was observed in 91 (90.1\%) as their inquiries were replied by doctors 98 (97.0\%) with 92 (91.1\%) having opportunity to ask questions from doctors. Mostly 98 (97.0\%) patients were told about indications of surgery, only 54 (53.5\%) were told about possible complications. Patients 75 (74.3\%) were informed about alternatives other than surgery. Significance was observed between education and factors due to which patients were not signing consent form themselves, language (p=0.03), better educational status (p=0.002) and patient not being informed by relatives before signing forms (p=0.02).

Conclusion
Study concludes that patients had adequate knowledge about the process of informed consent. Factors identified as barriers in signing of consent form by patients themselves included language, better educational status and not being asked by relatives. Clinicians need to inspire patients to sign the consent form themselves.
Changes in weight and waist circumference in adults during 16 years of follow up: longitudinal results from Tehran, Lipid and Glucose Study

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Introduction
One of the most important issues in controlling obesity is to know that which sub groups of our population are more prone to weight gain, so we can start our preventive and curative procedures from the correct point. The aim of our study is to evaluate the amount of weight and waist circumference (WC) change between three phases of Tehran Lipid and Glucose Study (TLGS) during 16 years (1999-2015) and compare different genders and age groups in Tehranian population as an urban population in Iran.

Materials & Methods
Data of 4895 subjects including 41.3% men and 58.7% women who attended phase I (1999-2001), III (2006-2008) and V (2012-2015) of TLGS project during 16 years of follow up was used in this longitudinal study. Subjects were divided into 10-year age groups. Annual changes was compared across sex and age groups. The means between three phases were assessed by Repeated measures analysis of variance. Also, Post-hoc Bonferroni correction was used. Statistical significance was two-tailed. SPSS statistical software package (Version 20.00) was used.

Results
Annual weight change between phase I-V in men and women was 0.39(95%CI 0.21-0.57) and 0.31(95%CI 0.16-0.46) respectively. Our data shows that men aged 20-49 gained weight significantly more than women of same age between phase I-III and I-V (p<0.001), but there wasn’t a significant difference in both sexes between phase III-V (p>0.05). In men aged 20-69, WC change was significantly higher than women of same age between phase I-III and III-V (p<0.001), but there was no significant difference between men and women over 70 years in all three phases, as well as all age groups over 30 years between phase I-V (p>0.05). Participants aged 20-29 years had the most weight and WC gain in both sexes.

Conclusion
Participants in TLGS project gained weight in all phases of our study between 1999-2015 but the amount of change was higher in phase I-III in comparison to phase III-V. Weight and WC change is strongly age dependent. As we can see, young men and women gained weight more than older ones. Therefore, as the age increase, annualized weight change gradually decrease and after 60 years, it starts to weight loss.
Impact of Pulmonary Tuberculosis on Mental Health and Quality of Life- A Case-Control Study

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Introduction
Tuberculosis is the most deadly transmissible disease and India accounts for one-fourth of its cases. Poor mental health is a crucial factor in influencing the treatment compliance and quality of life of such patients. The objective is to recognize this psychiatric co-morbidity among patients and analyse the socio-demographic factors associated with pulmonary tuberculosis.

Materials & Methods
This is a hospital based matched case control study. Purposive sampling is done. Group matched controls are selected using stratified random sampling. For assessing mental health, Beck’s Depression Inventory is used and for quality of life, SF36 is taken into consideration. Data is analysed using Statistical Package for Social Sciences. Odds ratio is calculated and independent t-test is used to compare between cases and controls. To determine the association between the selected socio demographic factors and mental health and quality of life, chi-square test is used. A p value < 0.05 is considered significant.

Results
This study was conducted among 60 cases and 120 controls; 108 males and 72 females. Mean age was 41.183 ± 10.293 years. Out of the total, 19.4% were illiterate and 42% were employed in the unskilled category. A majority lived in urban areas and 65% was diagnosed in a government hospital. Approximately 63% experience little interest or pleasure in doing things in the last week or month and 55% experience trouble falling or staying asleep. Poor appetite after the initial diagnosis was seen in 50%. Around 62% had trouble concentrating and 15% felt bad about themselves and believe that they have let themselves or their family down. The mean depression score on Beck’s Depression Inventory corresponds to moderate depression for cases and minimal depression for the controls. The case score on SF-36 in respective eight dimensions was suggestively lower.

Conclusion
The tuberculosis cases reported moderate depression and low health related quality of life. Hence, the need for a psychologically integrated approach in order to improve treatment adherence and general well-being is crucial.
Variation in the severity of depression symptoms during different phases of the menstrual cycle: A pilot study

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Introduction
PMS (Pre-menstrual Syndrome) and PMDD (Pre-menstrual Dysphoric Disorder) are characterised by symptoms such as depression, mood lability, headache, breast tenderness, etc. The assessment of depression symptoms during different phases of the menstrual cycle could provide a glimpse of the underlying PMS or PMDD that may be silently affecting the quality of life of women. The aim of the study was to assess the severity of symptoms of depression in the different phases of the menstrual cycle.

Materials & Methods
123 female students in the age group of 18-22 years with a regular menstrual cycle were part of this study. Women with diagnosed psychological illnesses and those using hormonal contraceptives were excluded from the study. They were asked to track their menstrual cycles using “period tracking” software applications for the past 6 months. Every participant responded to the Beck Depression Inventory (BDI) questionnaire in each of the three phases of the menstrual cycle- Follicular phase, Ovulatory phase and Pre-menstrual/Luteal phase. A gap of 30 days between each round of questionnaire distribution minimised recollection of previous responses and hence, reduced the reporting bias. Further, the severity of depression symptoms (minimal, mild, moderate or severe) in each phase was determined by assessing the BDI scores. Friedman test with post hoc analysis was used to check if the severity of depression in the three menstrual phases was significantly different.

Results
The severity of depression varied significantly in the three phases of the menstrual cycle. (p<0.001) The severity of depression in the pre-menstrual phase was significantly higher than that in follicular (z=-6.002, p<0.003) and ovulatory phase (z=-5.766, p<0.003). 44% participants reported mild-severe depression symptoms in the pre-menstrual phase, compared to just 16% in the ovulatory phase and 10% in the follicular phase.

Conclusion
The results suggest that women experience more depression symptoms during the pre-menstrual phase, as compared to other phases. This could be a part of underlying conditions like PMS or PMDD, high suspicion of which could lead to early diagnosis and intervention, if required. Being aware of these symptoms gives women the motivation to handle them better. This would lead to a more productive way of life.
Introduction

Background: Social Anxiety Disorder (SAD) is characterized as an extreme anxiety, emotional discomfort or fear about social or performance situations. These people have an intense fear of being judged or negatively evaluated by others. People with social anxiety disorder may avoid important activities such as attending classes and meetings or may attend but avoid active participation. They achieve less in school and work, and are less likely to have a relationship than people who do not have the disorder.

Objective: The objective of this study was to evaluate Social Anxiety Disorder among undergraduate medical students.

Materials & Methods

Study Design: Cross sectional study.
Study Setting and duration: March – May 2018.
Inclusion criteria: All medical students of either gender from first to final year MBBS (Bachelor of Medicine and Bachelor of Surgery) attending Allama Iqbal Medical College, Pakistan.
Data Collection and analysis: 150 medical students, fulfilling the inclusion criteria were included in our study. Every student was given a structured questionnaire consisting of Liebowitz Social Anxiety Scale (LSAS) and last academic performance. Data was entered and analyzed in SPSS version: 21.0. Mean and standard deviation were calculated for numerical variables like age, Liebowitz Social Anxiety Scale (LSAS) scoring. Variables used for SAD were fear and avoidance. Frequency and percentages were calculated for nominal variables like age, gender, residential status, medical school year and SAD. Cross tabulation was done for SAD with gender and residential status.

Results

Results: A total of 150 students were included, 67 (44.67%) were male and 83 (55.33%) were females. The age of the respondents ranged from 18 years to 26 years with the mean age of 21.2y. The percentage of females with mild, moderate and severe social phobia is 61.6%, 50.7% and 60% respectively as compared to males with 38.4%, 49.3% and 40%, respectively. The percentage of female's respondents with mild, moderate and severe degree of avoidance is 65.1%, 49% and 80% respectively as compared to males with 34.9%, 51% and 20 %, respectively.

Conclusion

Conclusion: The conclusion of our study was that females have greater tendency for fear and avoidance as compared to males, and students from urban background have greater tendency for fear and avoidance resulting in social anxiety disorder.

“Prevalence of Social Anxiety Disorder and its Socio-Demographic Correlates in Undergraduate Medical Students”

HAMZA, Mr (ALI)

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Association between dietary patterns, testosterone levels and dyslipidemia among middle-aged and elderly men with chronic kidney disease

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Introduction
Taiwan had the highest prevalence and incidence rate of chronic kidney disease (CKD). CKD is associated with low testosterone and dyslipidemia. Moreover, diet has been linked to many risks of chronic disease development and outcome-related disease.

Materials & Methods
Middle-aged and elderly men (n = 21376) aged of 40 years old or above with estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m² and positive proteinuria were recruited and their food frequency questionnaire and biochemical data were collected from a private health screening institute with multi-centers in Taiwan between 2008 and 2010. Three dietary patterns, the fried-processed dietary pattern (deep-fried foods, preserved or processed foods, organ meats and meats), vege-seafood dietary pattern (dark- or light-vegetables, legumes or beans, seafood and salad) and dairy-grain dietary pattern (dairy products, milk, bread, fruits and whole grains) were identified using principal component analysis.

Results
Subjects with lower tertiles (T1 and T2) of eGFR had significantly decreased testosterone levels by 0.8 and 0.9 nmol/L, respectively, compared with those with the highest tertile of eGFR. Furthermore, blood triglycerides (TG) were independently associated with decreased testosterone levels (β = -0.508, 95% CI -0.774 to -0.242). The higher tertile of fried-processed dietary pattern score was associated with decreased testosterone levels by 0.8 nmol/L, reduced testosterone-to-TG (T/TG) ratio by 1.8 units, and increased risk of dyslipidemia, progression to moderate/severe CKD and proteinuria severity by 15%, 35%, and 18%, respectively. In contrast, the vege-seafood had protective effects on dyslipidemia, progression to moderate/severe CKD and proteinuria severity after multivariable adjustment, but were associated with neither testosterone levels nor T/TG ratio.

Conclusion
The fried-processed dietary pattern is negatively associated with testosterone levels and T/TG ratio but positively associated with dyslipidemia, CKD progression, and proteinuria severity. However, the vege-seafood and dairy-grain dietary patterns appear to have protective effects.
Miscellaneous Health I

Chair
Non Nominatus

Presenters
Aguilar Mora, F.A (Fabio)
Gelhard, P. (Paul)
Kornienko, E.I. (Elena)
Krivoshein, G (Georgii)
Mohamed, A.A. (Ahmed)
Nikhil teja, B (Banthu)
Nwosu, O.K. (Onyeka)
Sengupta, A. (Abishek)
Subramanian, D (Divya)
Yugay, N.Y. (Nikolay)
Effect of dietary nitrates on vascular function: does age matter? - A randomized, placebo-controlled, double-blind crossover study -

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Introduction
Supplementation of dietary nitrates is shown to be promising in reducing cardiovascular disease risk in a number of clinical populations. However, it is currently unknown whether age can affect the blood pressure reducing effects of dietary nitrates. We sought to determine whether age modifies the effect that dietary sources of nitrates have on the vascular function of young and older people.

Materials & Methods
Twenty-five participants were recruited and stratified according to their age (18-35 years and &gt;55 years) for a double-blind, randomized, placebo-controlled, crossover trial. Participants were randomized into either, a single dose of 70 ml of beetroot juice (control) or 70 ml nitrate-depleted beetroot juice (placebo). Volunteers had blood pressure measurements taken at baseline and every 20 minutes following juice consumption, for a 3-hour period. Microvascular endothelial function assessments were also performed at baseline and 3 hours after the juice consumption.

Results
Under resting condition, dietary nitrates have no significant effectivity difference in the cardiovascular function regardless the age p=&lt;0.5. However, there is a higher interaction effect between dietary nitrates and systolic blood pressure of 2% (p= 0.01) in the elderly population. Finally we encounter periods in which the elderly population presents a recoil effect in the systolic blood pressure.

Conclusion
The efficacy of acute ingestion of nitrates on vascular function is the same regardless the age. However, the observed recoil effect should be studied further on unhealthy populations as it may lead to a better understatement of NOx metabolism during ageing and to further define more effective doses dietary nitrates as a possible prophylactic option for heart diseases.
Mesenchymal Stem Cells increase canonical activation of the NLRP3 Inflammasome in murine Bone Marrow Derived Macrophages

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Introduction
Therapeutic Mesenchymal Stem Cells (MSCs) ameliorate the development of Bronchopulmonary Dysplasia (BPD), a lung disease of preterm infants caused by chronic inflammation. Development of BPD is known to depend on NLRP3 inflammasome mediated caspase-1 activation. Hence, effects of MSCs on the development of BPD may be caused by MSC-mediated inhibition of the NLRP3 inflammasome. In this study we analysed the effects of human umbilical cord (huc) and bone marrow (BM) derived MSCs on NLRP3 inflammasome activation in murine bone marrow derived macrophages (BMDMs).

Materials & Methods
BMDMs of CL57BL6/N mice were differentiated in vitro using bone marrow aspirates in presence of 20ng/ml mM-CSF. Direct or transwell co-cultures of BMDMs and huc- or BM-MSCs were initiated 24h before inflammasome stimulation. The cells were primed with ultrapure LPS or poly(I:C) for 4h followed by activation of the NLRP3 inflammasome using ATP or Nigericin. IL-1α, IL-1β, TNFα and IL-6 in the cell free supernatants were measured by Cytometric Bead Array, whereas IL-1β depicts a surrogate for inflammasome/caspase-1 activation.

Results
Co-culture of BMDMs with MSCs did not attenuate the activation of the NLRP3/caspase-1 axis. Instead, transwell coculture of huc- or BM-MSCs led to significantly increased IL1β secretion of BMDMs following activation of the NLRP3 inflammasome with LPS/ATP. In contrast, direct coculture with BM-MSCs led to reduced secretion of TNFα and IL-6 by BMDMs. Priming of BMDMs with poly(I:C) instead of LPS followed by stimulation with ATP or Nigericin led to enhanced secretion of both TNFα and IL-1β in BMDMs co-cultured with huc-MSCs.

Conclusion
In contrast to the hypothesized effects, human MSCs do not inhibit activation of the NLRP3 inflammasome but lead to pro-inflammatory signaling of BMDMs in vitro. Therefore, MSC mediated amelioration of BPD progression may influence pathways other than the NLRP3 inflammasome. Further analysis of the MSC secretome are required in order to characterize the interaction of both cell types.
Fibrinolytic and proteolytic action of Sarocladium strictum proteases

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Introduction
The hemostatic system maintains a constant blood viscosity, prevents bleeding and the formation of blood clots. Failure of these systems leads to serious health complications. Proteinase preparations are widely used in medicine in connection with the treatment of diseases of the cardiovascular system, but these drugs are very few and they have disadvantages, such as high cost, toxicity and allergenicity. Therefore, the search for new drugs is still relevant. Micromycetes may be producers of such drugs, as they synthesize a whole complex of extracellular proteolytic enzymes. One of the promising producers is Sarocladium strictum. The enzyme complex formed by it possesses fibrinolytic and plasminogen activator activities.

Materials & Methods
Micromycetes were cultivated under deep conditions and the activity of extracellular proteases in the culture fluid was determined. To determine the specificity of the proteinases obtained, their activity was determined by various methods. Fibrinolytic and plasminogen activator activities were determined by the fibrin plate method. Proteolytic activity was determined by protein cleavage: casein, fibrin, fibrinogen.

Results
Fibrinolytic activity, determined in cultural fluid of S. strictum was 817,6 conv. units / ml and plasminogen activator activity was 472,8 conv. units / ml. Thus, plasminogen activator activity is approximately 50% of fibrinolytic activity. When revealing the ability to hydrolyze native proteins, it was shown that total proteolytic activity with casein is 29.2 μmoles Tyr / ml * min. Activity against fibrin and fibrinogen was 17.8 and 8.7 μm Tyr / ml * min, respectively.

Conclusion
The proteolytic enzymes of micromycete Sarocladium strictum showed high fibrinolytic activity against native fibrin, as well as high activity against casein. Fibrinolytic and plasminogen activator activities measured on fibrin plates showed high proteolytic properties. Plasminogen activator is more preferable for medical practice as it activates the patient’s thrombolysis system. Thus, the fibrinolytic complex formed by Sarocladium strictum is very promising for the clinical practice.
Optical and electrophysiological changes of motor nerve endings in Calcium Ringer

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Introduction
Investigations of neurotransmitter release and synaptic vesicle endocytosis processes occurring with the rapid depletion of the entire reserve of the recycling pool has attracted the interest of many scientists in the field of neurophysiology. In this paper, the process of neurotransmitter release was studied under the conditions of Ca-Ringer, where all external Na ions had been entirely replaced by Ca.

Materials & Methods
Experiments were made on frog cutaneous - thoracic neuromuscular preparations Rana ridibunda using optical (confocal microscopy with the fluorescent endocytic stain FM 1-43) and electrophysiological (intra- and extracellular recording of postsynaptic currents) methods in winter period of 2018-2019. Muscles were stretched and fixed in a glass bath and immersed in a Ca-Ringer solution containing 83 mM CaCl2, 2.5 mM KCl and 2.2 mM NaHCO3, pH 7.2–7.4, temperature 24-26°C. Also, the potassium channel blocker – 4-Aminopyridine to the solution was added. To depolarize motor nerve endings, method of focal depolarization by closely applied micro-electrode was used.

Results
When one impulse duration for 4 ms was applied in the presence of FM 1-43 dye and the potassium channel blocker bright luminous spots of a rounded shape in the nerve endings were revealed. Such spots are observed in the literature when dyeing by high-frequency stimulation or when exposed to a hyper-potassium solution. During intracellular recording of postsynaptic currents a huge evoked end-plate potential was discovered. Analysis of the quantum component according to the method of dividing the area of evoked end-plate potentials by the area of spontaneous miniature end-plate potentials showed 3000, which turned out to be less than an amount of the frog’s recycling pool of synaptic vesicles.

Conclusion
Based on the data obtained, it can be said that a single stimulation under the conditions of the hyper-calcium solution did not cause emptying of the recycling pool, however, the possibility of synaptic vesicles endocytosis was noted.
Rhythm Versus Rate Control for Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials


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Introduction
Atrial fibrillation (AF) commonly associated with an increased risk of thromboembolic and mortality events. We performed this study to compare the clinical efficacy of rhythm and rate control strategies in patients with AF.

Materials & Methods
A comprehensive search of six databases was conducted, using specific keywords. Dichotomous data on mortality and other clinical events were extracted and pooled as risk ratios (RRs), with their 95% confidence interval (CI), using RevMan software (version 5.3).

Results
Twelve studies (8451 patients) were pooled in the final analysis. The overall effect-estimate did not favor rate or rhythm control strategies in terms of stroke (RR= 0.97, 95% CI [0.79, 1.20]), all-cause mortality (RR= 1.13, 95% CI [0.88, 1.45]), major bleeding (RR= 1.10, 95% CI [0.90, 1.35]), and thromboembolism (RR= 1.06, 95% CI [0.64, 1.76]) rates. In younger patients (<65 years), Rhythm control was superior to rate control in terms of lowering the risk of all-cause mortality (p=0.0003), HF (p=0.003) and major bleeding (p=0.02). The rate of rehospitalization was significantly higher (RR= 0.72, 95% CI [0.57, 0.92]) in the rhythm control group, compared to the rate control group.

Conclusion
Both rate and rhythm control strategies have similar rates of mortality and major clinical outcomes for older AF patients and those with concomitant HF; therefore, choosing a suitable strategy should consider individual variations, such as comorbidities, patient preferences, and treatment cost.
Use of electroretinogram (ERG) in the early diagnosis of diabetic retinopathy (DR) while there is no significance of visual evoked potential (VEP)

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Introduction
Retinopathy is a severe and common complication of diabetes, a leading cause of blindness worldwide. At least 80% of new cases could be reduced if there were early diagnosis and monitoring of the eyes. Electrical changes plausibly precede structural changes assessed by fundoscopy in DR. We aimed to assess if the electrophysiological methods VEP and ERG help in early diagnosis of DR. These methods are safe, repeatable and objective.

Materials & Methods
It is a Cross-sectional study done on 32 diabetics, of which 12 are fundoscopically positive retinopathy patients, 20 are fundoscopically normal long-standing diabetic patients (diabetic past 4-25 years). VEP and ERG are recorded. Parameters measured are P100 latency, b/a ratio, Oscillatory Potential P1-amplitude and latency. Binary logistic regression analysis method was used to predict the data with fundoscopic status (positive/negative) as the dichotomous variable and predictor variable used were P100, b/a ratio, OSP1_amplitude, and OSP1_latency.

Results
The analysis revealed that OSP1_amp was a statistically significant predictor of fundoscopic status with a two-tailed P-value=0.029 and actual one-tailed p-value=0.0145. Odds ratio is 0.75 indicating that the probability of positive fundoscopic status increases as the amplitude of the wave decreases. To assess multicollinearity, Pearson correlation coefficients were calculated between pairs of predictor variables and their statistical significance was assessed. P100 latency and OSP1_latency did not contribute significantly to the model, hence are omitted from further analysis. Binary logistic regression is done again with two predictors i.e., OSP1_amp and b/a ratio. The P-value for this two-tailed test is 0.022. As the decline in amplitude was expected and well documented in the literature, it is properly a one-tailed test and the actual P-value is 0.011. The odds ratio is 0.856 indicating that the probability of fundoscopic positivity significantly increases with a decline in the amplitude of OSP1. Of the 20 fundoscopically negative diabetics, 5 have been predicted to have diabetic retinopathy.

Conclusion
The results of the study lend evidence to the hypothesis that electrophysiological methods have the potential for early diagnosis of Diabetic retinopathy. Oscillatory potential P1 wave-amplitude of ERG is significantly predictive of incipient Diabetic retinopathy in fundoscopically negative patients. They are specific and sensitive than fundoscopy.
Hypolipidaemic Effect of Aqueous Extract of Desmodium velutinum leaf on Wistar Rats Fed with High Fat Diet

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Introduction
As foods containing high lipoprotein abound and people are expected to live longer, they are more likely to acquire lipid-related disorders that eventually cause hyperlipidaemia. The world today uses plant parts for development of drugs and Desmodium veletinum (DV) remains significant among them as it serves in many therapeutic purposes. In this study, we examined the effect of aqueous extract of leaves of DV on serum lipid profile of rats fed with high fat diet. We also examined the phytochemical compositions of the aqueous extract of DV leaf.

Materials & Methods
Quantitative and qualitative phytochemical screening was done using Trease and Evans method. In the animal experimental model, twenty-five (25) rats were randomly distributed into five groups (A, B, C1, C2, D) of five rats each. Group A was the negative control that was fed with normal feed for 14 days. Group B was the positive control that was fed with high fat diet for 14 days. Groups C1 and C2 were fed with high fat diet for 14 days followed by treatment with DV aqueous leaf extract at 150 and 300 mg/kg b.wt. respectively for 5 days. Group D were fed with high fat diet for 14 days followed by treatment with a known drug (Atorvastatin) at 5 mg/kg for 5 days. Serum Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and Triglyceride (TG) levels were determined from blood samples collected on the 15th day for Groups A and B and on the 20th day for Groups C1, C2 and D.

Results
The result showed that the extract treatment and Atorvastatin significantly (p<0.05) reduced the serum TC, LDL and TG. HDL was not significantly reduced. Alkaloids, tannins and flavonoids were found to be highly present while saponin, steroids and terpenoids were found to be moderately or lowly present.

Conclusion
The study indicated that the use of the extract treatment will enhance the serum lipid lowering potential. The findings therefore may be of clinical importance to individuals at risk of cardiovascular disease.
Structural changes in pre-retinopathic retina in patients of Systemic hypertension and Diabetes mellitus - An Optical coherence tomography based study.

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Introduction
Diabetes mellitus and Systemic hypertension are a common scourge on human populace and responsible for a considerable portion of avoidable blindness. Prevention is a key in such cases and would ameliorate to an extent the vast physical, social, and, economic burden of these diseases. Our study aims to identify early changes in the retina of patients suffering from hypertension and diabetes mellitus to help better understand the natural history of these diseases.

Materials & Methods
We recruited 50 patients (100 eyes) over a period of 1 month of which 77 eyes met the desired criteria. The patients were divided into four groups i.e. Diabetic only, Hypertensive only, Diabetic and Hypertensive, and Control. We used Heidelberg Spectralis V6.9a to measure the Central Macular thickness (CMT) and Retinal Nerve fibre layer thickness (RNFL) of the four retinal quadrants. Mean ± Standard deviation of the CMT and RNFL of Superior, Inferior, Nasal and temporal quadrants was calculated for the 4 groups. The findings of the former three groups was compared against the control group. Analysis was done in MS Excel. Student’s t test with one tailed and two tailed hypothesis was used to determine significance, taking p<0.05 as significant.

Results
The mean age of the population was 56.3±2.9 years of which 61.03% were male. Of the 77 eyes, 27(35.06%) were Control, 24(31.16%) Hypertensive only, 13(16.88%) Diabetic only and 13(16.88%) Diabetic and Hypertensive. The CMT and RNFL of superior, inferior, nasal and temporal quadrants for the diabetic only group was 268.3±39.1, 105.5±27.1, 114.9±16.3, 63.7±17.1 and 66.6±19.2 respectively, and that of control group was 270.6±27.6, 116.3±29.8, 117.9±24.6, 75.4±19.5 and 69.2±12.3 respectively. In general, the retinal thickness among the diabetic only population was thinner than the control group, but, only Nasal RNFL thickness was significantly thinner on one tailed hypothesis(p= 0.04). No other groups had any significant difference than the control group.

Conclusion
Nasal RNFL thinning may be one of the earliest finding in the retina of a patient of diabetes mellitus though further study into this domain is needed.
Study of correlation between the intelligence level and language proficiency among young Indian adults using Cattell’s Culture Fair Intelligence Test

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Introduction
Intelligence is the ability to learn and adapt rapidly and is highly variable among individuals. As per American Psychological Association, intelligence is the difference between individuals in their ability to comprehend complex ideas and effectively adapt to the environment, learn from experience, engage in various types of reasoning and thoughtfully overcome obstacles. The existence of language can be attributed to brain and its capability to learn. Language, therefore, must be learnable by children. Thus, language in itself becomes a limiting factor of the existing abilities of the brain. Very few studies correlate the language skills and the intelligence level of the person. India is a country that boasts of many languages and thousands of local dialects. Therefore, we hypothesised that the mental circuitry responsible for linguistic skills must be more refined among those who know more languages. Their discriminatory learning could be better. A correlation between intelligence and multi-linguistic ability could help in interventional therapeutic option in children with mild learning disabilities as well.

Materials & Methods
A correlational questionnaire based study was conducted on 205 subjects of age group of 19-22 years, who were required to fill in a case study form and take an IQ test (Cattell’s Culture Fair Intelligence Test). SPSS 11.5 and Pearson Correlation Coefficient were used to analyse the data.

Results
The number of languages known among the 205 participants ranged from 1 to 6. Out of 205 respondents, 0.4% knew 1 language, 47.3% knew 2 languages, 32.1% knew 3 languages, 12.1% knew 4 languages, 4.3% knew 5 languages and 3.4% knew 6 languages. When Pearson Correlation was used, we did not find significant difference among the groups and no correlation between the number of languages and the IQ of a person was evident. (The Pearson Correlation Coefficient -0.029 and p = 0.677).

Conclusion
With the increase in the number of languages known, there does not seem to be increase in the Intelligence Quotient. It could be a myth to presume that knowing multiple language will improve intelligence level. Better results could be revealed if a bigger sample size with comparable numbers of respondents in each group could be used.
Fast and easy visualization method of impression cytology probe with microbiota detection on the ocular surface

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Introduction
Impression cytology is non- or minimally invasive technique used for ocular surface examination. This technique is in constant expansion due to its advantages and high diagnostic potential. Usually the conjunctival cavity and its microbiota are examined by light microscopy or bacteriological culture methods. However, limitations of the light microscopy method do not allow to visualize properly the bacterial component of the probe. After that, microbiological culture methods are time consuming and some types of bacteria can't be cultivated in standard conditions, what can lead to false negative results. Identification of the pathogen is crucial on behalf of choosing an antibacterial therapy. This challenge can be solved by scanning electron microscopy. At the same time, conventional sample preparation is quite a long process. We aimed to use a new fast two-step lanthanoid contrasting method with subsequent visualization on scanning electron microscope.

Materials & Methods
12 patients participated in the study. 6 of them had specific signs of infectious inflammatory process on the ocular surface. Other patients didn't suffer from ocular surface diseases. Topical anesthesia was not required, because flexible plastic cover slips didn't cause any discomfort to the patients. The specimen preparation included 2 stages: treatment with neodymium and with plumbum (BioREE-B staining kit). Further, these specimens were examined on the scanning electron microscope.

Results
In visualized samples we found squamous epithelial cells, mucosal components and microbiota. Epithelial cells seemed to enter the apoptotic process (karyopicnosis and cytoplasm vacuolation). In two out of six cases with supposed infectious process increased density of coccomorphic organisms compared with “healthy” donors was detected. Sometimes it was possible to visualize intercellular contacts.

Conclusion
It is the first time, when pictures of ocular surface were obtained so fast and with so high resolution. New contrasting method with neodymium and plumbum treatment enable to give the morphological assessment of the most superficial layers. Furthermore, quality of the images allows to evaluate not only functional status of corneal cells, but also microbiota activity.
Poster session 2
Anesthesiology and General Surgery

Chair
Gertrude J. Nieuwenhuijs-Moeke MD

Presenters
Emam, A.H. (Amir Hossein)
Kunte, Kishan J Kunte (Kishan)
Mazo, A.M.C. (Andrea)
Shadin, K.I. (Konstantin)
Steen, van der, K. (Koen)
Vasa, D. (Divyata)
Xiao, Q. X. (Qingyu)
Ofsar cream is more analgesic than EMLA in pain relief after inguinal hernia surgery


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Introduction

Pain is described as a discomfort feeling and since a long time ago people have used different ways to suppress this feeling. Analgesic herbal medicine is one of these methods. Analgesic effect and mechanism of action of this herb is proven in laboratory animals as well. In this study the analgesic effect of Artemisia absinthium %5 (Ofsar) cream is compared with 2.5% lidocaine-2.5% prilocaine (EMLA) cream, in patients with surgical pain after herniorrhaphy.

Materials & Methods

This study was a double-blind randomized controlled clinical trial on 50 patients with unilateral hernia has been anesthetized by spinal anesthesia with bupivacain 0.5%. The patients were randomly allocated into two groups A and B; We applied Ofsar cream for A group and EMLA cream for B group after surgery and around incision of herniorrhaphy. In both groups, the pain severity was assisted by Numerical Rating Scale (NRS) every 8h for 48hours and then 25 mg pethidine intravenously administrated for pain management as PRN. Eventually, we determined and Comparison pain severity and total amount of pethidine consumed, in each group.

Results

This study demonstrate analgesic effect of both Ofsar cream and EMLA. The Ofsar cream significantly showed more analgesic effect than EMLA(P<0.05). Also, in Ofsar group, the total consume dose of pethidine was significantly less than EMLA group (P<0.05).

Conclusion

We conclude that Ofsar cream is more analgesic than EMLA for postoperative pain management in herniorrhaphy surgery. This study confirmed the analgesic effects of both Ofsar cream and EMLA.
PERI-OPERATIVE RISK FACTORS FOR PULMONARY COMPLICATIONS AFTER NON-CARDIAC SURGERY

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Introduction
Postoperative pulmonary complications (PPC) are one of the most common complications following anesthesia and surgery. They lead to increased morbidity, mortality, length of hospital stay and cost to the patient. Preoperative assessment of factors associated with the occurrence of PPC help in risk stratification and planning optimal interventions to decrease their incidence. This study was conducted to assess the incidence of PPC after noncardiac surgery in our hospital and to determine the risk factors associated with their development.

Materials & Methods
This prospective observational study was conducted on 1170 patients undergoing non-cardiac surgery in a tertiary care hospital between March 2016 and December 2016 after obtaining Institutional Ethical Clearance and written informed consent. Pre, intraoperative and postoperative data on patient, surgical and anesthetic factors was collected and patients were followed up for the entire duration of their hospital stay for the occurrence of PPC. A step wise logistic regression analysis was used to find the risk factors associated with development of respiratory complications.

Results
The incidence of PPC was 5% in our hospital with respiratory infections being the most important cause. Univariate analysis showed that higher age > 50 years, American Society of Anesthesiologists (ASA) status > 2, anemia, preoperative arterial oxygen saturation (SpO2) < 96%, preoperative respiratory symptoms, positive cough test, general anesthesia, emergency surgery, upper abdominal incision, increased duration of surgery, presence of nasogastric tube, intraoperative blood transfusion, intraoperative pulmonary complications and high ARISCAT score were significantly associated with the development of pulmonary complications. Length of hospital stay was increased in patients with PPC. Multivariate analyses revealed higher ARISCAT score, higher age, positive cough test, presence of nasogastric tube and intraoperative pulmonary complications as risk factors.

Conclusion
The independent risk factors associated with the development of PPC were higher age, high ARISCAT score, positive cough test, presence of nasogastric tube and intraoperative pulmonary complications. Identification of the high risk patients based on these predictors can help target aggressive preoperative and intraoperative measures to reduce the occurrence of PPC and improve patient outcome.
Effectiveness of clonidine vs. morphine as coadjuvants to spinal anesthesia with hyperbaric bupivacaine in cesarean patients


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Introduction
The main adjuvants of bupivacaine are opioids and clonidine; the first opioid used by the epidural route was morphine, which since 1979 has demonstrated benefit of its intrathecal and extradural use, for the management of chronic and postoperative pain.

Objective: determine the analgesic effectiveness of morphine vs. clonidine added to spinal anesthesia with hyperbaric bupivacaine in patients undergoing cesarean section.

Materials & Methods
A quasi-experimental correlational clinical trial. 60 parturients, carrying a singleton fetus at term, scheduled to undergo cesarean section under spinal anesthesia were randomized in one of the two groups. Group BC (n = 30) received 10 mg hyperbaric bupivacaine and 75 μg clonidine; Group BM (n = 30) 10 mg hyperbaric bupivacaine and 100 μg morphine.

Results
Statistically significant difference, \( p = 0.02 \), were found between the time of 14.5 ± 2.1 hours since the administration of anesthesia to the application of the first dose of additional analgesia in morphine group vs. clonidine group 8.18 ± 2.91 hours. Pain at the time of the application of postoperative analgesia was superior in clonidine group with 6.4 ± 1.0 points in AVE vs. morphine with 0.93 ± 2.4 points. \( p = 0.001 \). AVE values were also significantly higher for clonidine in relation to morphine at 6, 12 and 18 hours. No significant hemodynamic and respiratory changes occurred in either group. For morphine the most frequent side effect was itching in 66.7 % of patients. The level of sedation was the same for clonidine and morphine in all the patients.

Conclusion
Add 100 μg of morphine to hyperbaric bupivacaine for spinal anesthesia prolongs the time and significantly improves quality of the postoperative analgesic period greater than 75 μg of clonidine. The most common side effect is itching.
Validation of a New Training Biomodel for Laparoscopic TAPP Inguinal Hernia Repair

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Introduction

Using of tissues and organs of farm animals is becoming an integral part of the training programs for laparoscopic surgery. New biological model for TAPP hernia repair made of a full-layer flap of preserved porcine stomach with inverted outward mucosa was created in our University. This model, imitated the posterior wall of the inguinal region, allows performing the main stages of hernia repair: incision of the "peritoneum", dissection and intracorporeal suture. The aim of research is compare the mechanical properties of porcine stomach mucosa and human peritoneum for validation of a new simulation model for TAPP hernia repair.

Materials & Methods

Mechanical tests were performed on TX MicroStableSystems texture analyzer. Six samples of mucosa and 6 full-layer sections from the body of 3 preserved porcine stomachs were used. Samples of human tissue from the groin area were taken from 2 male and 2 female cadavers. The elastic moduli of the human peritoneum and porcine stomach mucosa were compared in uniaxial tensile tests, the forces of peritoneum and mucosa layer separation - in T-peel tests. Additionally, nine experienced surgeons assessed the tactile sensations during training on a 5-point scale.

Results

The thickness of human peritoneum and porcine mucosa differed slightly (1.74+0.39 mm vs. 1.73+0.32 mm, p = 0.168). Close elastic moduli of the mucosa and peritoneum were obtained (13.5 +4.2 kPa vs. 15.8+6.7 kPa, p = 0.531). However, the force required for the detachment from the underlying tissues was almost 2 times greater for mucosa than for peritoneum (0.212+0.014 N / mm vs. 0.11+0.086 N / mm, p = 0.038. The median (IQR) rate for the dissection stage was 4 (4–5), and for intracorporeal suture - 5 (5–5). The stage of dissection was the most difficult, but some surgeons attributed this to the advantages of the model.

Conclusion

The similarity of the mechanical properties of the human peritoneum and the porcine stomach mucosa makes it possible to recreate maximum realism in performing the main stages of the laparoscopic TAPP hernia repair on the biomodel. This easy reproducible model can be used in the training programs of surgical residents.
The added value of laparoscopic intraoperative ultrasound of the liver

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Introduction
Ultrasoundography is an extremely cheap, safe and valuable diagnostic tool in the hands of a skillful user. Intraoperative ultrasound is considered the gold standard for hepatic neoplasms in open surgery. Although laparoscopic intraoperative ultrasound (LIous) is also considered essential for laparoscopic liver surgery, not much research is done to confirm this.

Materials & Methods
92 patients who underwent 106 laparoscopic hepatic procedures between 2014 and 2018 due to suspected malignancy in which ultrasound was used, were retrospectively analyzed. All ultrasounds were performed by a surgeon. We counted when new information gained from LIous changed the plan of surgery. Also, LIous results were compared to the preoperative CT and MRI scan. False positive and false negative lesions were defined by comparing between the imaging techniques and checking the pathology results and information gained from follow up.

Results
12% of all operations changed because of information gained during LIous. Surgery was not continued in two cases i.e. one due to extensive spread of the disease and one because LIous suspected benign cysts which was confirmed with frozen section analysis. In all the other cases, lesions were justly removed or left behind. Positive predictive value was 86% for LIous, 73% for CT and 65% for MRI. LIous, CT and MRI were false negative in 5%, 9% and 6% of the patients respectively. The number of false negatives is underestimated in this research because it is not always clear whether a lesion is new or was missed before. These results cannot be seen separately from each other. Information from one investigation was used in decision making for other investigations. For example, during LIous information from CT and MRI was used as reference and MRI was often done when in doubt after CT scan. Also, there could be a time bias as ultrasound is obtained during surgery and other imaging beforehand.

Conclusion
LIous changed the plan of surgery in 12% of all cases. Although retrospectively analyzed, this study shows the added value of LIous as diagnostic tool. LIous should be considered in every liver procedure with suspected malignancy.
Amputation and phantom limb perception

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Introduction
A large number of patients who have had a limb amputation has experienced phantom limb- the impression that the limb is not only still present but also painful at times. Phantom limb sensations are believed to be associated with conditions like pre amputation pain management, condition of stump, emotional trauma, etc. The phantom limb sensation, especially the phantom limb pain- which may last for years after amputation- affects the quality of life of the patient to a great extent and can be equally debilitating as any other physical pain. This study aims to find out the prevalence of phantom limb among patients undergoing amputation in tertiary care teaching hospitals and the other triggering/alleviating factors related to phantom limb pain.

Materials & Methods
Observational study carried out among 60 patients aged above 18 years undergoing emergency/elective amputation in Surgery department of tertiary care hospitals of Ahmedabad city, who consented to participate in the study, interviewed with the help of a pilot tested questionnaire and re-interviewed 15 days after their surgery to check for the presence of phantom limb sensation.

Results
The prevalence of phantom limb was 48%. 35.07% of the patients were chronic smokers. 34% of the individuals suffered severe pain before amputation, 13% of them continued to suffer severe phantom limb pain after amputation. The type of pain in the limb before amputation corresponded to the same type of pain in the phantom limb post amputation. 5 patients described several vivid phantom limb experiences suggesting cortical remapping. The stumps of the patients who did not experience phantom limb sensations were ideal stumps.

Conclusion
Pain management before amputation, aiming for making of an ideal stump and proper stump care post amputation play an important role in reducing the duration and severity of the phantom limb pain. Active distraction of the patient from paying attention to the phantom limb also helps in alleviating the pain. In the patients with severe and debilitating pain, psychotherapy can be attempted. “Mirror box therapy” can also be attempted to relieve pain.
The effect of wrist dorsiflexion by five-centimeter wrist elevation on ultrasound-guided radial artery catheterization using dynamic needle tip positioning technique in adult patients: a randomized controlled clinical trial

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Introduction
During radial artery catheterization, it is generally recommended to keep the wrist joint mildly dorsiflexed, but the effect of wrist dorsiflexion on ultrasound-guided radial artery catheterization using dynamic needle tip positioning technique was unknown. Therefore we assessed the success rate of two groups with or without wrist dorsiflexion in adult patients.

Materials & Methods
This is a randomized, parallel-controlled clinical trial. We involved adult patients undergoing major surgical procedures that required radial artery catheterization and randomly allocated them into two groups: Group E (elevation group) and Group N (non elevation group). The primary outcome was first-attempt success rates of two groups. Secondary outcomes were overall success rates within five minutes, numbers of insertion and cannulation, catheterization time and complication rates. Success rates and numbers of attempt were evaluated using χ² test or Fisher exact test. Two-sample independent t test or Mann-Whitney U test were applied for analysis of catheterization time.

Results
One hundred and twenty patients with the age from 22 to 83 years old were evaluated. First attempt success rate was 88.3% in Group E and 81.7% in Group N (P=0.444). Overall success rate within five minutes was 93.3% in Group E compared to 90.0% in Group N (P=0.743). Numbers of insertion and cannulation, overall catheterization time, time durations of localization and insertion, complication rate did not show significant difference between two groups. Mean cannulation time was longer in Group N (35.68 seconds) than in Group E (26.19 seconds; P <0.05).

Conclusion
Wrist dorsiflexion by five-centimeter wrist elevation did not affect first attempt success rate, overall success rate, overall time or complication rate, but decreased cannulation time of ultrasound-guided radial artery catheterization using dynamic needle tip positioning technique in adult patients.
Biomaterials

Chair
Prof. Henny C. van der Mei MD PhD

Presenters
Bestepe, F. (Furkan)
Imaniarti, D.N.I (Destria)
Petlenko, A. (Antonina)
Sarma, N. A. S. (Nivedina)
Shrestha, J. (Jesus)
Volkova, M. (Marina)
Yang, K. (Ke)
Zavvar, T.S (TaranehSadat)
Dose, treatment and time dependent toxicity of superparamagnetic iron oxide nanoparticles on primary rat hepatocytes

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Introduction
The aim of the current study is to investigate the concentration-dependent (0-400 μg/ml) and the exposure-dependent (single dosing vs. cumulative dosing) effects of superparamagnetic iron oxide nanoparticles (SPION) (d=10 nm) on primary rat hepatocytes in a time-dependent manner, which to the best of our knowledge has not been reported previously. SPION are the only clinically approved metal oxide nanoparticles and have a vast variety of biomedical applications including magnetic resonance imaging, targeted delivery of drugs or genes, tissue engineering, hyperthermia of cancer, magnetic transfections, among others.

Materials & Methods
Sandwich cultured primary rat hepatocyte model was used to evaluate viability (evaluates the mitochondrial conversion of resazurin to resorufin by accepting electrons from NADPH, FADH, FMNH, NADH and cytochromes; and fluorescent live/dead assay), hepatocyte specific functions (albumin and urea synthesis) and reactive oxygen species level.

Results
Both in single dosing and cumulative dosing groups, statistically significant effects on the viability of the primary rat hepatocytes were observed upon treatment with SPION with 200 μg/ml and 400 μg/ml at 24th hour (p<0.05 for 200 μg/ml, p<0.01 for 400 μg/ml) and 48th hour (p<0.01 for 200 μg/ml and 400 μg/ml) after the start of treatment. Live/dead assay carried out at 7th day after the start of treatment illustrated that damaging effect of SPION on the viability of the primary rat hepatocytes was progressive with time. The results also revealed the loss of hepatocyte specific functions, albumin and urea synthesis, upon treatment with SPION in a dose and time dependent manner; significantly (p<0.05) more deleterious effects on the functions were observed at 48th hour after the start of treatment in the cumulative dosing group. All concentrations of SPION induced highly significant (p<0.01) production of reactive oxygen species (ROS) at 30th minute; and then, statistically significant differentiation (p<0.05) among concentration groups took place at certain time points within the 18 hour time lapse experiment.

Conclusion
A combination of various biomarkers should be employed for the evaluation of the effect of superparamagnetic iron oxide nanoparticles on liver, and each biomarker should be analyzed in a time- and exposure dependent manner.
Synthesis of Propolis Nanofibers using Electrospinning Method

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Introduction

Wound can heal naturally through four important stages that are hemostasis, inflammation, proliferation, and remodeling. However, infection from bacteria and excess exudate fluid can impede the process. Nowadays, the development of wound dressing leads to wound dressing that can accelerate wound healing and to promote proliferation of fibroblast.

Materials & Methods

In this research, nanofiber formulas were developed using a mixture of chitosan-gelatin and chitosan-polyvinyl alcohol for encapsulating propolis as the active agent. The aim of this study is to develop mixture hydrogel formula of PVA/chitosan and gelatin/chitosan with optimization of polymer concentration and flow rate that can form nanofiber using electrospinning which has uniform size, high porosity, biodegradable and strong antioxidant activity. The electrospinning production was optimized including polymer concentration and flow rate. The electrospinning process parameters selected were at 18 kV, the flow rate of 1 µL/minutes, and the nozzle to collector distance of 10 cm.

Results

The uniform nanofibers were produced using solution concentration of 20% w/v and 40% of PVA-chitosan and gelatin-chitosan, respectively. The maximum propolis incorporation in those nanofibers were 40% and 15%. PVAChitosan formula containing 30% propolis produced the best uniform nanofibers with average fiber diameter of 58.32 ± 21.07 nm, porosity 47.19±17.31\%, water absorption capacity of 442.5±10.61\%, and antioxidant activity of IC50 is 81.04±3.03 ppm analyzed using DPPH.

Conclusion

Propolis have been successfully incorporated to nanofiber using electrospinning method. Nanofiber using PVA/chitosan as base could be produced at 20% w/v, while nanofiber using gelatin/chitosan as base could be produced at 30%, 40%, and 50% w/v. The best hydrogel mixture from those 2 base is PVA/chitosan.
Changes of the structural and mechanical characteristics of xenogenic vascular prostheses under the influence of cosolvents in supercritical carbon dioxide

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Introduction

Often to replace the pulmonary artery for congenital malformations conduits from the jugular bovine veins (JBV) are used. Stabilization and elimination of the immune response of the tissue are provided by treatment with a glutaraldehyde solution. Residual aldehyde groups and cellular components cause the calcification of the tissue. Processing with supercritical carbon dioxide (scCO2) devitalize the tissue in a sparing mode for the extracellular matrix. Variation of treatment modes with cosolvents can provide the prosthesis with the required properties.

The aim of the study was to determine the effect of cosolvents on the mechanical, physical and structural properties of JBV tissues. The following detergents were selected as cosolvents: anionic SDS, non-ionic Tween-80.

Materials & Methods

Devitalization of JBV tissue was carried out in a dynamic mode: pressurization up to 17 MPa at 37 °C in the reactor with samples of JBV with 1% detergent, then it comes decompression to 8 MPa (injection of cosolvent) and repeated injection of CO2 to a pressure of 17 MPa, the cycle repeats twice. The microstructure of the samples was evaluated by FE-SE, TEM; histology was performed to determine the effectiveness of devitalization; mechanical and strength properties were studied in the radial direction.

Results

Treatment of veins in scCO2 environments with cosolvents and detergents increase the strength of the tissue. The greatest increase in the strength in the radial direction was achieved by treating the veins with: scCO2/SDS- $\Delta \sigma = 90\pm10\%$, scCO2/Tween-80- $\Delta \sigma = 30\pm5\%$, $p<0.05$. There is a significant increase in the stiffness of the veins treated in combination with SDS - $\Delta=$70±10%. Histological examination has shown that the use of scCO2 in combination with detergents in a dynamic mode allows to devitalize the vein tissue significantly.

Conclusion

The use of non-ionic detergent Tween-80 in combination with scCO2 is most preferable, since it doesn't reduce the smoothness of the structure of the inner surface of the veins and doesn't lead to the disorganization of collagen fibrils in the vein matrix. The use of CO2 in combination with detergents (SDS,Tween-80) in case of dynamic exposure allows the vein tissue to be significantly devitalized.
Leveraging Photovoltaic Nanomaterials to Address Heart Tissue's Inability to Self-Repair

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Introduction
The Center for Disease Control reports that heart disease is the leading cause of death in the western world and myocardial infarction is the primary form of heart failure. Many treatments for myocardial infarction cause scar tissue to develop over coronary muscle because cardiomyocytes are so highly specialized that they are incapable of regeneration. Therefore, dense and electrically inactive scar tissue impedes heart contractions and introduces arrhythmia, which further perpetuates risk of heart failure.

Materials & Methods
We use photovoltaic silicon nanomaterials to transduce an electric signal that polarizes cardiomyocyte membranes influences calcium ion dynamics between electrically aberrant cells. The nanowires are embedded into a flexible, anisotropic SU8 mesh to create a tissue scaffold that provides both the mechanical and electrical cues to actively support heart tissue after trauma.

Results
Profilometer measurements indicate that the nanowires are capable of wave-guiding light, which is efficient for targeting single cells and providing an environment that mimics the electrical and anisotropic properties of the extra-cellular matrix. Dynamic mechanical analysis shows that the scaffold adheres to wet tissue through capillary action, matches the modulus of native heart tissue, and will withstand hundreds of millions of heart muscle contractions. Patch clamp tests demonstrate that the nanowires effectively pace heart cells to consistently beat at a target frequency and also indicate a memory effect through which the cells continue beating after stimulation. Pre-clinical studies illustrate sustained synchronous beating of adult rat hearts after optical stimulation through the silicon nanowire mesh scaffold. Cytotoxicity studies indicate that photostimulation does not induce cell death.

Conclusion
We leverage biomimetic, photovoltaic nanomaterials to design a tissue scaffold that actively supports heart tissue after infarction. The scaffold's mesh structure provides mechanical cues for heart tissue development and p-i-n silicon nanowires are embedded into the mesh to provide electrical cues that modulate membrane voltages. The free-standing scaffold is applied to the surface of the heart through capillary action and promotes synchronous beating, which address arrhythmia and intercepts recurrent heart failure.
Fabrication and Optimization of Lung-on-a-Chip using 3D Printing

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Introduction
Lung-on-a-chip has been used to study the pathophysiology of diseases like COPD, asthma, lung cancer etc. along with the discovery of new potential therapeutics and toxicological studies. We want to use the novel technology of 3D printing to fabricate our own design and specifications. The main aim of the project is to make the chip fabrication process cost effective, time and resources saving as compared to existing conventional methods of fabrication.

Materials & Methods
The design process started with Computer Aided Design modeling (CAD) using SOLIDWORKS 2016 Software; Solidworks was used to design a mold for the casting of PDMS layers. Initial channel dimensions were chosen according to literature and later modified to suit fabrication constraints. The chip and the channel dimensions were selected and modified later for re-print. This was followed by printing the mold out of a photopolymer resin using a MIICRAFT Series Ultra DLP 3D printer. The resin curing process involves multiple steps before PDMS can be cast to make the chips. Bronchial epithelial cells (Calu3) were grown in an air-liquid medium. Once, confluent and fully differentiated, validation experiments were done to compare the results with the gold standard- transwells.

Results
Once chips were water-tight, we were able to experiment with different cell seeding densities and speeds to allow the maximum number of cells to attach to the membrane. We experimented with various combinations of different membranes and Extracellular matrices in different chips. The incubation time, washing time and seeding speed all had to be adjusted to get better results. We have achieved a confluent monolayer of cells on the membrane and the cells were alive up to 7 days.

Conclusion
The possibility of fabricating the chips using 3D printing; a cheaper, reliable and faster method compared to traditional methods will aid in research. The chip is still under the process of optimization, and with further developments, better results can be obtained in the near future.
Use of EPR-spectrometry to Study the Distribution Dynamics of Nanodiamonds Intravenously Injected in Animals

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Introduction
Detonation nanodiamonds can be used in many biomedical applications, and what is more important - they can be used as a carrier of medical substances in targeted drug delivery system. This approach allows to decrease dosage of medications, rise their effectiveness and minimize risks of side effects. Before using it for medical purposes it is necessary to study the biodistribution and elimination pathways of nanoparticles after injection. It was decided to use the method of EPR spectrometry, which allows to detect nanoparticles with paramagnetic centers.

Materials & Methods
For studies were used ICR mice (males, weight 26-28 grams) and medium-sized modified explosive nanodiamonds (d50 = 70.6 nm) with high colloidal stability in dispersion media. Hydrosol of modified nanodiamonds was injected into mice caudal vein at a dose of 40 mg/kg of animals' weight. In 2,5 hours and 10 days after injection animal organs (liver, kidney, lungs, heart, brain and thigh muscles) were homogenized and frozen in a liquid nitrogen for further investigations. The intensity of EPR-signals was measured on EPR-spectrometer Elexsys E580 (Bruker, Germany) and recorded at a temperature of 85 - 90 K. The content of nanodiamonds in samples was estimated by the magnitude of the EPR signal (g = 2.003, ΔH ≈ 10 G), which is proportional to the concentration of nanoparticles in biomaterial samples.

Results
It was shown that in 2.5 hours after intravenous injection of nanoparticles the highest amount accumulates in lungs and liver - 25% and 20%, respectively. Redistribution of nanodiamonds was detected in 10 days after injection to animals — 3 times more particles were detected in liver and 3.5 times less in lungs in comparison to 2.5 hours after injection. There were no significant changes in the total content of nanodiamonds in heart and kidneys of mice. Also, in 10 days after the intravenous injection nanoparticles were not registered by the EPR method in blood samples, brain and thigh muscles of animals.

Conclusion
In general, the results of the studies show the applicability of EPR-spectrometry for studying the dynamics of biodistribution, accumulation and elimination of detonation nanodiamonds intravenously injected to organism of experimental animals.
THz Spectroscopy for a Rapid and Label-Free Cell Viability Assay in a Microfluidic Chip Based on an Optical Clearing Agent

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Introduction
Cell viability assay is of great importance for the cell toxicology investigation and antitumor drug screening. Conventional methods are encumbered by the complex procedures or potential biological hazards from toxic reagents. Recently, THz spectroscopy has emerged as an attractive label-free detection technology. However, its exploration in measuring the living cells in complex solutions is restricted by the strong absorption of water throughout the THz frequency range. Here, we aimed to propose a rapid and label-free cell viability assay using THz spectroscopy in combination with an optical clearing agent (OCA) material and microfluidic technology.

Materials & Methods
Three kinds of OCA materials were first compared and the selected OCA was injected into a microfluidic chip to expel the culture medium around the attached human breast cancer cells (MDA-MB-231) cells. The validation of THz measurement of cell viability was accomplished with the flow cytometry analysis.

Results
We selected fluorinated oil, a new biomaterial, as the optimal OCA because of its lower THz absorption and lowest cytotoxicity. After the water molecules were replaced with fluorinated oil, THz energy attenuation and background signal interference can be significantly reduced. Thus, we observed an obviously clearer THz signal of living cells. Using this strategy, we measured the THz signal of MDA-MB-231 cells treated with two antitumor drugs. Obvious linear relationships were found between the THz signal and results measured by flow cytometry. Using biophysical properties, the THz responses of living cells can be directly utilized for quantification of cell viability and antitumor drug screening. The whole detection process was accomplished within 10 min and only required approximately 3,000 cells for one test.

Conclusion
Fluorinated oil was reported for the first time to function as an OCA material in the THz frequency range. With the aid of fluorinated oil and the water-replacement strategy, THz spectroscopy presents excellent quantification of cell viability and the advantages of great convenience and simplicity. Compared to other common methods, such as flow cytometry, microplate reading and optical microscopy, this novel cellular analysis platform enables rapid, label-free, nondestructive and noncontact detection. All of which are advantages in practical biomedical applications, such as cell toxicology evaluation and antitumor drug screening.
AS1411-targeted multimodal polymersomes for theranostic application

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Introduction
In this study, we reported synthesis and delivery of tumor-targeted, Gadolinium-doped Copper Indium Zinc Sulfide quantum dots (QDs) and doxorubicin (DOX)-encapsulated in PEG-PCL nanoparticles (NPs) as a dual magnetic resonance-fluorescence imaging and anti-cancer agent. Therapeutic and diagnostic effectiveness of the prepared nanoparticulate system were evaluated in vitro and in vivo.

Materials & Methods
Hydrophilic doxorubicin and hydrophobic QDs were encapsulated in polymersomes via double emulsion method. For targeting NPs, the AS1411-aptamer was covalently conjugated to the surface of the polymersomes. Cellular uptake and cytotoxicity of targeted and non-targeted formulations were evaluated in 4T1, MCF7 and CHO cell-lines. 4T1 tumor-bearing Balb/c mice were employed as an in-vivo model. The obtained results statistically examined via one-way analysis of variance (ANOVA).

Results
The obtained results demonstrated that AS1411-aptamer-conjugated-NPs (Apt-DOX-QD-NP) significantly enhance drug cellular uptake in 4T1 and MCF7 cell-lines and increase cytotoxicity of the DOX payload compared to non-targeted-NP (P<0.05). After a single intravenous injection of Apt-DOX-QD-NP and DOX-QD-NP, tumor volume decreased 84.68% and 62.36% respectively, in 4T1 tumor-baring Balb/c mice in comparison with PBS-injected control group. The difference in survival time for the DOX-treated group in comparison with the Apt-DOX-QD-NP group was statistically significant (ANOVA at a 95% confidence interval). T2-weighted MR images demonstrated a significant brightness in tumor site of the mouse receiving Apt-DOX-QD-NP, 12 h and 24 h post-injection. The quantity of fluorescence intensity was also determined using region of interest (ROI) analysis. Mean intensity of aptamer-targeted-NP in the tumor site of treated mice was significantly higher than non-targeted-NP 24 h post-injection (P<0.05).

Conclusion
In 4T1 tumor bearing mice, targeted-nanoparticles exhibited superior characteristics in terms of tumor growth inhibition and survival rate. The prepared formulation illustrated superior antitumor activity and lower in-vivo toxicity in comparison with free DOX. Additionally, MR and fluorescent imaging verified accumulation of targeted-nanoparticles in tumor site. The prepared theranostic nanomedicine has great potency to present a new approach for translational research.
Cell Biology II

Chair
Prof Cor F. Calkhoven MD PhD

Presenters
Araújo-Silva, H (Henrique)
Gazizova, A. (Adel)
Gholizadeh, F. G. (Fatemeh)
Lin, L.-L. L. (Liling)
Ozbaykus, A. C. (Abdullah)
Streletskaia, A.Y. (Alena)
Zgodova, A. (Arina)
Zhang, Y. (Yi)
Drygina, K. (Ksenia)
TAZ as a potential player in developmental lung metabolic rewiring

Araújo-Silva, H (Henrique) Bsc, Alves, MG (Marco) PhD, Correia-Pinto, J (Jorge) MD, PhD, Oliveira, PF (Pedro) PhD, Moura, R. S. (Rute) PhD

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Introduction
Lung morphogenesis is a complex process that depends on the interaction between several signaling pathways, which regulate multiple cellular events, culminating in proper pulmonary organogenesis. Hippo signaling has emerged as a key player in lung branching and it is known to be involved in organ size control. However, the correlation between Hippo and metabolism in early lung development has not been explored. In this sense, this work aims to unravel the potential role of Hippo signaling, namely its effector TAZ, in the metabolic reprogramming of the developing lung.

Materials & Methods
Embryonic chicken lungs were used to perform in vitro lung explant culture supplemented with a specific TAZ-enhancer or DMSO (control), for 48 hours. Lungs were morphologically analyzed to determine its impact in lung growth. Moreover, cultured lung tissue was collected, and the expression levels of metabolic-related genes assessed by qRT-PCR. Additionally, culture medium was collected, and 1H-NMR spectroscopy was performed for a metabolomic analysis. One-way ANOVA and post-hoc Fisher Least Significant Difference test were used to determine the statistical differences between groups, in the three approaches.

Results
Lung explants treated with the TAZ-enhancer showed an increase of around 12% in branching, in a dose-dependent manner when compared to controls. qRT-PCR analysis revealed an increase of about five-times in glut8 and mct8, and of approximately two and five-times in pdh and ldh expression levels, respectively, when compared to controls. 1H-NMR spectroscopy revealed an increase in the levels of succinate and acetate after treatment. All experimental data is presented as mean ± SEM (p<0.05, 95%CI).

Conclusion
TAZ manipulation had a mild impact in lung branching nonetheless it induced alterations in the expression levels of different enzymes/transporters of glucose catabolism. Furthermore, alterations in the amount of certain key metabolites was also noticed. Taken together, these results point to a potential role of TAZ in the regulation of the metabolic profile of the embryonic lung. This is the first study that demonstrates the contribution of Hippo signaling to metabolic reprogramming of early lung development through the modulation of gene expression. These findings may contribute to uncover new therapeutic targets to treat lung developmental disorders.
The role of immunoproteasomes in cellular reprogramming

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Introduction
The ubiquitin-proteasome system (UPS) is a multi-enzyme proteolytic complex whose main function is the removal of damaged and short-lived proteins. The major component of the system – the 26S proteasome – consists of the 20S core particle and various regulatory particles. Under certain conditions, catalytic subunits of the 20S proteasome – beta-1, beta-2, and beta-5 – are replaced by inducible subunits beta1-i, beta2-i and beta5-i, and this proteasome is designated as immunoproteasome (IP). It was proposed that IP’s main function is MHC-mediated antigen presentation, but there are literature data indicating an increased expression and a role of IP subunits in pluripotent stem cells. However, IP’s role in cellular reprogramming, as the process of acquiring pluripotency, has not been examined.

Materials & Methods
In this study, we have induced a pluripotent state of mouse embryonic fibroblasts obtained from beta2-i/Mcl-1-, beta5-i/LMP7-, and PA28-deficient embryos with the help of doxycycline-activated OKSM (Oct4, Klf4, Sox2, c-Myc) construct. Also, we have used immunohistochemical staining with antibodies against Nanog and teratoma tests to assess pluripotency status of generated induced pluripotent stem (iPS) cells.

Results
We have showed that IP-deficient fibroblasts have significantly decreased ability to be reprogrammed into iPS cells. Besides, teratoma assay demonstrated the inability of IP-deficient iPS cells to generate all three germ layers.

Conclusion
The obtained data indicate a novel role of IPs in acquisition of a pluripotent state during cellular reprogramming. Study was supported by RSF #19-14-00352.
Changes of hormone levels, mRNA expression involved in testosterone synthesis, and stereological investigation of testes tissues of diabetic rats treated with Stevia rebaudiana Bertoni

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Introduction
Diabetes Mellitus (DM) is a metabolic endocrine glands disorder with various effects on the male reproductive system. The present study aimed to examine the effect of Stevia rebaudiana Bertoni extract on the improvement of diabetes complications, mRNA expression involved in testosterone synthesis, and stereological parameters in rats' testes.

Materials & Methods
In this study, 48 rats were randomly divided into control, diabetic (streptozocin 60 mg/kg + nicotinamide 120 mg/kg), diabetic + Stevia (400 mg/kg), and diabetic + metformin (500 mg/kg) groups. Streptozotocin and nicotinamide were administered intraperitoneally while the Stevia extract and metformin were administered via gavages. At the end, Fasting Blood Sugar (FBS) level was evaluated using the calorimetric method, LH and testosterone serum levels were measured by ELISA method, and Star, Cyp11a1, and Hsd17b3 gene expressions were assessed using the Real-Time PCR method. In addition, changes in the testes' histology were evaluated via stereological techniques.

Results
The results indicated a decrease in body weight (p=0.003), LH serum level (p=0.026), testosterone serum level (p=0.001), star gene expression (p=0.01), spermatogonia (73%), spermatocytes (76.5%), round and long spermatids (84.7%-82.8%), Sertoli cells (61%), Leydig cells (p<0.05), and sperm count and motility (p<0.05), but an increase in FBS level (p<0.001) in the diabetic group in comparison to the control group. On the other hand, Stevia significantly reduced blood glucose level (p<0.001) and LH serum level (p=0.005) compared to diabetic rats, but it caused no significant differences in testosterone serum level and star gene expression. Stevia also resulted in an increase in weight, testes volume, the number of sexual lineage cells, and sperm count and motility in comparison to diabetic rats (p<0.05).

Conclusion
Due to its antioxidant and anti-diabetic properties, Stevia enhanced the alteration in spermatogenesis and stereological characteristics in diabetic rats' testes. Hence, Stevia could diminish the complications of diabetes in the reproductive system and improve infertility in male rats.


Pentraxin3, a biomarker for acute ischemic stroke

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Introduction
Studies have shown that pentraxin3 \( \text{PTX3} \) is closely linked to cardiovascular disease. This study aims to investigate the expression and predictive ability of PTX3 in acute ischemic stroke (AIS).

Materials & Methods
This study included 192 patients with acute ischemic stroke and 43 non-AIS participants in the first affiliated hospital of Shantou university medical college between May 2017 and October 2018. We collected data including age, sex, alcohol consumption, current smoking, hypertension, diabetes, levels of PTX3, uric acid, high-sensitivity C-reactive protein (Hs-CRP), homocysteine (Hcy), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and so on. The severity of AIS was assessed according to the National Institute of Health stroke scale (NIHSS). The short-term prognosis was assessed by the modified Rankin scale at 14th day.

Results
1. Levels of HsCRP and PTX3 in the serum of AIS patients were significantly higher than the control group \( (P=0.026, P=0.018) \) while level of HDL-C in the patients were lower than the control groups \( (P=0.003) \).

2. Compared to good prognosis group, NIHSS and level of PTX3 were increased in the patients of the poor prognosis group \( (P=0.000, P=0.028) \).

3. Compared to minor ischemic stroke group, mRS and level of PTX3 were increased in the patients of the severe ischemic stroke group \( (P=0.000, P=0.006) \).

4. In correlation analysis, level of PTX3 was moderate positively correlated with NIHSS at admission, NIHSS at 14th day, mRS, levels of high-sensitivity C-reactive protein (Hs-CRP). In partial correlation analysis, after adjusted other confounding factors, PTX3 was low positively correlated with NIHSS at admission \( (r=0.154, P=0.036) \).

Conclusion
In patients with acute ischemic stroke, PTX3 was predictive of short-term prognosis and severity.
IDENTIFICATION OF NOVEL HIT MOLECULES AGAINST B-CELL LEUKEMIA/LYMPHOMA-2 (BCL2)

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Introduction
Bcl-2, an anti apoptotic protein from the Bcl-2 family of proteins, is accepted as a potential target in cancer treatment since its oncogenic potential has been proven and is authenticated. [1] Bcl-2 can be considered as the first identified apoptotic regulator of the principal pathway of apoptosis.[1-2] This protein which conduce to tumor initiation, progression and resistance to therapy is overexpressed in many cancer cells. [3] The aim of the study is to discover and develop more effective and potential inhibitors compared to current and known treatments.

Materials & Methods
In this study, in order to identify new hits for BCL2, both ligand and structure-based techniques were applied. Initially 212520 small molecules were retrieved from Specs SC database and binary QSAR based models from MetaCore/MetaDrug platform were used to screen against a defined therapeutic activity, “cancer”. Crystal structure of BCL-2 (Protein Databank ID: 4LXD) and NMR structure of BCL-2 (Protein Databank ID: 1YSW,1YSI,2O2F) used for target-driven drug screening methods (i.e., molecular docking). These selected compounds were then used in Glide/high throughput virtual screening (HTVS) at the binding pocket of BCL2. Filtered structures were then used in more sophisticated molecular docking protocols (i.e., Glide/SP, Glide/IFD and GOLD); their docking scores were compared with known inhibitors (i.e., positive controls) and selected molecules were considered for molecular dynamics (MD) simulations. Selected hit molecules which are the molecules that have higher docking scores than positive controls and they construct known crucial interactions were used in MD simulations. Moreover, structural and dynamical properties of ligand-protein complex is investigated for better understanding of hit molecules at the binding pocket of the target.

Results
As a result of this project, we found molecules that are more effective than ABT-199, which is specific ligand of BCL-2, on inhibition of BCL-2 protein. Five molecules were identified as hit compounds (compound 43, 58, 243, 258, and 292). Obtained MD trajectories were used in post MD MM-GBSA free energy calculations.

Conclusion
Results of this study can be important for discovering novel BCL-2 family protein inhibitors.
Modulation of MCL-1 alternative splicing as an anticancer strategy

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Introduction
Contemporary oncotherapy focuses on the induction of apoptosis in tumor cells. However, cancer cells have managed to develop resistance to apoptosis, that is frequently accomplished through the elevated expression of Bcl-2 family proteins, particularly Mcl-1L. The increased level of Mcl-1L is found in many hematological and solid neoplasms. A great effort has been made to target Mcl-1L. Recently, a conceptually new approach has emerged that allows not only to antagonize the antiapoptotic functions of Mcl-1L but also get Mcl-1 on the apoptotic track – the approach of alternative splicing switch toward an exon-2 deficient proapoptotic isoform, Mcl-1S.

Materials & Methods
Analyses were implemented using techniques of RT-qPCR, PCR, flow cytometry, Western blotting, fluorescent microscopy.

Results
We observed that moderate doses of microtubule-damaging agents cause upregulation of Mcl-1S mRNA levels (on average, 7 and 20 times normal expression at 4 hours and 24 hours, respectively) and the relevant protein (increased by 10 times at 24 hours). Moreover, cells with Mcl-1L siRNA-knockdown demonstrate more rapid cell cycle progression after mitotic block (11.2 ± 3.0% more cells in G1-phase after 4, 6 or 8 hours of release from thymidine-nocodazole block, with the G2/M-fraction proportional decrease) and also more rapidly enter mitosis (significant increase in G2/M, and decrease in S-phase cells) in comparison with non-target-control. The consistent results were obtained upon plasmid expression of Mcl-1S. We also observed that moderate amount of Mcl-1S protein accumulates as cells entered the mitotic stage.

Conclusion
When entering mitosis, tumor cells are capable of switching the alternative splicing from antiapoptotic Mcl-1L to proapoptotic Mcl-1S form. However, it surprisingly seems that such shifting serves typically not as a cell death mechanism, but rather as a prosurvival function: Mcl-1S inhibits nuclear cell-cycle arresting influence of Mcl-1L, allowing normal cell cycle progression. Potentially, this effect can be used in oncotherapy for more rational and efficient sensitizing tumor cells to apoptosis.
COMPARISON OF NEUROPROTECTIVE PROPERTIES OF Pro-Gly-Pro AND ITS ACETYLED FORM IN THE CONDITIONS OF GLUTAMIC EXCITOTOXICITY

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Introduction
Glutamate (Glu) is one of the most common excitatory neurotransmitters. However, an excess of glutamate can cause a pronounced excitotoxicity. Glyprolines are a special group of glycine and proline-containing oligopeptides which are comprised into various regulatory peptides. One of them, Pro-Gly-Pro (PGP) is able to influence the structure of the central nervous system. Acetylation of PGP obstructs its N-terminus hydrolysis.

The purpose of this research was to investigate the effect of PGP and AcPGP on the survival of a neuroglial culture under glutamate excitotoxicity.

Materials & Methods
Primary neuroglial cell cultures were obtained from 1-day old Wistar rats cortex. Cells were grown in 48-well plastic plates under standard conditions and used as 11-12 day in vitro cells. PGP and AcPGP 10 μM was added 1 hour prior to glutamate exposure 33 μM. The neuron survival was assessed by the ratio of the living to the dead cells after 24 hours using an EVOS FL Auto microscope. The living and dead cells were determined using a Syto-13 and EthD-1 fluorescent probe, respectively.

Results
PGP 10 μM and AcPGP 10 μM are not neurotoxic. The survival rate of neuroglial cortical culture in these groups did not practically differ from the control and was 99 ± 5.7% and 88 ± 5.1%, respectively. The excitotoxicity effect of glutamate 33 μM was 45 ± 2.6%. The neuroprotective effect of PGP in wells with the combined action of Glu and PGP was 27%. Acetylation of the peptide obstructed the manifestation of the effect under study. The difference between the groups Glu and Glu + AcPGP was 6%.

Conclusion
The PGP 10 μM peptide can weaken the excitotoxic effect of Glu 33 μM on cultured cortical neurons. Consequently, this peptide in given concentration has the neuroprotective effect. AcPGP does not affect neuron survival. It can be assumed that the acetylation of the peptide at the N-terminus reduces the ligand-receptor interaction and prevents the manifestation of its neuroprotective effect.
Hypomyelination and mitochondrial dysfunction in catechol-O-methyltransferase-deficient mice: implication for schizophrenia

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Introduction
Catechol-O-methyltransferase (COMT) is one of the major mammalian enzymes involved in the metabolism of catecholamines and is considered a candidate for several psychiatric disorders. In our previous study tolcapone, an inhibitor of COMT, increased DA levels and affected myelin oligodendrocyte glyco (MOG) expression in frontal cortex (PFC) while induced schizophrenia-like behaviors in mice. The aim of this study was to further demonstrate the dopaminergic hyperactivity-induced white matter changes and explore the possible involvement of mitochondria in these changes by taking advantage of the COMT knock-out (KO) mice.

Materials & Methods
Adult male COMT KO and wild-type (WT) mice were used in this study. Behavioral tests were performed to assess the behavioral performances of mice, followed by ELISA for the measurement of DA levels, RT-PCR for mRNA levels of DAT and DAR, western-blot for protein levels of MAO, biochemical analysis for ATP levels, and immunohistochemical staining for evaluation of myelination in the mouse brain. All data were analyzed by independent student t-test. Statistical analysis was carried out using SPSS 22 software.

Results
Compared with WT mice, KO mice exhibited locomotor activity increase and impaired social recognition. Relative to WT mice, KO mice showed lower DA level in caudate putamen (CPU), but not in PFC, higher the mRNA levels of D1R in PFC, lower D2R and DAT in CPU, lower ATP in both PFC and CPU, and lower protein levels of MAO-A and MAO-B in CPU, but higher MAO-B in PFC. Furthermore, KO mice showed significantly lower number of oligodendrocytes and MBP immunoreactivity in both PFC and CPU compared to WT mice.

Conclusion
These results suggest that dopaminergic dysfunction may lead to hypomyelination in the brain of COMT deficient mice via impairing mitochondrial function thus enhance our understanding of the pathogenesis of schizophrenia.
Epidemiology

Chair
Prof. Harold Snieder PhD

Presenters
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Cai, W.C.C. (Weicong)
Chen, CZK (Zekai)
Chopdar, A. (Ankita)
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Qin, QHL (Hailun)
Yan, Y.S.Z (Shuzhen)
Frequency of the Ophthalmological Disorders associated with Headache.

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Introduction
Headache is one of the most common presenting complaint of patients but still it is not adequately treated. According to a study conducted to assess the global burden of headache, it was estimated that headache and accompanying presentations affect approximately half of the population of the world. The first physicians to evaluate the patients presenting with headache accompanied by visual disturbances are ophthalmologists. The aim of the study was to determine the frequency of ophthalmological disorders associated with headache.

Materials & Methods
This cross-sectional, descriptive study was conducted in outpatient department of Fatima Memorial Hospital from January 2018 to July 2018. The sample population was selected through non-probability, convenience sampling technique. A proforma was filled that included questions about the characteristics of headache and the ocular findings on examination. Complete eye examination was done by a consultant ophthalmologist. Statistical analysis was done using SPSS version 23.

Results
Out of the 180 patients, 127(70.6\%) were females and 53(29.4\%) were males. The mean age was 25.02 +/- 12.89 years ranging from 5 to 80 years. The disorders related with headache were divided into Ocular, Non-ocular, combined ocular and combined ocular with non-ocular causes. In the ocular causes, the most common were asthenopias present in 83(46.11\%) patients. They included 29 patients of convergence (16.1\%), 18 patients (10\%) with hypermetropia, myopia 15 patients (8.3\%), 7 patients (3.9\%) with presbyopia and 4 patients (2.2\%) with increased mobile and computer usage. The patients who suffered from other ocular causes such as keratoconus, hypertensive retinopathy were 2 each (1.1\%) and the number of patients presenting with acute uveitis, blepharitis, retinal detachment and squint were 1 each (0.6\%). In the non-ocular causes, most patients 61(33.9\%) presented with migraine.

Conclusion
Most of the patients with ocular causes had refractive errors and majority of the patients with non-ocular causes had migraine. A majority of cases that are of ophthalmic origin such as errors of refraction mostly present to a neurologist and have to undertake needless investigations that lead to waste of money and time of the patient. So headache should be evaluated by an ophthalmologist, prior to expensive diagnostic work to rule out a possible neurological cause.
Association of catechol-O-methyltransferase polymorphisms with multiple physical activity-related injuries

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Introduction
The catechol-O-methyltransferase (COMT) is a candidate gene to provide a promising evidence of psychiatric disorders, but there is a knowledge gap between the genetic factor and multiple physical activity-related injuries (PARIs). The aim of this study was to explore the contribution of COMT to the risk of PARIs in Chinese Han undergraduates.

Materials & Methods
Based on the two-stage cross-sectional design, a 1:1 matched case-control study of 61 PARIs cases and 61 healthy controls were carried out. DNA samples of the participants were isolated from saliva and genotyped on eight polymorphisms of the COMT gene (rs9265, rs4680, rs6269, rs4818, rs4633, rs165655, rs165656, and rs165722) using the Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) method.

Results
rs6269 and rs4818 were significantly associated with PARIs, and rs6269-GG and rs4818-GG contributed to the reduced risk of PARIs. Further haplotype analysis showed a four-marker C-G-C-G haplotype (rs165722-rs6269-rs4633-rs4818) acted as a protective role in the development of PARIs (P = 0.037; OR: 0.474, 95% CI: 0.269 to 0.834). However, the interactions between club membership and rs6269 or rs4818 would significantly increase the risk of PARIs (both P < 0.001, OR: 5.121 and 4.977, respectively).

Conclusion
This is the first study to find the contribution of COMT to PARIs occurrence, suggesting that the COMT polymorphisms and the gene-environment interactions may alter the risk of PARIs.
Higher ratio of triglyceride to high density lipoprotein cholesterol increases cardiovascular risk: 10-year prospective study in a cohort of Chinese adults

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Introduction
High serum triglyceride to high density lipoprotein cholesterol (TG/HDL-C) ratio has been identified as an independent predictor for cardiovascular (CV) events. However, there are few data regarding this correlation in cohort studies, especially in China. The present study aimed to explore the relationship between TG/HDL-C ratio and risk of CV events among Chinese adults during a 10-year follow-up.

Materials & Methods
We performed a prospective study using data from 96542 subjects in Kailuan between 2006 and 2016. Participants were divided into two groups by the median (0.8533) of the TG/HDL-C ratio. Major outcomes included major CV events. Incidence rates were expressed in cumulative incidence and person-year incidence. Cox proportional hazards analysis was used to estimate the risk of major CV events.

Results
At baseline, the mean age was 51.5±12.6 years, and 79.6% (n=76854) were men. During a mean follow-up period of 9.75 years, a total of 5422 major CV events occurred, including 4228 strokes and 1312 cases of myocardial infarction (MI). The cumulative incidences were 5.62% (5.47-5.76%), 4.38% (4.25-4.51%), 1.36% (1.29-1.43%) for total CV events, strokes and MI, respectively. Regardless of the risk of total CV events, or the risk of stroke or MI, the group with high TG/HDL-C ratio (>0.8533) was higher than the group with low TG/HDL-C ratio (<0.8533) and the hazard ratio was 1.26 (95%CI 1.19-1.33), 1.17 (95%CI 1.10-1.25), 1.58 (95%CI 1.40-1.78), respectively. Moreover, a line-shaped relationship was seen between TG/HDL-C ratio and the risk major CV events.

Conclusion
Among the Chinese population, elevated TG/HDL-C ratio is associated with increased risk of major CV events.
Risk Factors for Anemia among Type 2 Diabetes Mellitus Patients in Mangalore- A Case Control Study

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Introduction
Anemia is now an increasingly recognized morbidity in patients with diabetes mellitus. Studies have shown that life span of anemic diabetic patients is comparatively lesser than the life span of non-anemic diabetic patients. However, literature available on risk factors of anemia in patients with type 2 diabetes mellitus and on direct relationship of anemia and type 2 diabetes mellitus is limited. We aimed at finding out the risk factors for anemia in type 2 Diabetes Mellitus patients.

Materials & Methods
This is a record based case control study of 50 cases (Type 2 diabetic with anemia) and 100 controls (Type 2 diabetic without anemia) of patients in Government Wenlock hospital, Mangalore. Those patients were considered anemic who had reduced hemoglobin concentration below the normal level (as defined by WHO criteria \( \text{< } 13 \text{ g/dl for men and } \text{< } 12 \text{ g/dl for women} \)). Statistical software SPSS Version 17.0 was used for data entry and analysis. Univariate analyses using Chi-Square test were done to identify risk factors.

Results
The median age of cases as well as controls was 60 years while the duration of diabetes was 8 years for cases and 7 years for controls. Among 50 cases, there were 39 (78\%) males and 11 (22\%) females and among 100 controls, 68 (68\%) males and 32 (32\%) females. On univariate analysis using Chi-Square test it was found that the following factors were statistically significant because the \( \text{p value was } \text{< } 0.05 \).

- elevated serum urea levels (42\% of cases and 23\% controls)
- abnormal total protein levels (27.1\% cases and 10.1\% controls)
- serum creatinine levels (42\% cases and 19.4\% controls)
- abnormal albumin levels (44\% cases and 17.6\% controls)
- abnormal calcium levels (28.6\% cases and 5.9\% controls)

Conclusion
The values of serum urea, creatinine, albumin, total protein and calcium were statistically significant because the \( \text{p value was } \text{< } 0.05 \). The above parameters may be implicated to impaired renal function and hence we can conclude that impaired renal function is a risk factor for developing anemia in type 2 Diabetes Mellitus patients.
In-Hospital Mortality among Ischemic Stroke Patients in Gondar University Hospital: A Retrospective Cohort Study

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Introduction
Ischemic stroke is the third leading cause of mortality in low-income countries and the sixth in Ethiopia. The aim of this study was to determine the rate and predictors of in-hospital mortality due to ischemic stroke in Gondar University Hospital.

Materials & Methods
The study was conducted from April 1, 2017, to May 15, 2017, at Gondar University Hospital. A census using retrospective cohort study design was conducted on medical records of adult patients with the diagnosis of ischemic stroke attending the medical inpatient ward of Gondar University Hospital between November 2012 and September 2016. Cox hazard regression was used to determine the predictors of in-hospital mortality. A two-sided statistical test at 5% level of significance was used.

Results
The mean (±SD) duration of hospital stay was 11.55 (10.040) days. Of the total 208 patients, 26 (12.5%) patients died in the hospital. Cox regression revealed that only a decrease in renal function, particularly elevated serum creatinine (AHR=8.848, 95% CI: 1.616-67.437), was associated with a statistically significant increase of in-hospital mortality. The symptom onset-to-admission time varied greatly among patients and ranged from 1 hour to 168 hours.

Conclusion
The in-hospital mortality associated with ischemic stroke was found to be high. Mainly, elevation in serum creatinine was highly associated with poorer outcomes in terms of in-hospital mortality. Much work should be done on improving the knowledge and awareness of the community regarding ischemic stroke and stroke in general to encourage early medical seeking behavior and reduce mortality and long-term disability.
Association between the waist to hip ratio and long-term blood pressure variability: a cross-sectional study in Chinese adults

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Introduction
Waist to hip ratio (WHR) is an important indicator of abdominal adiposity and elevated WHR has been confirmed as an independent risk factor for hypertension, diabetes and cardiovascular diseases. Evidence has been accumulated showing that long-term blood pressure variability (BPV) is associated with cardiovascular diseases. However, the association between WHR and long-term BPV is currently uncertain. The present study aimed to identify the association between WHR and long-term BPV in the Chinese population.

Materials & Methods
Clinical data was from 32434 participants of Kailuan Study who attended physical examination every two years from 2006 to 2014, five times in total. The participants were divided into 3 groups according to WHR by using tertiles: low WHR (<0.86), medium WHR (0.86-0.92), high WHR (>0.92). Long-term systolic BPV was measured by average real variability (ARV). The average real variability of systolic blood pressure (ARVSBP) was calculated as \( \frac{|SBP2-SBP1|+|SBP3-SBP2|+|SBP4-SBP3|+|SBP5-SBP4|}{4} \). The variance analysis was used to compare differences in ARVSBP between each group. The stepwise multivariate linear regression and multiple logistic regression analysis were applied to assess the impact of WHR on ARVSBP.

Results
The mean age of participants was 46.6±11.3 years, 24490 were men and 7944 were women. After adjusting other confounding factors, stepwise multivariate linear regression analysis revealed that ARVSBP increased by 0.196 for every 0.1 units increase in WHR. The multiple logistic regression analysis indicated that, compared with low WHR, higher WHR was risk factor for an increase in ARVSBP. The corresponding odds ratio of medium WHR group and high WHR group were 1.01 (0.95, 1.07) and 1.10 (1.04, 1.15), respectively.

Conclusion
ARVSBP increases with the increase of WHR, and there was a positive correlation between them. Higher WHR is a risk factor for an increase in long-term BPV.
Characteristics and factors associated with post-exposure prophylaxis (PEP) treatment of dog- and cat-bites among left-behind children in two cities of China

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Introduction
Animal injury is a significant cause of morbidity and mortality worldwide. Dog bites account for tens of millions of injuries annually and the highest risk is among children. In China, many parents work outside and leave their children at home. However, children especially left-behind children may not receive post-exposure prophylaxis (PEP) treatment timely and appropriately after rabies exposure. We aimed to investigate the characteristics and factors associated with PEP treatment of dog- and cat-bites among left-behind children.

Materials & Methods
A cross-sectional study by using questionnaire was conducted at primary and high schools in two cities (Shenzhen and Shantou) of southern China. Chi-square test and binary logistic regression analysis were used to test the associations of factors with PEP treatment. PEP treatment was considered as the dependent variable in the binary logistic regression model. P-value < 0.05 was adopted to indicate statistical significance. In our study, animal bites only meant dog- and cat-bites.

Results
A total of 9380 participants were included and 2236 of them were with a history of dog- and cat-bites. 1188 (53.1%) boys and 1048 (46.9%) girls suffered from animal bites. Bitten in holidays were less likely to receive PEP treatment (OR 0.512, 95%CI 0.377-0.695) than those bitten in school days. Bitten while being with family (OR 1.418, 95%CI 1.040-1.934), bitten at roadside (OR 1.842, 95%CI 1.297-2.171), and bitten by unvaccinated animals (OR 1.745, 95%CI 1.246-2.443) tended to receive PEP treatment. Compared with unbroken skin, bleeding (OR 1.789, 95%CI 1.165-2.745), laceration (OR 3.834, 95%CI 2.310-6.366) were showed as treatment prompting factors.

Conclusion
Bitten in holidays is found as a risk factor of receiving PEP treatment of animal bites, implying that left-behind children lack self-protection awareness. Certain measures such as education intervention should be taken to raise left-behind children’s awareness of receiving PEP treatment timely and appropriately after dog- and cat-bites especially in holidays.
Genetics

Chair
Jan C. Oosterwijk MD PhD

Presenters
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Navarro-Espíndola, R. (Raful)
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Vartanova, V. (Valeriia)
Vasikhovskaya, V.A. (Valeriya)
ANALYSIS OF GENETICAL CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA IN LATVIAN PEDIATRIC PATIENTS.

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Introduction
Unconjugated hyperbilirubinemia is typical sign of Gilbert’s syndrome (GS). Most common molecular cause of this autosomal recessive disorder is (TA)7 allelic variant in UGT1A1 gene promoter. GWAS discovered also non-UGT1A1 variants associated with unconjugated hyperbilirubinemia, e.g. in SLCO1B3 and NUP153 genes, which encoded products are involved in bilirubin transport and conjugation. Aim of the study is to analyze non-UGT1A1 genetic variations rs2417940(SLCO1B3) and rs2328136(NUP153) association with unconjugated bilirubin level in pediatric patients.

Materials & Methods
The study included 503 patients with diagnosed unconjugated hyperbilirubinemia. UGT1A1 gene promoter TA repeat allele was detected by fluorescent PCR and capillary electrophoresis. TaqMan assay for rs2417940 and rs2328136 genotyping was used. Data statistical analysis was performed using SPSS v22.0 software. Central tendencies of data are described as median (IQR).

Results
158 (31.4 %) of patients were females, median age 14.7 (12-16) years, and 345(68.6%) were males, median age 15 (13.6-16.3) years. 437 patients are diagnosed with GS (TA7/TA7). Other patients had following genotypes- TA7/TA6 n=56, TA6/TA6 n=10. Analysis of rs2417940 genotype association with bilirubin levels shows that genotypes TT and CT are associated with higher total (p=0.011) and unconjugated (p=0.013) bilirubin levels. This association shows autosomal dominant inheritance pattern. For rs2417940 TT and CT genotypes median total bilirubin level is 40.0(31-56.6) and for CC genotype it is 35.9(29-58.8) mkmol/l. And median unconjugated bilirubin level for rs2417940 TT and CT genotypes is 30(20.8-44.3) and for CC genotype 26(20-37.3) mkmol/l. Bilirubin levels were not statistically different across rs2328136 genotype groups(p>0.05). Frequencies of rs2417940 and rs2328136 genotypes did not differ among UGT1A1 gene promoter TA repeat genotype groups.

Conclusion
For 437 patients hyperbilirubinemia is explained by GS (TA7/TA7). SLCO1B3 gene variation rs2417940 CC and CT genotypes are associated with higher total and unconjugated bilirubin levels. Rs2328136 genotype do not affect bilirubin levels.
ATG16L1 T300A genetic polymorphism in hyperuricemia and gout

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Introduction

Autophagy is a sophisticated intracellular recycling system used by cells to degrade cellular material and also involved in the modulation of pro-inflammatory cytokine production. The autophagy related 16 like 1 gene (ATG16L1) encodes a protein involved in the formation of the initiation complex of autophagosome formation. A single nucleotide polymorphism (SNP) in ATG16L1 (the T300A substitution) was linked to an excessive production of pro-inflammatory cytokines, such as IL-1β, and is a genome widely associated risk variant for Crohn's disease. Autophagy inhibition has also been shown to be a potential mechanism enhancing cytokine production in other autoinflammatory diseases such as gout.

The aim of this study was to investigate whether there is an association between the ATG16L1 T300A SNP and the progression to gout in patients with hyperuricemia.

Materials & Methods

We performed a case-control study in which we investigated the distribution of ATG16L1 T300A SNP in 147 patients with gout and 127 controls with hyperuricemia. Genotyping of individuals was performed using Taqman SNP genotyping assay. Statistical analysis was performed using Fisher's test and results were considered significant at p-value < 0.05.

Results

Our first findings show a frequency of 0.51 of the variant allele for cases and 0.49 for controls (OR=1.1; 0.8 - 1.5 95%CI; p-value = 0.7). The genotype distribution followed similar patterns in cases and controls. According to dominant and recessive risk association models, our data revealed an OR of 1.3; 0.8 to 2.3 95%CI in case of a dominant model and an OR of 1.0; 0.6 to 1.6 95%CI in case of a recessive one.

Conclusion

This is the first study to address the association of this SNP to gout. The results of our study failed to show a statistically significant difference between the SNP distribution in the two study groups. A limitation of this study could be the small size of the population analysed. Nevertheless, this study has the strength of addressing potential proinflammatory genetic risk variants in a case control design using hyperuricemic controls, thereby correcting for urate related susceptibility. Further studies in larger cohorts investigating immune related gene variants for gout susceptibility are warranted.
A novel frame-shift mutation in extracellular loop of human dopamine transporter leads to dopamine transporter deficiency syndrome

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Introduction

The activity of human dopamine transporter (hDAT) is critical for various physiological mechanisms and its dysregulation has been linked to different behavioral, psychiatric and age-dependent diseases including Schizophrenia, Major depression, ADHD, Parkinson disease and etc. Dopamine transporter deficiency syndrome (DTDS) is a rare complex movement disorder characterized by parkinsonian features and caused by mutations in SLC6A3 gene (encodes dopamine transporter). Studying the heterogeneity of mutations in this gene may help to improve the Genotype-Phenotype correlation of hDAT. Here, we report a mutation in the extracellular loop of hDAT as a cause of DTDS.

Materials & Methods

To find the cause of disease in a patient born to consanguineous parents with GDD, microcephaly and progressive pyramidal weakness in lower limbs, whole exome sequencing was employed. Confirmation and segregation in the family members for the identified variant was carried out using Sanger sequencing. Finally In order to provide evidence on pathogenicity mechanism of this mutation bioinformatic analysis and homology modeling were applied.

Results

After several filtering strategies, a novel frame-shift mutation in the SLC6A3 gene (c.1139_1150del/P. Gly380_Lys384delinsGlu) was identified, Sanger sequencing confirmed the variant and its segregation in other family members. This mutation affects the extracellular loop 4 (EL4) of DAT protein. Bioinformatic analysis and Drosophila based homology modeling indicated that this mutation is affecting a conserved domain which is crucial for the transportation of dopamine.

Conclusion

Our study highlights the importance of the EL4 in proper transportation of dopamine and links the mutation in this region to the pathology of DTDS.
Sexual development in the fungus Podospora anserina depends on organelle dynamics regulated by fission protein DNM1

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Introduction
Fission is a mechanism of utmost importance for cell dynamics. It accomplishes the division of two cell compartments by making use of molecular motors and adaptor proteins. One of the best-known proteins involved in fission is the molecular motor encoded by the DNM1L gene, dynamin1-like in humans, and its dynamin-like orthologs in other organisms. It’s noteworthy that peroxisomes and mitochondria share components of the fission machinery. Deletions of these proteins often cause a phenotype where organelles are completely fused and interfere with cell dynamics. In fungi, organelle dynamics are relevant for sexual development. Reports show that peroxisome localization, size, and shape progressively change during the sexual development of Podospora anserina. Deletion of an adaptor protein involved in fission (Fis1) causes these peroxisome features to become disrupted. In this work, we demonstrate that the fission of mitochondria and peroxisomes is essential for proper sexual development in P. anserina due to its importance in organelle dynamics.

Materials & Methods
We used homologous recombination to obtain a DNM1 deletion strain (ΔDNM1). Optic, epifluorescence and confocal microscopy were used to follow organelle dynamics through P. anserina vegetative and sexual development in the WT and ΔDNM1. Immunohistochemistry was performed for confocal and epifluorescence samples, and sexual differentiation and meiotic progression were analyzed in both strains. t-tests were used to compare sexual differentiation between WT and ΔDNM1.

Results
In a ΔDNM1 strain, we confirmed the shared fission machinery between peroxisomes and mitochondria by observing fused phenotypes for both organelles. In addition, we analyzed gametes for defects and assessed the different stages of sexual development. We found that sex did occur because meiotic-derived spores (ascospores) developed, but 50% of meiocytes (asci) produced abnormal ascospores (95%CI 27.6-62.5%). Therefore, we inspected nuclei segregation and organelle distribution in asci and spores. Also, there were defects in the packaging of peroxisomes into spores, as well as abnormal nuclear segregation during meiosis. Furthermore, we observed an aberrant formation of the meiotic and mitotic spindle during this process.

Conclusion
Fission protein DNM1 is involved in the sexual development of P.anserina by modulating organelle dynamics. Correct formation of the spindle during meiosis depends upon functional peroxisome-mitochondrial fission machinery.
Using Drosophila melanogaster as a model system to understand how alterations of mitochondrial dynamics trigger neuronal dysfunctions

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Introduction
The aim of this project was using the fruit fly, Drosophila melanogaster, as a model to study the molecular pathways of the gene DOR in Parkinson's disease (PD). DOR has a dual cellular function, being implicated in both regulation of transcription and regulation of autophagy. Over-expressing DOR rescues the PD-characteristic locomotor deficit caused by loss of the gene parkin in mice. To study whether DOR would have the same effect in Drosophila, the project focused on inducing dopaminergic (DA) neurodegeneration in fly brain and examining whether neurodegeneration is alleviated or exacerbated following DOR over-expression or knock-out, respectively.

Materials & Methods
Two fly PD models were used to answer these questions: the first model relied on poisoning with the oxidative stress-inducing herbicide paraquat (PQ), whereas the second model relied on point-mutations (A53T and A30P) in the neuronal protein α-synuclein. Both models were used concomitantly with survival assays to monitor fly viability, locomotion tests to monitor the development of movement deficits, and confocal imaging of GFP-labelled DA-neurons, to monitor neurodegeneration.

Results
Whole-body DOR knock-out flies were more susceptible to PQ poisoning than age-matched controls. While it had previously been found that whole-body DOR over-expression enhances survival compared to wild-type, over-expressing DOR specifically in DA-neurons did not rescue survival in the PQ experiments. Counting GFP-labeled DA-neurons showed PQ induced ~35% reduction in DA-neuron number in the optic lobes in both wild-type and whole-body DOR knock-outs. The higher death rate of DOR knock-outs in response to PQ poisoning was hence not accompanied by a higher rate of DA-neuron loss. In the point mutation models of PD, it was observed that mutant α-synuclein, paired with stressful conditions (29°C), led to pronounced locomotor deficits and DA-neuron loss in the flies. Surprisingly, under these conditions, DOR over-expression exacerbated rather than rescuing the PD phenotype.

Conclusion
The results suggest that DOR expression affects fly viability in the paraquat survival assay, but does so through non-DA-neuron-specific mechanisms. Furthermore, over-expressing DOR on a mutant α-synuclein background under stressful conditions seems to exacerbate neurodegeneration and locomotor deficits. The study implies that the model and experimental conditions used can strongly influence results when studying PD in Drosophila.
Expression of Long Non-Coding RNAs (UCA1 and CCAT2) in the Blood of Multiple Sclerosis Patients

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Introduction
Multiple sclerosis (MS) is an autoimmune and multifactorial disease, and its pathogenesis is associated with many genetic and environmental factors. Long Non-coding RNA (lncRNAs) are a group of genes that have recently been identified as predisposing genetic factors for the development of many cancers. This is a case-control study to evaluate the expression of two lncRNAs including Urothelial Carcinoma Associated 1 (UCA1) and Cancer-Associated Transcript 2 (CCAT2) in Relapsing-Remitting Multiple Sclerosis (RRMS) patients compared to healthy control group.

Materials & Methods
In this case-control study, the expression of UCA1 and CCAT2 was evaluated in 50 RRMS patients (37 females, 13 males with a mean age of 36.2 ± 2.9 years) compared to 50 healthy controls (38 females, 12 males with a mean age of 35.3 ± 2.1), using the TaqMan real-time PCR technique. This study was conducted during 2017 and 2018 at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Results
There was no significant difference between the overall expression of UCA1 (P = 0.282) and CCAT2 (P = 0.983) among the case and control groups. However, there was a significant difference in the expression of UCA1 in female patients older than 40 years in comparison with healthy age-matched females (P = 0.013). In addition, there was a significant correlation between the expression of UCA1 and CCAT2 (P < 0.0001).

Conclusion
These results suggest the synergistic effects of UCA1 and CCAT2 on pathogenic aspects of MS, by affecting cellular signaling pathways such as WNT and NF-kB.
Platform for creation and study inherited disease models with genome editing in human cells.

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Introduction
The development of genome editing tools has vastly reinforced our ability to study genes function and to modify genomes by altering existing genes or integrating transgenes. CRISPR-associated systems enabled investigators to create cell lines with site-specific modifications in relevant genes. Thus, via genetically modified cell lines it becomes possible to undercover roles of different genes, in particular in a disease modeling. Despite all advantages of novel editing systems, some problems, as the lack of preciseness of the CRISPR delivery remains unsolved. We aimed to create a basic cell model, carrying transgene of one of the components of CRISPR/AsCpf1 system – programmable endonuclease AsCpf1. This model will allow to effectively generate various numbers of transgenic cell lines by only delivering single guide RNA.

Materials & Methods
We used CRISPR/Cas9-mediated genome editing to insert transgenes of the nuclease AsCpf1 and of the tetracycline transactivator into the safe-harbor locus AAVS1 in HEK293A and iPSC lines. Plasmid transfection was used for the delivery of components; plasmids also carried antibiotic resistance genes, thus we selected cell populations by antibiotics (puromycin and neomycin). PCR analyze was performed for the screening of the clones with the correct transgene location. Next, we performed immunohistochemistry and Western blotting to confirm the expression of the nuclease AsCpf1 in the selected clones.

Results
We have created cell lines carrying doxycycline-driven transgene of the programmable nuclease AsCpf1 of HEK293A and IPS cell lines of a patient with Parkinson disease. For the genetically modified line HEK293A-AsCpf1, we managed to create 129 subclones, for IPS cell line m10.7-AsCpf1 – 3 subclones. We performed cell lines’ characteristics and proved the expression of the nuclease AsCpf1 with Western blotting.

Conclusion
We created human transgenic cell lines expressing the endonuclease AsCpf1 (the component of CRISPR/AsCpf1 genome editing system). These cell lines can be used as a platform for further high-effective genome editing. Delivery of different single guide RNAs allows creating various numbers of cell lines with relevant genome modifications.
New recombinant protein Cpf1 from Moraxella bovis

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Introduction
CRISPR system is known as last generation tool for genome editing. Searching for new nucleases from CRISPR systems is important work to expand the potential types of sequences where the modification of interest can be obtained. Cpf1 has some advantages over Cas9 such as less off-target activity and another PAM-site recognition but there are just a few characterized enzymes. It’s known that bacteria from genus Moraxella have CRISPR/Cpf1 systems but they have been poorly studied. We aimed to derive Cpf1 from genus Moraxella and characterize it.

Materials & Methods
The search of genes encoding Cpf1 in three Moraxella genomes was performed. Gene sequences were obtained using conservative regions of cpf1 genes from available Moraxella genomes in GenBank followed by «chromosome walking» procedure based on PCR suppression method. Gene cloning and expression were conducted using pET15b vector by In-Fusion recombination (Clontech). RNA was obtained by chemosynthesis. HPLC for protein purification was performed.

Results
Gene cpf1 was found in two available Moraxella strains: M. bovis and M. nonliquefaciens, complete nucleotide sequence was determined for cpf1 from M. bovis. The enzyme encoding gene was cloned in pET15b vector in two different forms – with and without His-tag. Purification method developed for His-tag variant led to almost homogeneous preparation of active protein in three steps of HPLC using such resins as Ni-NTA, Sephacryl S-200 and hydroxyapatite. It was shown that TTTN is PAM site for sufficient hydrolysis of plasmid DNA substrate. It was found that optimal NaCl concentration in the DNA hydrolysis is 100 mM and pH 7.0-8.5 doesn’t have any influence on the hydrolysis efficiency.

Conclusion
It was shown that Cpf1 from Moraxella bovis exhibits nuclease activity in vitro using the sequence TTTN as PAM site. Next studies and comparing with commercially available Cpf1 from Acidaminococcus and Lachnospiraceae bacterium could let to the effective and powerful tool for genome editing.
Immunology and Infectious Disease II

Chair
Prof. Ymkje Stienstra MD PhD

Presenters
Anand, A (Nandita)
Askarpour, B. (Bahram)
Bieńkowski, C. B. (Carlo)
Chikazunga, C.E.W (Christopher)
Cruz, N.S.C (Nathalia)
vан Blokland, I.V. (Irene)
Yang, X.Q.Y (Xiaqiang)
Zhou, M. (Meijin)
Outcomes of second line anti retroviral therapy among a cohort of people living with HIV/AIDS attending an ART centre in coastal South India

Anand, A (Nandita) Medical Student

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Introduction

In India, prevalence of HIV is 0.22% which is around 2 million people who are currently living with HIV. The prevalence has reduced when compared to 2007(0.34%), 2012(0.28%) and 2015(0.26%). However, there have been cases of failure to respond to first line anti-retroviral therapy due to reasons like drug adherence, multi drug resistance, late diagnosis of AIDS, virological failure or CD4 count <200 cells/mm³. This has led to increase use of second line drugs and various regimens have been formed which include combinations of NRTIs, NNRTIs and PIs to tackle multi drug resistance. There is very limited information regarding the efficacy of second line anti-retroviral drugs and their outcomes. Taking these facts into consideration, this study was planned to assess the outcomes of second line anti-retroviral therapy.

Materials & Methods

The facility based retrospective study was carried out in ART centre of Kasturba Medical College (KMC), Mangalore. The study participants included 200 PLHIV attending the ART centre between 2011-2017 and have completed 1 year of follow up, the study was approved by the Institutional Ethics Committee of KMC, Mangalore, the data was collected using a predesigned pretested semi structured proforma, The dependent variable was the clinical and the immunological outcome and the independent variables were the age, gender, occupation, year of starting the 2nd line, CD4 count and the ART Regimen. The data was analysed using SPSS version 20, and the results are expressed as mean (SD) and proportion.

Results

A total of 200 PLHIV who received second line ART following first line failure were analysed, Majority 122 (61%) were Males, the mean age was 43.41(10.22) years and majority were from low socioeconomic status, the mean CD4 count at the time of initiation of the ART was 261.61(133.68) and the latest CD4 Count was 489.64 (247.75), The most common ART regimen was AZT + 3TC + NVP (44.5%) followed by AZT + 3TC + EFV (16%), there were a total of 8 deaths in the present study.

Conclusion

Second-line ART has a satisfactory outcome in terms of clinical and immunological improvement following first-line failure in PLHIV.
Antibiotic Susceptibility Pattern in Staphylococcus aureus Isolated from Wound and Blood Cultures in Burn Patients

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Introduction
Burn remains a significant health problem in terms of morbidity and mortality throughout the world, especially in developing countries. Infection is a significant complication in burnt patients. The rate of antibiotic-resistant bacteria which were isolated from burn patients has increased. The aim of this study is determining the antibiotic susceptibility in Staphylococcus aureus (S. aureus) isolated from patients with burn wound infections.

Materials & Methods
This was a retrospective study which was conducted in the Burn Unit of Emam-Reza Hospital and all available wound and blood cultures of burn victims admitted during the 5-year period (March 2012-March 2016) were included. The sensitivity of isolated S. aureus samples was tested against 25 different antibiotic discs. Statistical analysis was done through SPSS version 24.

Results
Out of a total of 3188 Micro-organisms that were isolated from burn wounds and blood cultures, 185 (5.8%) of them were S. aureus. Susceptibility rates of some various antibiotics were as follow: Vancomycin (98.8%), Cefazolin (72%), Ciprofloxacin (75%), Gentamicin (74.6%).

Conclusion
Among all tested antibiotics, Vancomycin, Cefazolin, and Ciprofloxacin seemed to be the most effective agents for S. aureus. The widespread use of antibiotics in treating infections has led to the emerging of resistant strains. Routine microbiological surveillance and Careful invitro testing prior to antibiotic use may help in the prevention of raising antibiotic-resistant pathogens in burn infections.
The attitude of Polish women planning pregnancy and having children towards vaccinations


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Introduction
Vaccinations are the best method of preventing infectious diseases today. Some infectious agents known as TORCH can cause serious fetopathy. Some of them can be avoided by implementing appropriate prevention while planning pregnancy. Every pregnant woman should be vaccinated against: influenza, MMR, dTap, varicella, Hepatitis B.

Materials & Methods
This was a cross-sectional survey study. The questionnaire investigated the socio-economic status of women planning pregnancy or having children, their attitude towards vaccinations and the potential willingness to vaccinate their children. The attitudes towards anti-vaccine movements and "smallpox party" were also checked.

Results
The studied group consisted of 2384 women, age range was 16-54 years (median: 31 years). The most numerous group were women from cities &gt; 100,000 inhabitants (49.6%) and with higher education (71.9%). 80.4% of women were not vaccinated during pregnancy, and 86.1% did not vaccinate before pregnancy. 64.2% of women considered vaccination safe, and 79.3% said they were effective against infectious diseases. 74% knew that infectious diseases can cause fetal defects. Among the 5 most-feared pathogens, the following were distinguished: Toxoplasma gondii (78.3%), Rubella virus (65.9%), CMV (52.4%), Treponema pallidum (43.3%), HSV (34.4%). 54.9% of women totally disagreed with the anti-vaccine movements, 22.8% partially agreed, 11.8% had no opinion, and 6.3% fully agreed. Regarding the so-called "Smallpox party" as many as 80.4% of women considered this phenomenon to be dangerous for children's health, 12.3% had no opinion, and 3.9% considered it a good way for children to acquire immunity.

Conclusion
Most women in Poland have a positive attitude towards vaccination, consider vaccines safe and effective against infectious diseases. A significant proportion of women planning to become pregnant or being pregnant is not vaccinated, the role of the doctor leading the patient to be vaccinated is crucial in this matter. About 12% of women are the undecided fraction, and the educational role of the doctor is essential to convince them of the importance of vaccination.
No Effect Of The New Isoniazid Preventive Therapy Guidelines On The Adherence Of ART And IPT On HIV Patients In Lilongwe Urban ART Clinics:

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Introduction
Isoniazid Preventive Therapy (IPT) combined with anti-retroviral therapy (ART) is an effective way of preventing active TB among HIV patients. In Malawi, IPT has recently been adopted to be taken for life time among HIV patients living in the 10 high burden districts where IPT side effects are expected to clearly outweigh the benefits. However, this new strategy means an increased pill burden with increased risks of side effects. This research aimed to assess the effects of this new guideline on the adherence of ART and IPT.

Materials & Methods
This cross-sectional study was conducted in ART clinics of Lilongwe urban. Three ART clinics were randomly chosen using simple random method. It was a mixed qualitative and quantitative study which targeted HIV patients over 18 years of age on ART. Sample size was 170.

Results
In the 117 participants, the average ARV adherence before IPT implementation was 95.42% (95% CI 94 to 96.8). After IPT implementation the mean ARV adherence among 143 participants was 93.15 (95% CI 90 to 95.6). The ARV adherence was reduced from 95.42% to 93.15% with a p-value of 0.27. 20.21% of the participants were against the new IPT guidelines. 69.6% had a good IPT adherence, 20.3% had a poor IPT adherence while 10.1% were stopped by medical personnel. 66% of the participants ever experienced IPT side effects with numbness being the commonest side effect (37.7%) despite the use of Pyridoxine. Of the participants who started IPT and ARVs differently, 58% had no significant change in adherence, 23% had their adherence reduced by at least 5% while 19 % had their adherence increased by at least 5%.

Conclusion
There is no significant effect of IPT on ART adherence. This is because most of participants prioritize taking ART over IPT but this has resulted in poor IPT adherence. Interventions should target proper patient education on IPT.
The differential effect of white and brown adipose tissue on liver tumor and non-tumor cells: the role of the inflammasome adaptor protein ASC

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Introduction
Adipose tissue can mediate inflammation through secretion of cytokines and chemokines and can act as an energetic support to tumors, including liver cancer. There are different types of adipose tissue (white, brown, beige and pink), which can secrete different biomolecules. The purpose of this study was to investigate how white adipose tissue (WAT) and brown adipose tissue (BAT) can differently affect tumor (Hepa 1c1c7) and non-tumor cells (AML-12) lineage of hepatocytes, as well as to analyze the role of the inflammasome protein ASC present in these tissues in the modulation of the cell death, lipid droplets (LD) biogenesis and cytokines release.

Materials & Methods
WAT and BAT were collected from wild type (WT) and ASC knockout (KO) mice, and the product of their secretion was used to stimulate Hepa and AML-12 cells. Cell death and LD biogenesis were analyzed by flow cytometry and cytokines release by ELISA.

Results
Secretion from WT-derived BAT increased apoptotic cell death compared to WAT, whereas ASC KO-derived BAT mice induced necrosis cell death in Hepa cells. Moreover, BAT and WAT, both obtained from WT and ASC KO mice, did not induce differences on cell death profile in AML cells. In addition, metabolites secreted by BAT from WT mice induced more LD biogenesis than WAT in both cell lineages. However, the absence of ASC in WAT increased LD biogenesis in non-tumor cell lineage compared to BAT. We also observed differences in the release of IL-33 and CCL2 from both hepatocytes after stimulation with both tissues.

Conclusion
Taken together, our data suggested that secretion products of WAT and BAT can have different effects in cell death and LD biogenesis of hepatocytes and ASC protein has a significant role in this process. Moreover, this could be an important mechanism involved in the establishment of NAFLD and hepatocellular carcinoma linked to obesity.
Sex differences in leukocyte profile in ST-elevation myocardial infarction patients

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Introduction
Even though our knowledge of the pathophysiology of acute ST-elevation myocardial infarction (STEMI) has substantially increased over the past decades and inflammations showed to be an important player, the precise inflammatory mechanisms underlying STEMI remain unclear. Research on this field is prominently based on men. However, the female immune system differs substantially where sex hormones as steroids and estrogens are known to affect the immune system of men and women in different ways. Therefore, we aimed to study potential sex differences in the etiology of the inflammatory response post-MI by identifying clinical and biochemical determinants of leukocyte profiles in men and women presenting with STEMI.

Materials & Methods
A total of 532 consecutive patients presenting with STEMI was included in this study between July 2015 and November 2017. Inclusion criteria were indication for STEMI and age ≥ 18 years. Blood samples were collected at hospital submission. Due to the acute nature of myocardial infarction, all participants included in the study initially provided verbal consent, and written informed consent was obtained at a later stage. The study protocol was approved by the local Medical Ethics Review Board (METc 2012/296). Statistical significance was considered at a level of P=0.05.

Results
Of the 532 STEMI patients included, 142 (26%) were female and the mean age was 66 ±13 years for women and 63 ±11 years for men. Percentages of lymphocytes were significantly higher in women (21.7% ±10.1% vs. 19.0% ±8.78%, P=0.007). Percentages of monocytes and eosinophils were significantly higher in men (6.66% ±2.0% vs. 6.13% ±1.82%, P=0.015 and 1.48% ±1.29% vs 1.17% ±0.91%, P=0.02).

Conclusion
Leukocyte profiles differed between men and women presenting with STEMI, where men presented with higher levels of monocytes and eosinophils and women with higher levels of lymphocytes. This suggests that between sexes different immunological processes are ongoing during the process of STEMI. Further research is of key importance in order to develop targeted therapies for both men and women.
Defined host factors support HBV infection in non-hepatic cells

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Introduction
Hepatitis B virus (HBV) is a human hepatotropic virus and HBV infection is a major factor for hepatocellular carcinoma following liver cirrhosis. 240 million people throughout the whole world are chronically infected with HBV. However, HBV infection also occurs at extrahepatic sites, but the relevant host factors required for HBV infection in non-hepatic cells was poorly understood. In this study, we show that co-expression of the nuclear hormone receptors HNF4α, RXRα, and PPARα, and the HBV receptor NTCP support the entry and replication of HBV in 293T cells.

Materials & Methods
A non-hepatic cell culture model (293T-NE-3NRs) is constructed by exogenous expression of four host genes (NTCP, HNF4α, RXRα and PPARα) in human non-hepatic 293T cells. 150 Geq/cell HBV generated by HepG2.2.15 cell line were used to infect 293T-NE-3NRs cells. Supernatant were collected every two days till 10-13 days post infection, and cells were fixed by ice-methanol at the last day of infection. Then HBsAg, HBeAg and HBV DNA in the supernatant were detected by ELISA or real-time qPCR; and intracellular HBCAg and HBsAg were identified by immunofluorescence assay; In addition, pgRNA and cccDNA were extracted and examined. 293T and HepG2 overexpressing NTCP were set as negative or positive control, respectively. Data were analyzed by Student’s t-test. A P<0.05 was considered significant.

Results
This modified non-hepatic 293T cell culture model supports HBV entry, transcription and replication, as evidenced by the detection of HBsAg, HBeAg, HBV DNA, HBCAg, HBV pgRNA and cccDNA in 293T-NE-3NRs and HepG2-NE but did not detected in 293T. Our results suggest that the above cellular factors may play a key role in HBV infection of non-hepatic cells.

Conclusion
This study has successfully generated a novel non-hepatic cell model for HBV infection, which will facilitate the identification of host genes that support extrahepatic HBV infection as well as host factors required for liver tropism of HBV.
Detection of Diverse Novel Astroviruses in Wild Bird from Poyang Lake, Jiangxi, China

Zhou, M. (Meijin)

Introduction
The family Astroviridae has been classified into two genera: Avastrovirus and Mamastrovirus, infecting avian and mammalian species respectively. Currently, the ICTV has officially revealed 19 recognized species of Mamastrovirus (MAstV1-19) and three species of Avastrovirus (AAstV1-3), but the number of animal hosts infected astroviruses has expanded to at least 33 mammalian and 14 avian species nearly a decade ago. There are still numerous unclassified astroviruses, particularly detected from wild birds. It’s very limited about studying astrovirus genetic diversity in wild birds, although wild birds play an important role in virus ecology and evolution. Thus, the identification of novel astroviruses in wild birds will be crucial for a better understanding of astroviruses genetic diversity and evolution.

Materials & Methods
In this study, 2408 fecal swabs from 25 different sampling occasions of Jiangxi Poyang Lake collected from October 2016 to February 2017 were tested for astroviruses by heminested PCR. The rapid amplification of cDNA ends (RACE) technique was used to amplify astrovirus genome. Assessment of phylogenetic relationships was performed using programs of the MEGA 7 software. In addition, all astrovirus-positive samples were done for host identification by DNA “bar-coding” technique to better understand the host origins of selected wild bird droppings.

Results
A total of 450 out of 2408 (18.7%) fecal samples were positive for astrovirus. The positive rates of different sampling occasions ranged from 3.1% to 39.6%. Phylogenetic analysis of the partial RdRp sequence revealed a previously unrecognized and large diversity of astroviruses in more than 25 different bird species from Poyang Lake. Currently, we have got nearly full-length genome of 30 samples via RACE technique and detected multiple astroviruses circulating in a single host species.

Conclusion
This is the first novel astroviruses detection in wild birds from China mainland. The phylogenetic tree showed that a large number astroviruses detected in wild birds were closely related to mamastroviruses from NCBI. This result implied there were multiple interspecies transmission between avian and mammalian.
Miscellaneous Health II

Chair
Non Nominatus

Presenters
AL Sowayigh, O. (Omar)
ATAS, B.A. (Birce)
Bhatt, A. (Arohi)
Gróf, I.
Hazrati, N. (Nazanin)
Jakhar, F.J. miss (Fiza)
Prabowo, R.P (Rafik)
Ramezani, P (Pouria)
VanBilsen, N (Nicholas)
Yordi, S. (Sari)
Refractory Asthma Phenotyping based on Immunoglobulin E Levels and Eosinophilic Counts: A Real Life Study

Lababidi, H. Dr. (Hani)1, AL Sowayigh, O. (Omar)1, Bin-Howemel, S. (Samar)1, AlReshaid, K. (Khoolod)1, AlOtaiq, S. (Sultan)4, Bahnassy, A. (Ahmed)5

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Introduction
Background: Bronchial asthma is a chronic heterogeneous disease with variable severity. Refractory bronchial asthma is defined as uncontrolled asthma despite GINA Step 4 or 5 treatment. The serum IgE levels and Eosinophilic counts have been used as biomarkers to define treatment strategies with biological agents in refractory asthma.

Objective: The aim of this study is to determine the concurrence of high eosinophilic counts and elevated serum IgE levels in patients with refractory bronchial asthma.

Materials & Methods
A retrospective cross-sectional study was conducted on patients attending adult refractory bronchial asthma outpatient clinic between 2012 and 2018. The study would only include patients who have proven asthma diagnosis per GINA guidelines. Serum total IgE level and blood Eosinophils count on a matched date with spirometry and Asthma Control Test (ACT) scores were collected. Spearman’s and Pearson’s correlation were used to identify a relationship between IgE level, Eosinophils count and ACT score.

Results
A total of 142 patients with refractory bronchial asthma were included. The mean age was 43 years, mean eosinophilic count 564 cells/µL and mean serum IgE levels of 520 IU/ml. There was a significant correlation between serum IgE level and eosinophilic count. Serum IgE and eosinophilic count were concurrently elevated in 110 patients (78%). The patients were further categorized into four subgroups. Group A: IgE 30-100 IU/mL and EOS 150-300 cells/µL (7.3%), Group B: IgE &gt;100 IU/mL and EOS 150-300 cells/µL (19.1%), Group C: IgE 30-100 IU/mL and EOS &gt;300 cells/µL (14.5%) and Group D: IgE &gt;100 IU/mL, EOS &gt;300 cells/µL (59.1%).

Conclusion
The majority of refractory bronchial asthma patients exhibits both elevated serum IgE level and eosinophilic count.
The Physiological Changes Related to Looming Sounds in Movie Soundtracks

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Introduction
It is presumed that what makes you feel thrilled during a scary movie or trailer is the sound effects. However, the scientific evidence supporting that hypothesis yet to be discovered. One of the most commonly used sound effects is called the looming effect a.k.a. the ‘rise effect’, creates a tension by increasing the level of sound. The second most common effect is called the “hit” which is essentially a loud hit such as an explosion sound. In the current study, we aimed to evaluate changes in electrodermal activity (EDA) and heart rate (HR) caused by these audible stimuli, ‘rise and hit’

Materials & Methods
30 young adult volunteers planned to be included in the study. Currently 11 volunteers (Mean age: 19.8±0.87 years) participated in the pilot experiment. Sociodemographic questionnaire, STAI-1 and STAI-2, Coping with Stress Questionnaire (CSQ) were applied before the experiment. In the beginning of the experiment, baseline EDA and HR were recorded from all participants. During the experiment, volunteers listened four random blocks of auditory stimuli that are white noise, rise, hit or rise or only hit sound effects (without rise) and EDA and HR were recorded throughout the experiment.

Results
Preliminary findings of 11 participants are as follows. The mean scores for STAI-1,2 and CSQ were 30.36±4.24, 35.90±8.65 and 31.45±6.4 respectively. 54.5% of the participants stated their favorite genre of film is action movies. Mean EDA peak (µsiemens) and HR (BPM) respectively, were for the hit effect 0.50±0.2; 92.18±13.43, for rise effect 0.57±0.23; 93.36±19.62 , for rise and hit effect 0.79±0.31; 94.97±18.61 and for white noise 0.20±0.18; 82.09±12.

Conclusion
When compared to white noise, our preliminary findings showed that there is a significant effect of EDA for the rise (p&lt;0.05), hit (p&lt;0.05) and rise and hit (p&lt;0.001) effects. It is also important to note that when the rise and hit effects are combined together their effect on EDA and HR is higher than their solo effects. We hypothesized that combined effect may trigger a stronger alarm mechanism in amygdala indicating a potential dangerous situation.
Analysis of correlation between intraocular pressure (IOP) and central corneal thickness (CCT) in patients with refractive errors.

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Introduction
The variations in IOP have a variety of implications and influence the pathogenesis and prognosis of Ocular morbidities. Central Corneal Thickness is one of the most important factors related to the refraction of eye. Previous studies have revealed the positive relationship between CCT and IOP among adults. Every 10 µm increase in CCT leads to 0.15–1.0 mmHg increase in IOP. This study aims to evaluate the relationship between IOP and CCT in normal population.

Materials & Methods
Central Corneal Thickness, Intraocular Pressure and Refractive errors of the eyes were measured using Pachymeter, Non - Contact Tonometer and Automated refractometer respectively. Data was entered into the Microsoft Excel, 2016 version and was analysed for the sustainability of efficacy. Pearson’s Correlation Coefficient Test was used.

Results
Out of the data collected from 68 patients, of age 14 - 57 years, the mean CCT of right and left eyes were observed 0.5098 mm and 0.5053 mm respectively. Mean IOP of right and left eyes were observed 16.239 mmHg and 16.413 mmHg respectively. Mean Refractory error of right and left eyes were observed -1.320 D and -1.426 D respectively. The range of values of CCT, IOP and Refractory errors was observed 0.43 - 0.591 mm, 9 mmHg - 28 mmHg and -5 .D to +3 D

Conclusion
The association between CCT and age was not significant in the age group 14 – 40. There was regression in CCT by 0.0053 mm for every 4 years increase in age in the age group 40 – 57 years. For every 0.01 mm increase in CCT, the IOP changed by 0.1 – 0.63 mmHg. No linear pattern was observed to explain the subsequent increase. No significant relationship was observed between IOP values and age. It was observed that out of 52 patients with negative powers according to Automated refractometer (AR), 53.8% had CCT values between 0.430 mm and 0.515 mm. There was no significant relation between the power and CCT values. No significant relationship was observed between IOP values and the refractory errors of the patients.
A bronchial epithelial culture model to study cystic fibrosis and for pharmaceutical technology applications

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Introduction
Culture models of the respiratory system are not only important to study drug transport, but to better understand the pathomechanism of pulmonary diseases. Cystic fibrosis is a genetic disorder featured by thick mucus, altered pH, infections and inflammation in the lung. Based on clinical observations NaHCO3 inhalation may help to dilute the thick, acidic mucus and decrease the inflammation. To better understand and treat this disease more relevant culture models are needed. One of the most important aspects of these models is the reconstitution of the complexity of the respiratory system. Our research hypothesis was, that artificial sputum medium (ASM) containing mucin, would provide a physiological microenvironment for respiratory epithelial cells and create a better air-liquid interface. Our aim was to establish and characterize a new in vitro cystic fibrosis model using human bronchial epithelial cells co-cultured with human endothelial cells in different conditions and to test them with a model pharmacon.

Materials & Methods
For the co-culture model system human wild type and mutant CFBE bronchial epithelial cells, and endothelial cells were used. ASM with different compositions, pH and NaHCO3 levels were tested. The cell membrane changes were investigated by plasma membrane fluidity measurements. The barrier properties were characterized by electrical resistance measurements and permeability studies for marker molecules and a model pharmacon. The morphological properties were analyzed by immunohistochemical staining for junctional proteins.

Results
The presence of endothelial cells and the ASM induced better barrier properties in respiratory epithelial cells, as reflected by the higher resistance, the lower paracellular permeability and the stronger interepithelial junctions. The NaHCO3 treatment was non-toxic to epithelial cells, changed plasma membrane fluidity and altered the pH of the individual cells.

Conclusion
We established and characterized a new in vitro bronchial epithelial co-culture model for the investigation of cystic fibrosis. Furthermore we verified the effect of NaHCO3 in pathological conditions. This model could contribute to the development of new pharmacotherapy to more efficiently treat cystic fibrosis.
Immediate and Short-term Follow-Up of Aortic Coarctation Balloon Angioplasty and Stenting

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Introduction
Aortic Coarctation (CoA) is one of the congenital heart diseases with the prevalence of 5% to 8%. Severe heart failure in the neonatal period and hypertension in children and adults are among the common cause of mortality and morbidity in these patients. Whether surgical repair or interventional approach is always a debate. Acceptable advantages of nonsurgical repair being increasingly implemented. Surgical repair is along with some complications like re-intervention requirement, and hypertension remaining. In this study, balloon angioplasty with or without stenting was performed for 53 patients with native or Re-coarctation (Re-CoA) angioplasty.

Materials & Methods
This is a prospective cohort study, performed in Imam Reza hospital, Mashad, during the years of 2011 -2015. Balloon angioplasty with or without stenting was performed on 53 patients with native or Re-coarctation angioplasty (39 balloon angioplasty alone, and 14 balloon and stenting). The pressure gradient across the CoA segment was measured initially by Echo and pre, and Post-procedure. The successful procedure was determined when pressure gradient reduced less than 20 mmHg across the CoA site.

Results
Among 53 patients, 52.8% were male. There were 96.22% (n=51) native and 3.77% (n=2) Re-CoA. The mean age of patients was 8.65 ± 8.37 years, and the mean weight was 25.82±20.73 kg. The mean pressure gradient across the CoA site before angioplasty was 24.88±12.32, and The pressure gradient was 4.77±6.42 (p<0.001). One of the patients experienced aneurysm formation at CoA segment site post balloon angioplasty.

Conclusion
On the basis of these data, balloon angioplasty is safe and effective in the treatment of native or Re-CoA. These results suggest that CoA angioplasty could be an effective alternative to a surgical approach, and gives good immediate results, although follow up studies are necessary to evaluate complications, and the long term effect on blood pressure in comparison to the surgical approach.
Negative psychological approach of ICU staff towards ventilator care bundles in prevention of ventilator-associated pneumonia in a tertiary care hospital of South India

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Introduction

Various studies show high mortality rates associated with Ventilator-Associated Pneumonia (VAP) infections ranging from 20% to 76%. Recently established Ventilator care Bundle, comprising of semi-recumbent position, daily 'sedation vacation', daily assessment of readiness to extubate and peptic ulcer disease prophylaxis has proven to prevent VAP effectively. Mouth care with Chlorhexidine and Subglottic aspiration although not included are crucial to prevent VAP. The aim of this study is to focus on the attitude of ICU staff towards the implementation of the above-mentioned ventilator care bundle.

Materials & Methods

A Descriptive and Observational cross-sectional study using a structured self-administered questionnaire ascertained 150 Health care staff members viz. consultants, senior resident, interns, nursing and paramedical staff managing the functioning of ICU around the clock. Likert scale was used in grading of the questions. Analysis was done by Statistical Package for the Social Sciences using descriptive statistics.

Results

Out of 150 respondents, a majority of 84.5% of study population believe semi-recumbent position to be a crucial component of ventilator bundles. A minority of 37% fail to consider the need of daily sedation vacation. A slight majority of 50.5% do not consider daily spontaneous breathing trials to be necessary. 36.2% participants don’t consider peptic ulcer prophylaxis to be crucial. 24.3% fail to consider the necessity of deep venous thrombosis prophylaxis. 76.7% participants believe that Mouth care with Chlorhexidine and Subglottic aspiration should be included in a revised Ventilator Bundle more specifically aimed at VAP prevention. Majority of the staff 70.9% were aware of hand hygiene practices to be followed prior to handling of ventilation equipments and patients but only 39.8% practiced it rightly.

Conclusion

Majority of the study participants have a rough idea about the steps to be taken for VAP prevention however only 26.2 % are sufficiently familiar with all the measures that are included in ventilator bundles which when executed together are more efficient than if implemented individually. Due to this negative psychological attitude of ICU staff towards the implementation of the guidelines provided to them, the risk of VAP is ever-increasing suggesting a strict need for more workshops and sufficient responsibility on the part of ICU staff and doctors.
THE EFFECT OF QUAIL EGG YOLKS ON RAT (Rattus norvegicus) BODY WEIGHT AND LIPID PROFILE

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Introduction
Consumption of high cholesterol lead to increase the risk of cardiovascular disease. One of the foodstuffs that have high cholesterol levels is quail egg yolks. Quail eggs yolks contain cholesterol higher than the yolk of other birds. This research aims is to know the effect of quail egg yolks on body weight (BW) and lipid profile (LP) of rats.

Materials & Methods
This study used a quasi-experimental method with pre and post-test control group design and was conducted in the laboratory of physiology, Universitas Islam Indonesia (UII) for 2 weeks. This research used 24 male Wistar strain rats aged 1-2 months with BW of 100-180 grams. Rats were divided into two groups, one group were given the quail egg yolks (G1) and the other group was not given the quail egg yolks (G2). Before treatment, body weight and lipid profile i.e cholesterol total (CT), LDL and HDL were measured. The quail egg yolks were given to the control positive rats were given 5 ml/200 gram BW/day of quail egg yolks divided into 2 doses. After 2 weeks, body weight and lipid profile were measured for the second time. All data were expressed as mean ± SD were statistically analyzed using with SPSS 21 dependent type sample t-test. Values were considered significant at p < 0.05.

Results
The average of BW control negative rats after 2 weeks was 216,12 ± 34,74 gram and the average of LP (mg/dl) was 70,10 ± 2,68 (CT), 26,76 ± 1,81 (LDL), and 63,66 ± 2,18 (HDL). The average of BW control positive rats after 2 weeks was 193,12 ± 18,11 gram and the average of LP (mg/dl) was 212,78 ± 6,79 (CT), 76,12 ± 3,53 (LDL), 25,57 ± 1,61 (HDL). Result of independent t-test analysis for BW dan LP showed significant difference (p < 0.05).

Conclusion
Quail egg yolks significantly decrease BW and increase LP in positive group.
Synthesis of Hybrid Silica-coated Gd-Cu-In-S/ZnS Bimodal Quantum Dots for Epithelial Cell Adhesion Molecule Targeted Drug Delivery and Imaging

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Introduction

Dual-modal imaging probes based on fluorescence (FL) and magnetic resonance (MR) modalities have attracted great attention due to their ability to combine the target specificity and high penetration in body tissue.

Materials & Methods

In this study, we developed a potent nanocarrier with an effective photoluminescent emitting and the MR imaging capacity to deliver the doxorubicin to breast cancer 4T1 cells. The nanocarrier was fabricated using coating of quantum dots with mesoporous silica followed by aminofunctionalization of the silica surface. Then, the doxorubicin (DOX) was loaded into the silica pores and biheterofunctional PEG covalently attached to the surface of core-shell quantum dot mesoporous silica nanoparticles. In order to target the DOX-loaded nanoparticles, the EpCAM DNA aptamer was attached on the DOX-loaded PEGylated nanoparticles surface. The synthesized NPs were analyzed for their size distribution, morphology, zeta potential and magnetic susceptibility using TEM, SEM and VSM analysis.

Results

The quantum dot encapsulated with mesoporous silica revealed spherical shapes with an average particle size of 100 nm. The maximum encapsulation efficacy of doxorubicin in the silica pores was obtained 25%. The in vitro release assessment demonstrated the pH-sensitive release of doxorubicin from the designed formulations. Moreover, the cellular uptake studies revealed that the EpCAM aptamer enhanced the cellular uptake of doxorubicin in the 4T1 cell line. The in vitro cytotoxicity assays indicated that the aptamer targeted nanoparticles showed greater cytotoxicity than non-targeted NPs and free DOX toward 4T1 and MCF-7 cell lines. The in vivo studies in 4T1 tumor-bearing Balb/c mice demonstrated that EpCAM DNA aptamer could specifically deliver the DOX-loaded nanoparticles into the tumor tissue and cause remarkable inhibition of tumor growth as compared to non-targeted formulation and free DOX. Moreover, the MR images confirmed that the accumulation of targeted nanoparticle in tumor tissue was higher than non-targeted formulation and free DOX.

Conclusion

These results confirmed that the fabricated formulation with bimodal imaging ability could use as a potent theranostic agent for diagnostic and treatment of breast cancer.
Investigating the potential role of the vascular non-neuronal cholinergic system in protection against endothelial cell dysfunction

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Introduction
Cardiovascular disease (CVD) and oxidative stress are inextricably linked. Oxidative stress, characterized by elevated reactive oxygen species such as H2O2, results in endothelial cell (EC) damage. Because ECs release important vasodilators, EC dysfunction impairs vasodilation, further exasperating disease conditions. Cardiomyocytes have recently been shown to actively secrete the vasodilator acetylcholine (ACh). This cardiac non-neuronal cholinergic system (NNCS) exhibits a protective role in the heart, but whether a similar system exists in the vasculature remains unclear. Augmentation of such a system may prevent EC dysfunction, allowing vessels to maintain vasodilatory properties and decreasing mortality associated with CVD. We aim to discover a vascular NNCS and examine whether enhancing this system with a cholinesterase inhibitor can protect against EC dysfunction. We hypothesize that a vascular NNCS will significantly increase the vasodilatory ability of vessels exposed to oxidative stress.

Materials & Methods
Aortas were isolated from 12-16-week-old male C57BL/6 mice and segmented into 4 rings of approximately 2 mm in length. Each ring was set onto a DMT organ bath transducer at a resting tension of 1000 mg. We investigated whether H2O2-mediated EC damage can be prevented with pyridostigmine (PYR), a cholinesterase inhibitor. Experimental rings were pretreated with 10 μM PYR for 15 minutes, while control rings were bathed in Krebs solution. All rings were then incubated in 1.0 μM H2O2 for one hour to induce oxidative stress. Next, rings were preconstricted with 0.3 μM phenylephrine, a known vasoconstrictor, and exposed to 100 μM methacholine (MCh), an ACh analogue, to assess the ability to dilate. Experiments were replicated with 6 aortas (N=6), using the DMT organ bath transducer to measure ring tension. Significance was calculated using a one-tailed unpaired Student’s t-test.

Results
PYR-pretreated rings are expected to have significantly increased MCh-mediated vasodilation following exposure to H2O2 when compared to control rings.

Conclusion
Discovery of a vascular NNCS would have immense implications in treatment of CVDs, such as diabetes and hypertension. If we can demonstrate that enhancing this NNCS protects ECs from oxidative stress, future studies can investigate whether cholinesterase inhibitors may be a viable prevention strategy to prescribe at-risk cardiovascular patients.
Ocular Adnexal Amyloidosis: A Retrospective Case Series Analysis

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Introduction

Ocular adnexal amyloidosis (OAA) may represent a localized manifestation of an underlying systemic process. Accurate identification of the amyloid fibrils can guide systemic evaluation and management. The aim of this study is to characterize subtypes of OAA using immunohistochemistry and mass spectrometric analysis and to correlate the results with ocular and systemic involvement.

Materials & Methods

Retrospective case series review of patients with OAA subtyped by immunohistochemistry and mass spectrometric analysis at the Cleveland Clinic, USA, from June 1995 to June 2017.

Results

Out of 170 patients diagnosed with Amyloidosis, 10 had OAA. Immunohistochemistry identified AL amyloid protein in 67% (4/6) of specimens, while mass spectrometry identified AL amyloid protein in all specimens (10/10). AL lambda was identified in 50% (5/10) of samples, kappa in 30% (3/10), and both kappa and lambda light chains in 20% (2/10). Conjunctival amyloidosis was appreciated in five cases; of these, three cases were AL lambda while two were both lambda and kappa. Concurrent systemic involvement was identified in three cases; two of these had AL kappa amyloidosis with eyelid involvement, while the other case had AL lambda amyloidosis with uveal involvement.

Conclusion

Primary AL amyloidosis is the most common form diagnosed by mass spectrometric analysis in patients with OAA. Immunohistochemistry is less effective in the characterization of the amyloid deposits in a significant number of cases. Moreover, evaluation to exclude systemic involvement or associated underlying lymphoproliferative disorder is warranted.
Nephrology and Urology

**Chair**

Prof. Ron T. Gansevoort MD PhD

**Presenters**

Li, Z.W.L (zuwei)
Farshad, O.
Kaya, O. (Osman)
Lazić, M. (Miloš)
Sabirova, G.S. (Guzel)
Shen, P.-L.S. (Pei-lin)
van Furth, LA (Annick)
miR-204-5p is an exosomal biomarker and a tumor suppressor for bladder cancer

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Introduction
Bladder cancer (BC) is one of the ten most common malignancies in China with high morbidity, recurrence, and mortality. Dysregulation of miRNA exerts significant functions in the genesis and progression of BC. Exosomal miRNAs in serum are prone to be an ideal biomarker for cancer diagnosis.

Materials & Methods
56 BC patients, 13 cystitis patients, and 56 healthy volunteers were enrolled. Serum exosomal miR-204-5p expression levels were valued, and several statistical analysis was performed to assess its diagnostic ability. We measured the miR-204-5p cellular expression and exosomal expression (in cell-derived exosomes) of five BC cell lines. CCK-8 assay, wound healing assay, transwell assay, and flow cytometry assay was performed to clarify the role of miR-204-5p in BC cells. Luciferase reporter assays and western blot were performed to clarify the target regulated by miR-204-5p in BC.

Results
The expression of serum exosomal miR-204-5p was validated as a BC detective biomarker and discriminate BC patients by tumor size and grade. miR-204-5p was downregulated in BC cell lines but upregulated in cell secrete exosomes. Up-regulation of miR-204-5p inhibited BC cellular proliferation and invasion. Oncogene RAB22A was inhibited by miR-204-5p in BC cells.

Conclusion
miR-204-5p acts as a tumor suppressor in bladder cancer by inhibiting oncogene RAB22A. Serum exosomal miR-204-5p may serve as a potential diagnostic biomarker for bladder cancer. miR-204-5p is down-regulated in BC cells but enriched in the tumor-derived exosomes indicates that bladder cancer cells might dispose unwanted tumor suppressor miRNAs by loading them into exosomes for further expelling.
Role of Mitochondrial Impairment in Lithium-Induced Nephrotoxicity: In vitro and in vivo

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Introduction
Lithium is abundantly administered against bipolar disorder. On the other hand, lithium-induced renal injury is a clinical complication which commonly reveals as drug-induced diabetes insipidus. However, Lithium-induced cytotoxicity might also play a role in the adverse effects of this drug toward the kidney. There is no clear cellular and molecular mechanism(s) for lithium-induced nephrotoxicity. The current study was designed to evaluate the effect of lithium on kidney tissue oxidative stress biomarkers and mitochondrial function, and its relevance to drug-induced nephrotoxicity and electrolytes imbalance.

Materials & Methods
Rats were treated with lithium (Lithium carbonate, 25 and 50 mg/kg/day, i.p, for 28 consecutive days). Serum and urine biomarkers of kidney injury, kidney tissue markers of oxidative stress, and renal histopathological changes were assessed. Moreover, kidney mitochondria were isolated and several mitochondrial indices were monitored. Lithium-induced renal injury revealed as significant increase in urine phosphate, glucose, ALP, and γ-GT. Moreover, serum electrolytes imbalance including hypokalemia and hypophosphatemia as well as significant increase in BUN and creatinine were evident in the lithium group.

Results
Lithium caused an increase in the kidney reactive oxygen species (ROS) level and lipid peroxidation (LPO). Renal glutathione (GSH) reservoirs were also depleted and tissue antioxidant capacity decreased in lithium-treated animals. Significant tissue histopathological changes including necrosis, Bowman capsule dilation, and interstitial inflammation were evident in lithium-treated animals. On the other hand, significant decrease of mitochondrial dehydrogenases activity, collapse of mitochondrial membrane potential, LPO formation, and mitochondrial permeabilization were detected in lithium-treated animals. Moreover, increased GSSG level, as well as depletion of organelle GSH and ATP content were detected in the kidney mitochondria isolated from lithium-treated animals.

Conclusion
The data provided in the current study mention oxidative stress, mitochondrial dysfunction, and cellular energy crisis as the potential primary mechanisms for lithium-induced renal injury.
Protective and Therapeutic Effect of Carvacrol against Renal Ischemia Reperfusion Injury in Rats

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Introduction
Kidney one of the most vital organs. Ischemia-Reperfusion (I/R) injury is one of the most important causes of acute renal failure. This study was designed to investigate the protective and therapeutic effects of carvacrol (CAR) on renal damage induced by renal I/R in rats.

Materials & Methods
Thirty-two rats were randomly divided into four groups (n=8): (1) Sham group; (2) I/R group; (3) Protective group: CAR+I/R; (4) Therapeutic group: I/R+CAR. Protective and therapeutic effects of CAR were evaluated by biochemical values and histopathological observation. Kidney tissue levels of malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) were determined. Blood urea nitrogen (BUN), creatinine (CR), and albumine (AL) were evaluated as a biochemical value.

Results
I/R group demonstrated significant increased in the BUN, CR, AL and MDA levels in the renal tissue as compared with Sham group. I/R group demonstrated significant decreased in the SOD and CAT as compared with Sham group. CAR reduced the renal injury, oxidative stress and inflammation compared with that of the non-treated rats, as shown by the decreased levels of MDA, BUN, CR and the increased levels of SOD and CAT. Our histopathological findings were in accordance with these biochemical results. Additionally, there was no significant improvement in albumine.

Conclusion
These results indicate that CAR can provide preventive and therapeutic effects on I/R-induced renal injury in rats.
Association between GPX1 and SOD2 genotypes and the risk of Balkan endemic nephropathy

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Introduction
Balkan endemic nephropathy (BEN) is defined as a slow progressive renal tubulointerstitial disease that mainly occurs in the restricted areas of the Balkan Peninsula. Environmental exposure to toxins such as aristolochic acid (AA) or ochratoxin A (OTA) can be associated with BEN. It has been shown that during their detoxification process free radicals are produced and oxidative stress is increased. However, not all individuals exposed to AA/OTA suffer from this nephropathy, suggesting individual susceptibility to oxidative stress as a possible risk factor. Our aim was to determine whether gene polymorphisms of key enzymes involved in antioxidant defence, glutathione peroxidase 1 (GPX1) and superoxide dismutase 2 (SOD2), can be factors which influence individual susceptibility towards BEN.

Materials & Methods
A total of 240 participants (120 patients and 120 healthy subjects) from endemic areas were enrolled in this study. DNA was purified from EDTA-anticoagulated peripheral blood by QIAamp DNA Blood Mini Kit (Qiagen). GPX1 (rs1050450) and SOD2 (rs4880) genotypes were determined by real-time PCR.

Results
We didn’t find statistically different distribution of GPX1 and SOD2 genotypes between patients and controls. However, individuals carrying variant alleles of these genes, alone or in combination, showed trend towards increased risk of BEN development, but still didn’t reach statistical significance. This was especially observed in SOD2 *TT homozygotes who were in almost 2-fold increased risk of BEN development (OR=1,95 95% CI= 0,93-4,09, p=0.08).

Conclusion
According to our results GPX1 and SOD2 genotypes are not significantly associated with risk development of Balkan endemic nephropathy.
The functional state of the kidneys in patients with hypertension and diabetes mellitus

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Introduction
Chronic kidney disease (CKD) is a condition that reflects the progressive nature of kidney disease, which is based on the mechanisms of formation of nephrosclerosis. The prevalence of CKD is comparable to diseases such as hypertension (HD) and diabetes mellitus (DM), since arterial hypertension and hyperglycemia have a major impact on the functional state of the kidneys. We aimed to conduct a comparative study of glomerular filtration rate (GFR) in patients with HD and comorbid state (HD + DM).

Materials & Methods
We studied the functional status of the kidneys in 53 patients. They were divided into 2 groups: 21 patients with hypertonic disease and 32 patients with comorbid pathology of hypertonic and diabetes. All patients underwent general clinical examination and assessment of the functional state of the kidneys - calculation of GFR using the CKD-EPI formula. Differences were considered statistically significant at p <0.05.

Results
In the HD group, the average value of GFR was 63.12 ± 11.34 ml/min/1.73 m². In the group of HD + DM, the average value of GFR was 58.51 ± 18.05 ml/min/1.73 m². Despite the prevalence of patients with reduced renal function, both in frequency and quantitative terms in the comorbid pathology group, the differences are statistically insignificant (p = 0.302). The content of blood glucose in the group of patients with diabetes was significantly higher than in the group of patients with hypertension without diabetes (p <0.001). Correlation analysis revealed an inverse relationship of the average force between the GFR and the level of the systolic blood pressure (r = -0.417; p <0.05) and diastolic blood pressure (r = -0.449; p <0.05); direct dependence of the GFR value on the HDL content (r = 0.370; p <0.05).

Conclusion
Among the risk factors for CKD in patients of a therapeutic hospital, the leading factors are arterial hypertension, diabetes mellitus, hyperlipidemia, and the level of blood pressure has a greater effect on GFR than hyperglycemia. The combination of two factors (HD and DM) leads to a more noticeable reduction in renal function than the effect of only one factor.
Bladder preservation approach versus radical cystectomy for high-grade non-muscle-invasive bladder cancer: a meta-analysis of cohort studies

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Introduction
High-grade non-muscle-invasive bladder cancer is superficial; nonetheless, it is an aggressive cancer. Proper management strategy selection following transurethral resection between bladder preservation (BP) and radical cystectomy (RC) could result in delayed or excessive treatment. Hence, selecting the optimal treatment modality remains controversial to date.

Materials & Methods
We searched MEDLINE, The Cochrane Library, EMBASE, China National Knowledge Infrastructure, and Wanfang database through 12 April 2018. Quality and publication bias were assessed using the Newcastle-Ottawa Scale and Begg's/Egger's test. We collected 2-year, 5-year, 10-year, and 15-year survival rate and hazard ratio (HR) for overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS). Using the Review Manager 5.2 software, we used the odds ratio (OR) of specific years and HR for meta-analysis. Subgroup analysis was performed by the original tumor state, radical cystectomy timing, bladder preservation modality, and age.

Results
In total, 11 cohorts with 1735 patients were selected for the meta-analysis. All OR of OS supported BP as a better treatment option; however, all OR of PFS had no significant differences. As for CSS, only the 15-year OR reflected a statistical significance preferring RC. Subgroup analysis showed that BP is more appropriate for patients older than 65 and G3 tumor. Limited data demonstrated that late RC (> 3 months) is more effective compared to early RC (< 3 months) and intravesical Bacillus Calmette–Guerin was not statistically different from that of RC. The mixed BP modalities were significantly better compared to RC in OS and worse in CSS, with both having a very low evidence strength.

Conclusion
BP is a superior treatment modality compared to RC, especially for older patients and T1G3 or lower grade tumors. However, the superior BP modality was unclear. Conversely, RC could be a better option for younger patients. More specifically, late RC may be more beneficial but had a very-low-level of evidence. Quality of life should be considered equal to survival outcome; hence, post-treatment follow-up needs to be performed. Prospective randomized studies should be performed to overcome the limitations of this metaanalysis study.
The effect of cimetidine on the glomerular filtration rate during normothermic machine perfusion

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Introduction
Kidneys with questionable quality are being accepted as donor kidneys nowadays and tested with the help of normothermic machine perfusion (NMP). Interpretation of kidney function during NMP is therefore really important since the verdict to transplant the kidney depends on it. In this research, the effect of cimetidine on glomerular filtration rate (GFR) of porcine kidneys is investigated during NMP. Cimetidine blocks the active secretion of creatinine in the renal tubuli, theoretically enabling to measure the GFR more accurately and to not overestimate kidney function.

Materials & Methods
A cimetidine group (n=6) is compared to a control group (n=6). All kidneys undergo 30 minutes of warm ischaemia (WIT), followed by 3 hours of oxygenated hypothermic machine perfusion (HMP) and 4 hours of normothermic machine perfusion (NMP). The perfusion medium consists of autologous leukocyte-depleted blood from the pig supplemented with anti-inflammatory medicines, a vasodilative agent, antibiotics, and a mixture of different nutrients. In the experimental group, cimetidine is added to the perfusion solution during HMP and NMP. During the NMP blood and urine samples were obtained after 15 minutes and for four hours thereafter. At the end of the experiment we performed a biopsy.

Results
No significant difference in terms of creatinine and inuline clearance was found between the two groups. The same accounts for other kidney function markers as fractional sodium excretion and proteinuria. No differences were seen in perfusion parameters like flow rate during HMP and NMP. Also no differences were seen in the relative mRNA expression of OCT2 and MATE2.

Conclusion
Cimetidine has no effect on the glomerular filtration rate in this model and this indicates that creatine clearance during NMP is a filtration driven process. GFR is therefore a safe way to assess kidney function during NMP. Furthermore, the addition of cimetidine did not result in any other significant effects.
Neurology II

Chair

Prof. J.B.M. (Jan) kuks MD PhD

Presenters

Badripour, A. (Abolfazl)
Gadama, Y (Yohane)
Ghaffarpasand, F.G. (Fariborz)
Ibrahimi, J.I. (Jehona)
Luo, MY (Meng)
Mufida A.K (Aldeka Kamilia)
Padvoiskaya, N. (Natallia)
Exploring the potential effects of Spinal Cord Injury on seizure threshold: Results of an animal study

Badripour, A. (Abolfazl) MD

Introduction

Studies have illustrated that 1.2% of the US population suffer from active epilepsy which is one of the most common neurological diseases globally. Furthermore, it has been shown that epilepsy could result in spinal cord injury (SCI) in some patients. Case reports have shown that SCI patients could experience different forms of seizure as well. Interestingly, the effects of SCI on seizure threshold have not been studied before. In addition, prior research has suggested that SCI could lead to inflammatory processes and structural alterations in the brain. The effects of this indictment could uncover potential considerations needed for treatment of epilepsy in SCI patients. In the current study we aimed to evaluate the potential effects of SCI in an animal model of epilepsy and reveal the potential mechanisms involved in this process.

Materials & Methods

In a mice model, SCI was induced by using clip-compression on T9-T10 segments. Then, Pentylenetetrazole (PTZ)-induced seizure threshold was evaluated and compared to sham operated animals 1, 3, 7, 14 and 28 days after SCI. Samples from the frontal section of the brain were taken from another group of saline-receiving SCI mice at each time point to assess the pathological changes and molecular pathways involved in this process.

Results

Results indicated that SCI led to a significant decrease of seizure threshold which lasted through the 28 days' period of study. Moreover, the histopathological assessment of animals' brain indicated the presence of chronic inflammation which was associated with disrupted M1, M2 macrophage ratio. In addition, tissue assessment revealed increased TNF-α and decreased IL-10. These findings were also associated with increased expression of HMGB-1, TLR-4 and NFKB.

Conclusion

The current study shows that SCI leads to decreased seizure threshold through induction of inflammation. Considering these findings further evaluation of CNS alterations and seizure threshold in SCI patients, seems to be a necessary query.
FACTORS OF THE HYPER-ACUTE STROKE PATHWAY MOST INFLUENTIAL IN PRODUCING GOOD PATIENT REPORTED OUTCOMES AT 6 MONTHS

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Introduction
More than 70,000 patients experience a stroke every year in the United Kingdom. In most cases, treatment is provided according to available evidence and consensus about best clinical practice. Post discharge from hospital, clinician-reported outcomes have traditionally been used to judge treatment outcome. Very little information is gathered to understand patient-reported outcomes post-stroke treatment and how these outcomes are linked to the treatment the patients received. Using the complete clinical pathway data collected by the SIGNAL team, this study aims to identify the factors of the stroke pathway that are influential in producing good patient-reported outcomes at six months.

Materials & Methods
We will use data collected from stroke patients between 1st July 2017 and 30th June 2018. We will report the descriptive summaries of; 1) set of clinician-reported outcomes (mRS, NIHSS scores), 2) set of the patient-reported outcomes (SIS, PROMIS). Using the Pearson correlation coefficient, we will try to correlate the patient- and clinician-reported outcomes. A multivariate regression analysis will be done to ascertain factors of the hyper-acute pathway associated with either good or bad outcomes at 6 months.

Results
We hope to report the demographic and baseline clinical characteristics of patients, the summary measures of the different outcome assessment scores, the relationship of the different outcome assessment tools and the relevant factors to be utilized in improving stroke outcome.

Conclusion
The findings of this study are going to inform the adjustments/ improvement in the current data collection of the complete stroke follow-up currently being done at University College London Hospital. We expect to inform the current data collection of the optimal time to complete the patient-reported outcomes (at 3 months or at 6 months) or if both time points are necessary for capturing this data. The knowledge on the factors that influence the outcomes at 6 months will be necessary to stroke professionals to help improve the delivery of care.
Determination of miRNA-199a and its Target Genes in Degenerative Lumbar Intervertebral Disc

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Introduction
Low back pain (LBP) remains among the most common causes of disability and physician referral worldwide. MicroRNAs are short nucleoid intracellular players on various physiologic and pathophysiologic processes in human body. The aim of this study was to determine the expression profile of miRNA-199a-5p in IDD and its correlation to the grade of IDD.

Materials & Methods
This case-controlled study was conducted during a 6-month period from 2017 to 2018 in two university hospitals in Shiraz, Iran. We included 15 patients with grade 3 and 4 of Pfirrmann and 5 patients with traumatic lumbosacral fractures with grade I. Total discectomy was performed in all the individuals and the samples were sent to the laboratory. The NP cells were isolated and the RNA was extracted. cDNA was synthesized by reverse transcriptase and the expression was measured using real-time polymerase chain reaction (RT-PCT).

Results
We overall included 20 patients in two study groups. Both study groups were comparable regarding the baseline and clinical characteristics except for age (p=0.026). The fold change (p=0.007) and relative expression (p=0.012) of the miRNA-199a-5p was found to be significantly higher in patients compared to controls. The fold change (p=0.001) and relative expression (p<0.001) were also associated with the Pfirrmann grading. We found that the area under curve (AUC) was 0.880 (95%CI: 0.721-0.938) indicative of moderate accuracy.

Conclusion
Expression of the miRNA-199a-5p is increased in the IDD. The expression of the miRNA-199a-5p was also associated with the grade of the degeneration based on the Pfirrmann grading.
Pre-stroke statin use was associated with lower risk of in-hospital death

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Introduction

Prior studies suggested that statins might have a neuroprotective effect in patients with acute ischemic stroke. The aim of this study was the evaluation of the short-term effects of statins following ischemic stroke among non-thrombolysed patients.

Materials & Methods

In this cohort retrospective study we have included 810 ischemic stroke patients (mean age 69.7±11.5, 48.6% females), non-thrombolysed on admission. Based on their prior medication history, patients were categorized into pre-stroke statin user and non-statin user patients. The risk of in-hospital mortality was compared between two groups.

Results

Of the 810 ischemic stroke patients, 146 (18.2%) were using a statin before stroke. Statin therapy before stroke-onset was associated with a lower risk of in-hospital mortality (3.4% vs. 26.9%), p<0.001. In the multivariable analysis, statin use was independently associated with a favourable outcome (OR = 0.119, 95% CI = 0.047-0.299, p < 0.001).

Conclusion

Prior statin therapy in patients with non-thrombolysed acute ischemic stroke is associated with lower risk of in-hospital death, and this is independent of other risk factors.
Adaptive changes in dopaminergic system in adult C57BL/6 mice after recovery from cuprizone exposure during early adolescence: implication for schizophrenia

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Introduction
The cuprizone-exposed mouse has been used as an animal model of schizophrenia, a brain disease with abnormalities in dopaminergic function and white matter structure. Previous studies have shown dopamine (DA) changes in brain regions with white matter damage in mice exposed to cuprizone. The aim of the present study was to test a possibility that dopaminergic changes may present in the brain after recovery from an attack to white matter damage.

Materials & Methods
C57BL/6 mice at three-weeks age were used and divided into normal control (CNT) and cuprizone-exposure (CPZ) group, in which mice consumed cuprizone-contained (0.2%, w/w) diet for 10 days starting on postnatal day 28 (P28). Half number of mice in each group were sacrificed on P38, whereas the remaining half number returned to normal diet for 30 days and sacrificed on P68 after behavioral tests. As such protocol, all mice were referred to as CNT38, CPZ38, CNT68, and CPZ68. The brain tissue of sacrificed mice was used for further analyses including ELISA, RT-PCR, and immunohistochemical staining.

Results
Compared to CNT38 group, mice in CPZ38 showed evident demyelination in the prefrontal cortex (PFC) and oligodendrocyte loss in PFC and caudate putamen (CPU). Compared to CNT68, mice in CPZ68 displayed comparable performances in the social interaction and puzzle box tests, but showed anxiety-like behavior in open-field test. No demyelination was found in CPZ68, but oligodendrocyte loss existed in PFC and CPU of the mice. Interestingly, CPZ68 showed a significant DA increase in CPU, but not in PFC. RT-PCR analysis revealed a significant increase in mRNA levels of dopamine 2 receptor (D2 R) in PFC, but not in CPU of CPZ68 mice. The two groups showed comparable mRNA levels of D1 R in both PFC and CPU.

Conclusion
The results suggest a possibility that white matter damage may lead to dopaminergic changes in levels of DA and D2 R mRNA in PFC and CPU, two brain regions compromised in schizophrenia patients.
The Potential of GEMPITA as One of Community-Based Dementia Prevention Program

Tansir, ART (Arif)\textsuperscript{1}, Dianti, NAD Nurita (Nurita)\textsuperscript{1}, Adhari, AIR (Amalia)\textsuperscript{1}, Belarosa, DB (Diadikma)\textsuperscript{1}, Muflidah, AKM (Aldeka)\textsuperscript{1}, Mayza, Adre\textsuperscript{1}

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Introduction
Life expectancy in Indonesia has been increasing from 68.6 to 70.8 years old until 2015. Elderly people is naturally undergone a diminished cognitive and physiological functions. Thus, they are considered prone to degenerative diseases such as dementia. Dementia could be prevented and detected early, one of which is by reservating brain and cognitive functions. Unfortunately, a comprehensive prevention do not available yet. The objective of this study is introducing a program containing an integrated instruments for early detection and prevention programs of dementia called GEMPITA.

Materials & Methods
GEMPITA was attended by 22 elderly people from Lio Village, West Java. The elderly was assessed before and after participating prevention programs using the ABCDEF assessment including Activity based on the Katz Index of Independence; Balance; Cognitive with Mini Mental State Examination (MMSE); Diseases; Emotions, using the Geriatric Depression Scale; and Risk Factors. Prevention programs held were physical activity, watching historical videos, playing Angklung (music instrument), and sharing.

Results
GEMPITA can increase people knowledge about dementia and score of ABCDE screening component after the activity. Knowledge was assessed from average score of pre-test and post-test which increased from 39 to 68. The assessment of activity showed an increase from 6.79 to 7.0. Elderly people who have balance also increased from 16 people to 17 people. The assessment of cognitive using MMSE increased from 25.8 to 26.8 in average. Furthermore, GDS average score which assesses emotion decreased from 12,965 to 12,956.

Conclusion
GEMPITA program can improve the elderly ABCDE component so that it can be used as an effective and comprehensive prevention solution for community-based prevention of dementia.
Algorithm for diagnosing spontaneous dissection of patients with non-atherosclerotic lesions of the main arteries of the head and neck

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Introduction
Currently, dissectional lesions of the brachiocephalic arteries are one of the main causes (up to 25–25% among others) of ischemic stroke and transient ischemic attacks at a young age (up to 45 years), less often - isolated cervical or headache. Timely diagnosis and proper treatment of dissection prevent ischemic and hemorrhagic complications.

Materials & Methods
The main group included 30 patients with non-atherosclerotic (group 1), the control group consisted of 30 conditionally healthy volunteers, matched by sex and age (group 2). All the subjects were subjected to a detailed collection of anamnestic data in order to determine the predisposing and provoking factors, clinical signs, the duration and dynamics of the development of a dissection, the presence of TIA, past surgery and associated diseases. Statistical analysis of the results was carried out using the Statistica 10.0 package.

Results
In patients with non-atherosclerotic lesions of arteries, compared with conditionally healthy control, the most frequent signs of spontaneous dissection were visualization of a double artery lumen (p = 0.011), target sign or crescent sign (p = 0.020), prolonged stenosis (p = 0.039), headache in anamnesis (p = 0.042), prolonged forced position of the head (p = 0.046), change in hemodynamic parameters (p = 0.051), pain in the neck (p = 0.053). According to the results of the binary logistic regression, the identification of the above described signs of spontaneous dissection in patients with non-atherosclerotic lesions of arteries significantly increased the probability of diagnosing a dissection. The odds ratio for these symptoms ranged from 4 to 6. In accordance with statistical significance, the signs were divided into large (statistical significance from 0.01 to 0.02) and small (statistical significance from 0.03 to 0.05). For the selected criteria when conducting ROC-analysis, the sensitivity was 92.9%, specificity - 91.1%, AUC = 0.94.

Conclusion
The proposed algorithm for diagnosing spontaneous dissection is a diagnostic model of excellent quality (AUC = 0.94) with high sensitivity (92.9%) and specificity (91.1%). The algorithm makes it possible to diagnose spontaneous dissection with a high probability, which makes it possible to conduct pathogenetically justified treatment and prophylaxis in a timely manner.
Oncology II

Chair
Annemiek Walenkamp MD PhD

Presenters
Enache, M.I. (Mihaela)
Atreya, C N (Bijjal)
Limonov, D. (Dmitrii)
Miranda-Ramírez, M.W. (Montserrat Wendolyn)
Rozhkova, V. (Veronika)
Shinkevich, V.A (Veronika)
Usalka, O (Olga)
Xu, Q (Qian)
A case series study of concurrent endometrial carcinoma in women with a biopsy diagnosis of endometrial intraepithelial neoplasia

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Introduction
Endometrial intraepithelial neoplasia (EIN)/atypical hyperplasia (AH) is defined as a monoclonal premalignant lesion. Women with EIN have a 45 times increased risk of developing endometrial carcinoma (EC) than those with benign hyperplasia. Also, studies showed that EIN coexists with well-differentiated endometrial carcinoma in 39% of cases.

The aim of this study was to (1) determine the prevalence of concurrent endometrial carcinoma in patients with EIN diagnosis on endometrial biopsy and (2) review Papanicolaou (Pap) tests results in relation with EIN and/or EC presence.

Materials & Methods
We gathered hysterectomy and Pap test results from women with a biopsy diagnosis of EIN (n= 74 patients, age range= 26-77 years old). The patients were diagnosed between January 2018 and December 2018 in the Department of Pathology of the University Emergency Hospital in Bucharest.

Results
Twenty patients had no hysterectomy results in our center. From the patients who underwent hysterectomy, 22.97% (n=17) had EC, 13.51% (n=10) had EIN, 25.67% (n=19) had benign hyperplasia and 10.81% (n=8) had other benign lesions, such as leiomyomas, adenomyosis or endometrial polyps. There were 60.81% (n=45) women without documented Pap results. A diagnosis of atypical glandular cells (AGC) was found in 14.86% (n=11), while 22.97% (n=17) had no glandular modifications and 1.35% (n=1) had inflammation. Eight patients had both EC at hysterectomy and AGC on Pap smear. While Pap smear can’t be used as a screening method for endometrial cancer, abnormal results warrant the need for further investigations.

Conclusion
The rate of concurrent endometrial cancer in our sample was at the low end of the commonly accepted range. Considering the significant number of patients without hysterectomy results, the real value might be higher. Most patients with hysterectomy results presented benign hyperplasia. This finding can have multiple explanations. First, EIN can appear in patients who already have benign hyperplasia. In some cases, the premalignant lesion can be removed in its entirety upon biopsy. Secondly, EIN can involute, leaving the patient with non-atypical hyperplasia or normal endometrium. Therefore, we emphasize the importance of sampling the entire endometrial mucosa in patients with a previous biopsy diagnosis of EIN.
Peri-Areolar Administration of Methylene Blue Dye as an Independent, Cost Effective and Reliable Technique for Sentinel Lymph Node Biopsy in Early Breast Cancer

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Introduction
Sentinel Lymph Node (SLN) biopsy is the standard technique of pathologically staging a clinically negative axilla for decisions on adjuvant treatment. Multiple techniques and materials can be used to identify sentinel lymph nodes, of which, Blue Dye or Radioisotopes are commonly used. Due to high costs of radioisotope techniques, dyes are preferred in the underdeveloped countries. Studies demonstrate dye techniques being equally effective when compared to radioisotopes. In our study, we analyze the efficacy of Methylene Blue for identifying the SLN in clinically negative axilla of early breast cancer patients and determine the best site of administration for superior identification rates.

Materials & Methods
The prospective study between May 2015 to April 2016 comprised of 40 newly diagnosed early breast cancer patients undergoing treatment in the Department of Surgical Oncology of a tertiary medical center in South India. Following Institutional Ethical Committee clearance and informed consent, 3ml of 1% Methylene Blue was injected in the peri-areolar/peri-tumor area of the affected breast. The SLN was identified intra-operatively, and the data was statistically analyzed using SPSS version 24.

Results
Accuracy of identifying the SLN was 94.7% with a false negative rate of 5.26%. The technique demonstrated a sensitivity and specificity of 89% and 100% respectively with a positive predictive value of 100% and negative predictive value of 93.3%. The Identification Rate of Periareolar administration (96%) was significantly (0.003) superior to the Peri-tumoral site (79%).

Conclusion
The high accuracy rate with low false negative rate of Methylene Blue suggests a reliable alternative to radioisotopes or a combination of Radioisotopes and Dye techniques for the detection of SLN biopsies in early breast cancer patients with clinically negative axilla. The Periareolar route of administration should be used to attain better results and higher efficacy rates.
Cancer drug - talazoparib can promote the transformation of normal human cells into cancer cells with BER deficiency.

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Introduction

The BER system is one of the main DNA repair systems in human cells. Suppression of BER in cancer cells is widely used in the treatment of malignant tumors. There is a group of pharmacological agents (e.g. talazoparib) that inhibit one of the key factors of the BER system - PARP-1. Currently, talazoparib is in clinical trials. The effect of talazoparib on cancer cells is well known, but its effect on normal cells has not been studied. The present study was conducted on the effect of PARP-1 inhibition by talazoparib on the functioning of the BER system in normal human fibroblasts HFF-10.

Materials & Methods

HFF-10 cells were treated with either talazoparib in DMSO or DMSO as a control. Using Western-blot analysis, the effect of talazoparib on key repair proteins in these cells was detected: XRCC1, PARP-1, p21, p53, and ATM. Flow cytometry was used to analyze the cell cycle, using the BER-analysis, the DNA repair effectiveness by BER was estimated, and the effect of talazoparib on proliferative ability of HFF-10 cells was also studied.

Results

By the Western-blot was shown that in normal human cells HFF-10 under the influence of talazoparib changing the level of key BER proteins occurred (decreasing of: XRCC1 by 42% CI 3.4-4.7%, PARP-1 by 39% CI 2.8-4.3%, ATM by 45% CI 3.4-4.6%; increasing of: p21 by 141% CI 1.2-2.2%, p53 by 17% CI 3.5-4.9%, pATM by 147% CI 3.7-4.9%) compared to control cells. talazoparib has a significant impact on the DNA repair efficiency by BER system (it decreases by 45% CI 2.3-4.6%) and proliferation of HFF-10 cells (decreased by 49% CI 2.5-4.4%). The increase of the number of cells in the G2 / M phases (by 8% CI 1.6-3.7%) and decrease cells in the G0 / G1 phases of the cell cycle (by 11% CI 2.3-4.4%) is observed.

Conclusion

Many cancers are associated with BER deficiency. There are the decrease of BER efficiency, the arrest of the cell cycle, reduction of cell proliferation after treatment HFF-10 cells with talazoparib, which can cause the transformation of normal cells into cancer. Using talazoparib as a drug against cancer could be dangerous.
Utility of complete blood count and serum albumin levels in the prognosis of brain metastases from solid tumors

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Introduction
Cancer incidence has been increasing; further increasing the risk of brain metastases (BM). BM are associated with high mortality and disability. Clinical markers have been associated with prognosis in patients with BM; however, to date, no serologic markers have been identified. Therefore, we aimed to determine the utility of complete blood count (CBC) parameters and serum albumin levels as prognostic markers in patients with BM.

Materials & Methods
A retrospective review was performed of the records of patients with a confirmed histologic diagnosis of cancer who were referred to the neuro-oncology unit at three centers. Patients for whom CBC and serum albumin levels were obtained within 72 hours of the diagnosis of BM or before the initiation of therapy were included.

Results
In total, 567 patients with BM were included. Breast, lung, urologic, gynecologic, and head and neck cancers were the most common primary cancers. Median overall survival was 11.9 months. A longer survival was observed in patients with hemoglobin (Hb) levels ≥ 12.5 g/dL, albumin levels ≥ 3.5 mg/dL, neutrophil-to-lymphocyte ratio (NLR) ≤ 4, and lymphocyte-to-monocyte ratio (LMR) ≤ 2 (P < 0.0001) and a shorter survival in those with absolute neutrophil count ≥ 5200/mm³ (P < 0.001). After multivariate analysis, adjusted for age, gender, primary cancer, and performance status, all factors remained statistically significant except NLR and LMR.

Conclusion
Hb levels, absolute neutrophil count, and serum albumin levels are individually associated with survival in cancer patients with BM at the time of primary cancer diagnosis.
Factors influencing survival after pancreaticoduodenectomy: unicenter experience

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Introduction
Pancreateicoduodenectomy (PD) is considered as one of the most complicated surgical procedures in abdominal cavity. Despite significant decrease of mortality rate, PD is followed by high level of post-operative complications. The most common ones are pancreatic fistula (POPF) – 10-15% and delayed gastric empting (DGE) – 20-50%. The purpose of our study was to determine the incidence of DGE and POPF, assess impact of these and other potentially risk factors (age, differentiation grade and range of lymphadenectomy) on overall survival. Also we aimed to assess the influence of POPF on the occurrence of DGE.

Materials & Methods
We analyzed 73 patients who underwent pancreaticoduodenectomy between 2012 and 2014 for malignant and benign tumors of pancreato-duodenal region. Complications were defined according to the guidelines of the International Study Group of Pancreatic Surgery. Categorical data were compared using the Fisher’s exact test as appropriate. Kaplan–Meier survival curve estimates and log-rank tests were used to compare survival rates.

Results
POPF was present in 36 patients (49,3%), comprising grade A in 3 (4,1%), grade B in 17 (23,3%), and grade C in 16 (21,9%). DGE was present in 58 patients (79,5%), comprising grade A in 33 (45,2%), grade B in 11 (15,1%), and grade C in 14 (19,2%). Patients with POPF grade C had lower OS, compared with patients who had POPF grade A and B or didn't have this complication at all (p=0,0005). DGE had a significant association with POPF (p=0,007). We didn’t find correlation between POPF incidence and extent of lymphadenectomy (p=0,071). Also we didn’t prove impact of DGE grade, patients’ age (two groups were defined according to WHO standards - <44 and ≥44 y.o.) and grade of tumor differentiation on OS (p=0,55, p=0,093 and p=0,1054, respectively).

Conclusion
POPF (especially grade C) negatively affects overall survival and is associated with DGE incidence. Extent of lymphadenectomy, patients’ age and tumor differentiation have no influence on OS.
Experimental model of DNA-vaccination against neuroblastoma based on the tyrosine hydroxylase gene

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Introduction
Morbidity of neuroblastoma is very common in children under 5 years old. Most of them at the time of diagnosis have an extensive metastatic tumor and, accordingly, an unfavorable prognosis. DNA-vaccination is a kind of therapeutic vaccination, where antigen is supplied as a DNA construct. The aim of the work was to conduct experimental DNA vaccination of mice against neuroblastoma based on the tyrosine hydroxylase (TH) gene, followed by an assessment of the immune response development.

Materials & Methods
As the object of study to assess the survival in the experiment used mice of the A/J line (n = 53), aged 8-10 weeks. NB41A3 cells in the amount of 1 million were inoculated subcutaneously into mice (n = 36). On the 5th, 10th and 15th day after tumor grafting, an intramuscular injection of the DNA vaccine pING-miniTH-PVXCP was performed in an aqueous solution and in combination with 8 kDa polyethyleneimine (PEI) in a 1:5 ratio. To assess the development of the immune response were used immunological research methods.

Results
The immunogenicity of DNA vaccine with PEI, as a carrier, leads to an increase in cytotoxic activity in mice (p <0.05, median - 38.3% versus 13.4%), as well as an increase in the production of interferon gamma in the Elispot test in three times (p = 0.12) compared with the control. In the group of mice that received the vaccine preparation with PEI, the lowest rate of tumor progression was observed compared with the placebo group (p = 0.015). The overall survival of this group of animals was also significantly higher compared with the placebo group (81% vs 10%, p <0.01).

Conclusion
It was found out that vaccination of mice with plasmid DNA conjugated to polyethyleneimine (PEI) leads to a significant decrease in tumor progression in the mouse neuroblastoma model and an increase in the survival rate of mice compared to the placebo control group and the group receiving the vaccine aqueous solution.
The influence of bortezomib and docetaxel on chromatin modifications

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Introduction
Disruption of the epigenetic regulation of transcription is one of the processes, leading to carcinogenesis. DNA methylation and histone modifications play a key role in epigenetic regulation of gene expression. Histone modifications are controlled by the balance between different modifying enzymes – histone deacetylases, acetyltransferases and methyltransferases, while DNA methyltransferases mediate DNA methylation. Changes of these enzymes activity lead to chromatin structure alterations and defects in in normal gene expression profile.

In this study, we investigated influence of docetaxel and bortezomib treatment on expression of genes, that encode chromatin-modifying enzymes, and histone H3 and H4 modifications.

Materials & Methods
The following genes were selected for the study: HDAC1, SIRT1, SETD1A, SETD1B, HAT, GCN5, DNMT1, DNMT3A, DNMT3B. Gene expression analysis was performed using Real-Time PCR. Changes in the level of histone modifications H3acK9, H3me3K4, H4me3K20, H3me3K9 were analyzed by Western blotting.

Results
We showed that bortezomib treatment causes decrease of expression of DNMT1, DNMT3a and DNMT3b genes and increase of SETD1B expression level. Docetaxel treatment led to statistically sufficient increase in SIRT1, SETD1A expression and to decrease in mRNA levels of GCN5 and HAT genes. Further we demonstrated that bortezomib treatment reduces level of H4me3K20 (typical mark of tumorigenesis) and increases level of histone modification H3me3K4 (typical for active chromatin).

Conclusion
Taking into account that bortezomib inhibits expression of DNA methylation genes and alters histone modifications we propose that bortezomib can activate epigenetically repressed genes and might be investigated as an adjuvant epigenetic therapy for various tumors. However, docetaxel treatment is able to provoke negative epigenetic changes leading to chemoresistance.
Non-specific immunoglobulin G is effective in preventing and treating cancer in mice

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Introduction
Previous accidental findings showed that administration of immunoglobulin G (IgG) in treating autoimmune diseases was able to inhibit cancers that happened to grow in these patients. However, such treatment has not been used to treat cancer patients clinically. The mechanism and optimal dosages of this treatment have not been established. Subsequent animal experiments confirmed this effect, but all previous studies in animal models used human IgG which was heterogeneous to the animal hosts and therefore could adversely interfere with the results.

Materials & Methods
We tested different dosages of mouse IgG in treating and preventing three syngeneic cancer types (melanoma, colon cancer, and breast cancer) in three immune potent mouse models. The expression of Ki67, CD34, VEGF, MMPs, and cytokines in tumor tissues were examined with immunohistochemistry or quantitative real-time PCR to evaluate tumor proliferation, vascularization, metastasis and proinflammatory response in the tumor microenvironment.

Results
We found that low-dose IgG could effectively inhibit cancer progression, regulate tumor vessel normalization, and prolong survival. Administration of IgG before cancer cell inoculation could also prevent cancer from developing. In addition, IgG caused changes of a number of cytokines and skewed macrophage polarization toward M1-like phenotype, characterized by proinflammatory activity and inhibition of proliferation of cancer cells.

Conclusion
Our findings suggest that non-specific IgG at low dosages could be a promising candidate for cancer prevention and treatment.
Paediatrics

Chair

Elisabeth M.W. Kooi MD PhD

Presenters

Kreicberga, Z.K. (Zane)
Kuśmierczyk, H. (Hanna)
Mesceriakova, V.M. (Vitalija)
Myslytska, H. (Hanna)
Novysedláč, R. (René)
Ortemenka, Ye. (Yevheniya)
Yuwanto, Maulidyah, F. (Fatika)
PARENT ASSESSMENT OF VACCINE-PREVENTABLE DISEASE SEVERITY

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Introduction
Although vaccination is available for every child, there are cases of vaccine-preventable diseases in Latvia with severe complications, it begs to question, why parents still choose to not vaccinate their children. Therefore the purpose of study was to determine parent assessment of vaccine-preventable disease severity and to evaluate differences of severity assessment depending on the child's vaccination status.

Materials & Methods
An anonymous survey of parents whose children are younger than 7 years was conducted. Data was collected by questionnaires in 6 kindergartens during December 2018 and on the internet site www.facebook.com in January 2019. Parents were asked to evaluate severity of 11 vaccine-preventable diseases in a scale from 0 to 10 (10 being the most severe).

Results
1084 parents participated in survey, 93 parents in kindergartens (group-1) and 991 in Facebook (group-2). In group-1 87% of parents vaccinated their children, 10% - partially vaccinated and 3% did not vaccinate their children. In group-2 79% of parents vaccinated their children, 14% - vaccinated partially and 7% did not vaccinate their children. In both groups vaccinated kids' parents evaluated diseases more severely than in not vaccinated, by giving diphtheria - 8.71, tetanus - 8.81, pertussis - 8.56, measles - 7.81, chickenpox - 6.54, tick-borne encephalitis - 8.77, influenza - 7.29, rota virus - 6.65, virus hepatitis B - 8.54, mumps - 7.82, tuberculosis - 8.89 points. Nonvaccinating parents evaluated diseases as less dangerous, giving fewer points, to some diseases more than twice less, by giving diphtheria - 6.51, tetanus - 6.80, pertussis - 5.32, measles - 4.65, chickenpox - 2.88, tick-borne encephalitis - 5.77, influenza - 3.68, rota virus - 2.98, virus hepatitis B - 5.74, mumps - 4.64, tuberculosis - 5.91 points.

Conclusion
Parents who do not vaccinate children assessed diseases as potentially less dangerous than those who vaccinate their children. Overall parents consider chickenpox to be the mildest disease, then rota virus and then influenza, but most severe - tetanus, tuberculosis and diphtheria. Parents who do not vaccinate their children are more active on the internet and express their opinion more than parents in kindergartens.
Multicentre evaluation of glycemic control in children and adolescents with type 1 diabetes in Poland

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Introduction
Despite great therapeutic advancements, majority of children and adolescents with type 1 diabetes (T1D) present unsatisfactory diabetes control assessed by glycated haemoglobin (HbA1c). This creates a need for systemic interventions and improvements in diabetes care system. However, such steps must be based on reliable, large-scale studies assessing the present state of glycemic control and verifying effects of any interventions.

Materials & Methods
Invitations to participate in the first nationwide study were sent to all paediatric diabetes care centres in Poland. In those who accepted, the study was carried out simultaneously for one week in March 2018. During visits, each child treated for T1D over 1 year was included into study. The protocol included collection of capillary blood sample and a clinical questionnaire filled by the doctor or nurse. Afterwards, blood samples and matching questionnaires were blinded and sent to the organising centre. HbA1c was measured by high-performance liquid chromatography. Patients whose clinical data were incomplete or whose treatment model was changed within the last 6 months were subsequently excluded from analysis.

Results
Out of 28 approached centres, 25 agreed to take part in the study, providing adequate samples and data for 902 patients [52% boys, median age 12.6 years (25-75%: 9.7-15.5), median diabetes duration 45 years (25-75%: 2.7-7.3)], which covered approximately 8% of the whole Polish pediatric population with T1D. Majority of the patients (80%) were treated with continuous subcutaneous insulin infusion, 26.5% used some type of continuous glucose monitoring. Median HbA1c in the studied group was 7.1% (25-75%: 6.6-7.8), 22.8% of the children achieved the target level of HbA1c according to Polish Diabetes Guidelines (HbA1c ≤ 48 mmol/mol [≤6.5%]), and 45.2% according to ISPAD Consensus Guidelines 2018 (HbA1c &lt;53 mmol/mol [&lt;7.0%]). During one month preceding the study, 1% of children experienced severe hypoglycemia and 0.55% suffered from ketoacidosis.

Conclusion
Overall glycemic control in Polish children with T1D is satisfactory, although there is still room for improvement. As a first nationwide assessment, the study provided a good reference point for the future.
The greatest impact on parents opinion about children vaccination is made by health care specialists

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Introduction
Global vaccination is one of the greatest achievements in medicine, which resulted in the decrease of life-threatening illnesses. However, over the past decade, the number of people who doubt the benefits of vaccination has increased.

Materials & Methods
A questionnaire survey was conducted in Vilnius pre-school institutions in the period from 2017.12 to 2018-05. 329 parents of children aged from 1 to 4 participated in the survey. The respondents were compared by gender, education level, age, number of children in the family and which healthcare specialist they usually apply to. The data are processed by SPSS 22.0 program, the difference between the compared groups is considered significant when p≤0.05.

Results
250 (75.99%) of the respondents assessed the benefit of the vaccine by 8 points or more in the scale from 1 to 10. Parents who at least once have visited homeopath to value vaccines benefit only 6.33 out of 10 points. Parents with lower education are more likely to believe that it is better for their children to gain immunity by illness than get vaccinated (lower - 41.33%, and higher education - 24.39%). 52 (38.24%) mothers and 13 (9.35%) dads state that their children do not need vaccinations from diseases that are not common now. Most parents, 175 (94.09%) mothers and 121 (85.21%) dads came across negative information about vaccination. Most parents have received negative information from the Internet 229 (69.60%). However, such parents tend to rate benefits of vaccines much better (8.24 out of 10 points), than respondents (57 (17.3%)), who at least once received negative information from health care specialists (6.40 out of 10 points).

Conclusion
The common respondents’ opinion on the vaccines is good. Gender and education have a significant influence on the perception of vaccines, but the biggest impact on the opinion is shaped due to an insufficient amount of the reliable information and the negative information received from healthcare specialists.
Cytological profile of induced sputum in school age children with severe atopic bronchial asthma

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Introduction
Published data regarding the association of the asthma severity with a type (eosinophilic, noneosinophilic) of airway inflammation remains controversial. The aim of the survey was study the cytological profile of induced sputum in children with severe atopic asthma.

Materials & Methods
In pulmonology department of the Chernivtzi Regional Children Clinical Hospital 43 school age children with atopic BA have been examined. A cytological analysis of induced sputum has been done by the method of Pavord I.D. (1996). The first (I) group was formed from 24 children with severe BA. The second (II) group included 19 patients with moderate BA. The results were analyzed by parametric (Pt, Students’ criteria) and nonparametric (Pu, Mann-Whitney U test; Pφ, Fisher’s angular transformation) methods of calculation.

Results
The cellular composition of the induced sputum of children with severe asthma was: 7,3±1,4% of eosinophils; 51,0±3,9% of neutrophils; 33,0±4,9% of alveolar macrophages, 10,9±2,9% of lymphocytes. In the cytological profile of sputum in patients of the II group there were included: 4,1±1,8% of eosinophils (Pu<0,01), 56,0±6,7% of neutrophils (Pt<0,05), 28,2±6,4% of macrophages (Pt<0,05), 11,2±3,7% of lymphocytes (Pt<0,05). Amount of eosinophils in induced sputum ≥3% has been noted in 70,8% of patients with severe BA, but only in 26,3% of patients in the II group (Pφ<0,01). It should be noted that the relative content of lymphocytes in induced sputum was three times higher than the normal regional rate (3,1±0,6%) in children with severe asthma (10,9±2,9%; Pt<0,05) as well as in patients with moderate BA (11,2±3,7; Pt<0,05). Severe BA associated with significant (the number of desquamated cylindrical epithelial cells in sputum ≥50%) damage of bronchial epithelium in every third (29,3%) patients in comparison to the quarter of cases in II group (Pφ<0,05).

Conclusion
The severe phenotype of atopic asthma in school-aged children characterized by mixed (hypereosinophilic response with moderate lymphocytic reaction) type of airways’ inflammation, associated with expressive damage of bronchial epithelial layer.
Comparison of metabolic control of children with T1D onset before 6 years of age by type of treatment

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Introduction
Modern technology has changed the patient's DM I type therapy, and their effective use in young children has not yet been mapped. The aim of our study was to evaluate the effect of CGM use on metabolic control in this age category and compare its effectiveness with different treatment modalities (Pens or pumps).

Materials & Methods
The study included 109 children with Type I DM (56 boys) follow up at the Pediatric Dpt Motol Hospital and with T1D onset between 6 months and 6 years of age between 2014 and 2018. We analyzed data of metabolic control in the 3-months period since onset for next 2 years retrospectively. Use of the CGM sensor, type of treatment - pen, pump, HbA1c, basic biochemical values, weight were compared. In addition, time in target (3.9-10 mmol / l), time in hypoglycaemia (&lt;3.9 mmol / l), mean glycaemia and standard deviation of glycemia were analyzed in all patients on CGM in the last 14 days in 3-month interval. The data were statistically processed using the random effect model of repeated measurements.

Results
The mean age of T1D onset in our cohort was 3.2 ± 1.7 years and the mean follow-up was 3.1 ± 1 years. Of the cohort, 63 patients (58%) used at least 50% of the time CGM since onset. CGM using led to significant improvement of metabolic control (HbA1c 49 vs 56 mmol / mol, p = 0.006). Of the total number of 63 children, 24 individuals (38%) were treated by insulin pump for at least 50% of the follow-up time. Time spent in the target range (65 vs. 67%, p = 0.8), time spent in hypoglycaemia (7 vs. 6%, p = 0.7), mean glycaemia (8.3 vs. 8.3 mmol / = 0.9), variability (SD 3.2 vs. 3.3, p = 0.7) was not significantly different between CGM-insulin-treated patients and CGM and insulin pump.

Conclusion
The therapeutic modalities leading to improved metabolic compensation in the youngest children is CGM regardless of insulin pen or pump therapy.
Influence of the long-term use of low/medium or high doses of inhaled corticosteroids on development of obesity and growth retardation in children with bronchial asthma

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Introduction
The low adherence of children with bronchial asthma (BA) to long-term control treatment is partly associated with the patients' fear of obesity and growth retardation due to the use of inhaled corticosteroids (ICS). The aim of the survey was to evaluate the physical development of children who have had background long-standing controller therapy of asthma by low/medium or high-dose ICS.

Materials & Methods
On the basis of the pulmonological department of the Regional children clinical hospital in Chernivtsi city 50 school-aged patients with persistent BA have been examined. Anthropometric examination has been performed for all patients. The assessment of physical development with the calculation of the body mass index (BMI) of patients has been done by a centile method, taking into account the age of the patients. In the I clinical group 21 patients under the long-term usage of low/medium doses of ICS were enrolled, and the second (II) group consisted of 29 patients who used long-lasting high-dose ICS to control asthma.

Results
Patients of the II group have been received high-dose IGC significantly longer (6.7±0.7 years) relatively to patients of the I group who has had background therapy of low/medium doses of ICS on average for 4.2±0.7 years (P <0.05). In spite of the fact that short stature (growth with respect to age <10 percentile) has been registered in children who received high-dose ICS twice as frequently (10.3% of cases) as patients of group I (4.8%), this difference was statistically insignificant (P> 0.05). Although obesity (BMI> 25 kg/m²) has been registered three times more common in patients of group II (13.8% of cases) than children of the I group of comparison (4.8% of subjects; P< 0.05), the correlation analysis did not reveal statistically significant relationship between overweight (according to BMI) and the duration of high-dose ICS use (r = 0.16; P=0.42).

Conclusion
At that, prolonged background therapy by low/medium or high-dose ICS had not had statistically significant influence on the physical development of the school-aged asthma patients.
Novel Expressive Art Therapy Can Decrease Maladaptive Behaviour on Acute Illness and Hospitalized Preschool Children

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Introduction
Minor and major procedures can be the main sources of pain and stress for preschoolers who the ones with acute illness and experiencing their first hospitalization. The adaptation process of children with hospitalization stress is dominated by maladaptive behaviour. Expressive Art Therapy is novel therapeutic modalities for increasing children's understanding about their conditions and easier expressing the feelings. The aims of this study was to assess the effectiveness of expressive art therapy towards maladaptive behaviour on acute illness and hospitalized preschool children.

Materials & Methods
Quasi-experimental with pretest-post test control group was conducted in hospitalized preschool children on 32 samples in Type B Hospital around Malang City. Purposive sampling was employed in two groups: treatment and control. Pre test and post test conducted through Children Behavior Checklist 1½ - 5 (CBCL) to assess maladaptive behaviour in preschool children. The Expressive Art Therapy was given to treatment group by using a combination of method choosing coloured images, storytelling and singing for 30 minutes each meeting for 3 consecutive days, while control group received hospital standard treatment in same duration. Thirty two preschool children included for analysis and the score of two group were analyzed using independent t-test. P-value <0.05 was considered as statistically significant.

Results
In treatment group, mean level of maladaptive score was 90.63 (pre test) and 75.19 (post test). In control group, level of maladaptive score was 87.38 (pre test) and 81.13 (post test). Independent T-test shows that the Treatment group exhibited a significant decrease in maladaptive behavior (p <0.05) compared to the control group.

Conclusion
Expressive art therapy can decrease maladaptive behaviour on acute illness and hospitalized preschoolers. This novel therapy has potentiality to be used as a non-pharmacological treatment in preschoolers to decline maladaptive behaviour.
Pathology

Chair
Bert van der Vegt MD PhD

Presenters
Dsouza, A.L. (Adail)
Huang, Q (Qin)
Nahari, S. (Sahira)
Sachdeva, S.S (Sanjana)
Shetty, A. S. (Ananya)
Tukinova, G. (Gulfairuz)
Yuan, YMH (MingHeng)
Expression of Ki-67 in papillary urothelial neoplasms of low malignant potential and non-invasive papillary urothelial carcinoma

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Introduction

Urothelial carcinoma (UC) is the second most common malignancy of the genitourinary tract. According to the World Health Organization (WHO 2016), noninvasive papillary urothelial neoplasms include papillary urothelial neoplasm of low malignant potential (PUNLMP), noninvasive papillary UC-low grade (LGPUC) and high grade (HGPUC). Inter-observer variability on histomorphology leads to marked subjectivity in diagnosis. In this study we have evaluated the utility of Ki-67 expression to differentiate noninvasive papillary tumors of the bladder.

Materials & Methods

This is a retrospective time bound observational study conducted over a period of 5 years (2013-2017) in a tertiary health care center in South India. The study was commenced after acquiring approval from the intuitions ethics committee. All cases reported as PUNLMP, LGPUC and HGPUC on histomorphology were reviewed and analyzed with IHC marker Ki-67 done on representative slides. The Ki-67 expression percentage was calculated as the ratio of cells with moderate to strong nuclear staining with Ki-67 per the total number of cells in the area under high power magnification. A cut off of 10\% was used to divide cases into low and high Ki-67 expression. Chi-square test was used to determine the p value. A p value of \textless 0.05 was considered statistically significant.

Results

A total number of 43 cases- PUNLMP (n=7), LGPUC (n=35) and HGPUC(n=1) were studied. The Ki-67 staining in all PUNLMP cases was \textless 10\% with a mean of 4.86\%, 1-50 in LGPUC with a mean of 14.78\%. The above parameters could not be assessed in HGPUC due to limited sample size (n=1). Ki-67 staining correlated significantly with an increase in histological grade (p=0.006). The histomorphology of few cases were reviewed following a discrepant Ki-67 staining and reclassified based on a consensus of 2 observers.

Conclusion

An increased Ki-67 was seen with increasing grade of the lesion. Thus Ki-67 helps in differentiating these lesions and can be used as an adjunct to histomorphology to increase the accuracy of diagnosis.
Validation of the laboratory specific Ki67 cutoff value as a prognostic factor in ER-positive, HER2-negative, stage I-III invasive ductal breast cancer

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Introduction
Immunohistochemical assessment of Ki67 has been proposed as a valuable marker to distinguish high-risk patients in estrogen receptor (ER)-positive, HER2-negative breast cancer. Nevertheless, the cutoff value to define higher and lower Ki67 expression remains controversial in different studies, and the most common of these are 14 and 20%. Since the measurement of Ki67 has not been standardized among institutions, the laboratories are therefore likely to have their specific Ki67 cutoff values, which might be more reliable than the value of 14% and 20%. Here we aimed to calculate our laboratory specific Ki67 cutoff value and validate its prognostic value.

Materials & Methods
Tissue samples from primary ER-positive, HER2-negative, stage I-III invasive ductal breast cancer patients were collected. Male patients, patients received preoperative chemotherapy, patients had previous malignant tumor and patients with bilateral tumors breast cancer were excluded. Ki67 was assessed as a continuous variable by immunohistochemistry. Time-dependent survival receiver operating characteristic (ROC) curve was generated to determine our laboratory specific Ki67 cutoff value. We validated its prognostic value by evaluating the correlation between higher Ki67 with the overall survival (OS) and with other prognostic factors.

Results
A total of 385 patients (median age 50 years, range 24–82 years) were enrolled between August 2000 and October 2016. Median Ki67 was 30% (1-90%), and median follow up was 36.9 (range 1.0~85.9) months. The optimal cutoff value calculated by time-dependent ROC curve was 30%. In the univariate analysis, higher Ki67 (≥30%) was significantly associated with worse OS (log-rank P=0.04). Compared with patients with Ki67≥14%, patients with Ki67<14% showed no significant association with longer OS (log-rank P=0.10); whereas patients with Ki67<20% and ≥20% also had similar OS (log-rank P=0.07). Moreover, Ki67≥30% was significantly correlated with adverse prognostic factors such as younger age, larger tumor size, PR negativity and higher histologic grade. In the multivariate Cox analysis, after adjusting for other clinicopathologic features and treatment, Ki67≥30% remained an independent prognostic factor for OS (HR=9.11, 95% CI 1.08–77.15, P=0.043).

Conclusion
Our results showed that our laboratory specific Ki67 cutoff value was 30%, which was more reliable than the value of 14% and 20%.
Aberrant expression of CA-125 and CA 19-9 in diffuse large B-cell lymphoma with relation to clinicopathological features and prognosis

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Introduction

CA-125 and CA 19-9 are carbohydrate antigens that are expressed in some epithelial tumors especially ovarian and pancreatic cancers. Serum CA-125 level was reported to be associated with adverse prognostic factors and worse survival in non-Hodgkin lymphoma (NHL) patients. Exact relations with cases of diffuse large B-cell lymphoma (DLBCL) are not conclusive. Previous studies had focused on serum levels, but not tissue expression of CA-125. Moreover, CA 19-9 expression in cases of nodal DLBCL was not previously investigated.

We aimed to explore whether CA-125 and CA 19-9 are expressed in nodal DLBCL tissues using immunohistochemistry (IHC) and whether these expressions are related to clinicopathological features and survival of the patients as in case of serum levels.

Materials & Methods

Sixty-five cases of DLBCL were included in this study with revision of all their clinicopathological data and tumor slides. Manual TMA blocks were constructed using modified mechanical pencil tip method, immunohistochemical staining for CA-125 and CA 19-9 was done and semi-quantitatively scored. All relations were analysed using established statistical methodologies.

Results

CA 19-9 was aberrantly expressed in 8 (12%) of cases, however, there was no expression of CA-125 in any of the cases. Seventy-five percent of the cases that showed positive CA 19-9 were significantly associated with anemia and performance status 1 (p=0.009 and p=0.024 respectively). Also, 75% of the cases that showed positive CA 19-9 were females, however this approached but didn't reach statistical significance (p=0.052). The median overall survival for cases that showed aberrant CA 19-9 positivity was 18 months, compared to 43 months for negative cases (p=0.879). So, CA 19-9 expression is not an independent prognostic factor in cases of DLBCL.

Conclusion

CA-125 was not expressed in nodal DLBCL tissues, necessitating re-evaluation studies of serum CA-125 levels in DLBCL patients specifically, not in all NHL patients. On the other hand, CA 19-9 was aberrantly expressed in 12% of nodal DLBCL cases with significant relation to anemia and PS 1 but not with survival. Therefore, further studies are recommended to elucidate the possible relation of serum and tissue CA 19-9 levels to further clinicopathological features of nodal and extranodal DLBCL patients.
**p16 expression in Urothelial tumors: Experience from a tertiary care hospital of coastal India**

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**Introduction**

Human papilloma virus (HPV) is a known etiological factor for cervical cancer. There have been several hypotheses that HPV can also be the causative agent in several other cancers involving the epithelium such as urinary bladder, prostate, penile skin. A relationship between urinary bladder cancer and HPV has been indicated in several studies but the results have been controversial. p16 immunohistochemistry (IHC) is a proven surrogate marker for presence of HPV infection. p16 expression has been seen in 4% to 50% of tumors in different studies. Hence, we conducted the study to evaluate p16 antigen expression in urothelial tumors and correlate with clinico-pathological and morphological features of the tumors.

**Materials & Methods**

p16 expression was evaluated in 72 cases of urothelial tumors and 20 cases of non-neoplastic bladder lesions. IHC was done and p16 staining intensity was graded on a scale from 0 to 3+. Nuclear and cytoplasmic staining of more than 50% cells was taken as positive (3+). A descriptive analysis was made of all the study variables. In order to compare the variables, cross tables were generated, and associations were analyzed using the Chi-Square test and Fisher’s exact test.

**Results**

p16 expression was seen in 19 (26.4%) of the cases (3+ positivity seen). High grade urothelial neoplasms were significantly associated with p16 expression (p-value=0.004), similarly 73.7% of the tumors with positive p16 expression were of invasive type (p value<0.05). There was no significant association between clinico-pathological characteristics like age, gender, size of tumor and p16 expression. None of the non-neoplastic urothelial lesions or precursor lesions showed positive p16 expression.

**Conclusion**

p16 expression can provide essential information on the prognosis of patients by correlating with tumor grade and stage. The presence of p16 in urothelial tumors will provide a new target allowing individualized patient treatment. Also, HPV vaccine is available and optimal evaluation of it for preventing bladder cancer may be done.
A study of p63 expression in papillary lesions of the breast to evaluate its utility as a marker to distinguish benign from malignant lesions.

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Introduction
Papillary lesions of the breast are very rare. Overlapping clinical and radiologic features are demonstrated by these lesions but may have diverse clinical outcomes. Identification of myoepithelial cells plays an important role in the categorization of these tumors into benign and malignant. There are numerous studies in literature describing the usage of various myoepithelial cell markers in breast tumors in general. But studies pertaining to papillary lesions are very rare.

Materials & Methods
This retrospective study of samples collected over a period of five years. Detailed clinical information was recorded from case sheets. All the histopathological sections were stained with Haematoxyline & Eosin (H&E) and reviewed. We performed Immunohistochemistry (IHC) for marker P63 on these tumors. We graded p63 staining in the tumors from 0 to 5 depending on the percentage of the cells showing positivity.

Results
Of 1737 cases of breast specimens we received, we had total 36 cases (2%) of papillary lesions of the breast. All these are excision specimens. We had 14 cases of papillomas, 7 cases of papilloma with atypical ductal hyperplasia (ADH)/ductal carcinoma in situ (DCIS), 2 cases of intraductal papillary carcinoma (IDPC), 3 cases of intra cystic papillary carcinoma (ICPC), 2 cases of solid and 8 cases of invasive papillary carcinomas (IPC). In benign papillomas all cases showed myoepithelial staining for the peripheral rim of the tumor. Staining of the central part of the tumor varied in different tumors. In case of Papilloma with DCIS/ADH, IHC with p63 there was negative staining in atypical areas. In IDPC, ICPC, solid PC, IPC p63 was negative in the tumoral and peripheral rim of the tumor.

Conclusion
All the cases of IPCs, IDPCs, ICPCs, solid PC showed negative staining for p63. Papilloma with ADH/DCIS showed negativity in atypical areas. Thus p63 is a valuable tool in identifying and confirming the malignant papillary tumors.
Comparison of morphofunctional features in testes of rat exposed to activated and non-activated manganese dioxide.

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Introduction
The results of long-term experimental studies conducted by pathomorphologists showed hypersensitivity of reproductive system after radiation effect. The majority of these studies were conducted using external radiation sources. However, there is no consensus on the effect of other irradiation options to the testicular tissue. In our work we have tried to determine the effect of the combined of radiation due to the inhalation pathway to the male reproductive system.

Materials & Methods
In experiment we used 4 groups, namely sexually mature “Wistar” male rats in an amount of 180, weighing 190–237 g. The 1st group was represented by the rats irradiated by manganese dioxide by a neutron flux. The 2nd group consist of the rats exposed to inhalation of non-activated manganese dioxide. The 3rd group of the rats subjected to total γ-irradiation. The 4th group was control rats. Euthanasia of animals was carried out on the 3rd, 14th and 60th day after exposure. Histological and immunohistochemical methods are used.

Results
On the 3rd day: there was a significant decrease in the number of spermatids in the epithelium in group with a higher dose of 56Mn. The dynamics to decrease of glandulocytes number was noted, which was significant in group exposed to inhalation. On the 14th day: there was an increase of the tubular lumen. A significant decrease of glandulocytes number was found in group of inhalation. Content of p53 protein dramatically increased. Of Ki67-positive cells number decreased in the group of inhalation, while in the other groups there was increased. On the 60th day: a sharp excess of lumen of convoluted seminiferous tubules was revealed. The p53 content was repeatedly exceeded in the studied tissues. There was an increase in the content of Ki67-positive cells. The excess of 56Mn over the control in high doses group reached 3,2 times.

Conclusion
The study of 56Mn effect on rat testes revealed the level of risk of low-dose internal irradiation that is confirmed by the presence of inflammatory, dystrophic and necrobiotic processes.
MicroRNA-488 inhibits motility and migration of tumor cells via down-regulating Fascin in breast cancer

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Introduction
Breast cancer is the most common cancer in female worldwide, and metastasis is the leading cause of mortality in patients with breast cancer. Accumulating evidence demonstrated that miRNAs contribute to carcinogenesis and metastasis as oncogenes or tumor suppressor genes. However, only a few microRNA target genes were elucidated in the mechanism of metastasis. In this study, we focused on Fascin, an actin bundling protein, and miRNAs regulating Fascin expression in promoting motility and migration of breast cancer cells, and aimed to reveal the underlying mechanism of metastasis in breast cancer.

Materials & Methods
Candidate miRNAs targeting Fascin were predicted using TargetScan. Western Blot and RT-PCR were performed to examine the expression level of Fascin and candidate miRNAs. Reporter gene containing 3'-UTR of Fascin was used to confirm the regulation mechanism of Fascin. Wound healing and transwell assays were conducted to examine Fascin and candidate miRNAs’ effects on mobility and migration of breast cancer cells.

Results
Using TargetScan, miR-488 was predicted to be candidate miRNA regulating Fascin. In breast cancer cells, the expression of miR-488 was negatively associated with Fascin level. Reporter assay showed that miR-488 directly targeted Fascin and down-regulated the expression of Fascin. Wound healing and transwell assays indicated that miR-488 could inhibit the mobility and migration of breast cancer cells, and the suppression effects of miR-488 could be rescued by overexpression of Fascin.

Conclusion
In conclusion, our study demonstrates a new tumor suppressor gene—microRNA-488 in breast cancer, inhibiting the migration and invasion of breast cancer cells, via down-regulating the Fascin level, which provides a new theory for the effect of Fascin on breast cancer cells motility.
Pharmacology II

Chair
Leo E. Deelman PhD

Presenters
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Aranda, N. A. (Nicolás)
Goswami, K.S. (Kavisha)
Shiravand, S.S.H (Sepideh)
Shour, S.SH. (Sara)
Titov, O (Oleg)
Yu, Z. (Zijia)
Zhukova, O.V. (Oksana Valentinovna)
Kothari, A. (Arpit)
The cytotoxic compound derived from Sophora pachycarpa’s root extract is Alopecurone A.

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Introduction
Cancer is to be known as one of the most major causes of mortality throughout the world. As synthetic drugs which are used as the treatment, have a wide range of side effects and interactions, investigation for finding natural cytotoxic agents as sources of anti-cancer compounds in plants are attracting more attentions. Some species of Sophora genus from Fabaceae family, have shown anti-proliferative effects and also induced apoptosis activity in human’s prostate cancerous cell lines (DU145). In This study, the active cytotoxic compound in Sophora pachycarpa’s root was recognized.

Materials & Methods
The powdered root of the plant was solved into dimethyl sulfoxide and injected to reverse-phase HPLC device and different fractions were isolated. To distinguish the cytotoxic fractions, same concentrations of each fraction were applied to cancerous cells. Then, cell viability was measured by alamarBlue assay. The cytotoxic root fraction was collected and powdered and Thin-layer chromatography (TLC) method was used to isolate different compounds. Three isolated compounds were incubated with cells and cytotoxic compound was isolated by alamarBlue assay. The structure of the cytotoxic compound was recognized by Nuclear Magnetic Resonance spectroscopy (NMR) Liquid Chromatography–Mass Spectrometry (LC-MS) method.

Results
Cytotoxicity test on root fractions showed significant cytotoxicity on a fraction with The half maximal inhibitory concentration (IC50) values of 7.546µg/ml for DU145 cells. The cytotoxicity test revealed that one of the purified compounds isolated by TLC, had more significant cytotoxic effect with IC50 value of 2.44(µg)/ml on DU145. The final purified compound was identified as Alopecurone-A using NMR and LC/MS.

Conclusion
The aim of this study was to determine the molecular structure of the cytotoxic compound in the plant Sophora Pachycarpa’s root extract which is a potential compound to play an anti-cancerous role in prostate cancer cells. HPLC results showed one randomly isolated fraction has cytotoxicity in prostate cancer cells. This cytotoxic fraction’s LC/MS diagram, contained a peak which coincided with the molecular weight of Alopecurone A in Dictionary of Natural Products. So, the active cytotoxic compound in the root of this plant was revealed to be “Alopecurone A” which is a potential anti-cancer compound for further investigations.
Rosuvastatin effect in CF-1 mice

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Introduction
Pain is defined as an unpleasant sensorial or emotional experience associated to actual or potential tissue damage. There are different types of analgesic agents in its therapy, as NSAIDs, opioids and adjuvants. The deficient response to pharmacological pain treatment is common, demanding a constant research including new applications of drugs showing analgesic effects. In this study the acute antinociceptive effect of rosuvastatin, a statin, was assessed in an acute phasic pain model called hot plate assay.

Materials & Methods
CF-1 mice were used, 32 animals were randomly assigned to form 4 groups. 30 min before and 30 min after the drug administration, each animal was individually placed in a metallic plate at 50±0.5 °C to define the basal and experimental latency time respectively, with a cut off time of 30 seconds. The latency response was considered as the time required to show an antinociceptive behavior (licking of the paws, repeatedly exploratory activity or miction). A single intraperitoneal dose of rosuvastatin was administrated before the antinociceptive assay, the doses used in each group were 10, 30, 100 and 300 mg/kg. Basal latency and experimental latency were measured twice each. Statistical analysis and a dose response curve were made.

Results
The intraperitoneal administration of rosuvastatin induced a dose dependent antinociceptive effect, increasing, with statistical significance, the latency time in the hot plate assay from 13.50±0.81 sec to 22.10±0.53, with an ED50 of 55.73±4.07 mg/kg.

Conclusion
The findings in the present research show an antinociceptive effect of rosuvastatin that suggest its potential use in the treatment of pain. This beneficial effect may be a result of its activity on diverse proanalgesic and proinflammatory factors associated to the pleiotropic effects of statins.
Evaluation of Drug Prescription Patterns and Health Related Quality of Life (HR-QOL) in Patients of Epilepsy.

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Introduction
Epilepsy being a chronic disorder, is linked to social stigma, especially in developing countries like India. Newer drugs have not yet been included in the hospital formularies, posing a pharmacoeconomic concern. Polytherapy increases the chances of side effects and drug-drug interactions. Also, the medication adherence (MA), demographic characters, seizure frequency, and extended period of the disease are related with poor HR-QOL.

Materials & Methods
127 patients from the OPD of Neurology at a tertiary care hospital consented to participate in the study. Quality of Life in Epilepsy-10 (QOLIE-10) questionnaire was used to measure QOL in patients. Morisky's medication adherence scale-8 was used to assess the MA. SPSS software and Graphpad prism were used to analyze the variables in the study.

Results
Patients of 20-30 age group were more commonly affected (37.80%) with a male predominance (56.69%) and about 41.73% were unemployed. The difference in HR-QOL between patients and controls in all three domains (Epilepsy effects, mental effects, role function domains) of QOLIE-10 was found significant (p=0.0002), indicating better QOL in controls. The worst QOL scores were found in Epilepsy effects domain. Metabolic adverse effects (38.58%) were the most encountered ADRs. Sodium Valproate was the most effective in controlling seizures in most cases as the last seizure episode on an average was 15 months. QOL correlation between patients receiving monotherapy and polytherapy was found significant (p=0.026) in which monotherapy was found to render a better QOL. Comparison of QOL between patients taking the conventional and the newer drugs was not found significant (p=0.1768). Correlation between QOL and MA scores was significant (p=0.0176) indicating that the patients (74.06%) with high MA had a better QOL.

Conclusion
Our study nullifies the claims that newer drugs are better than the conventional drugs since no such benefit has been found in terms of QOL as well as ADRs. Also, our findings ruled out the belief that cases of epilepsy are better controlled with polytherapy. Patients with good medication adherence had a better QOL.
LPS preconditioning protects against maximal electroshock- and pentylenetetrazol-induced seizure reactivity in rats

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Introduction
Preconditioning is a state that a subthreshold noxious stimulation protects against a later severe damage. Various preconditioning stimuli are used for neuroprotection in different CNS diseases. Seizure tolerance has been demonstrated using a variety of seizure preconditioning approaches like electroconvulsive shocks and low doses of excitotoxins. Since Lipopolysacharide (LPS) is a well proven agent in preconditioning contexts, the present study aimed to investigate the protective effect of LPS preconditioning in two seizure models in rats.

Materials & Methods
In this study four separate groups of male Wistar rats, weighting 250-300 g were used (N=7). In two groups, LPS or its vehicle was administered intracerebroventricularly (i.c.v.) at the dose of 1.2µg/rat, 4 days before pentylenetetrazol (PTZ; 70 mg/kg, intraperitoneal) induction of seizure. In the other two groups, LPS or its vehicle was injected at the same dose i.c.v., 4 days before maximal electroshock (MES; 50 Hz, 60 mA and 1 sec, three times at 2 h intervals) induction of seizure. Then onset latency and duration of seizure responses in PTZ model and duration of seizure in MES model were measured.

Results
Obtained results of this study revealed ultra-low dose LPS-preconditioning increases onset latency and shortens duration of seizure in PTZ model. Also in MES model, the duration of seizure reactivity was decreased in LPS-pretreated rats in comparison with corresponding control.

Conclusion
Based on the results of this experiment, LPS-induced delayed preconditioning protects against seizure. Further mechanistic studies on LPS-preconditioning would help identifying innovative strategies to prevent or at least reduce seizure activity and related neuronal damages.
The plant Sophora pachycarpa has chemical cytotoxic compounds in its root

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Introduction
As cancer is becoming one of the main reasons of mortality in the world, investigation on plants for developing anti-cancer medicines is becoming more popular. Sophora pachycarpa is a plant known for its cytotoxic effects and some species of this genus have shown anti-proliferative effects and induced apoptosis activity in some human cancer cell lines. The aim of this study was to determine the plant's organ with the maximum cytotoxic effect.

Materials & Methods
Leaf, flower, fruit and root of the plant were extracted by maceration method in a 1:1 ratio solution of methanol-Dichloromethane. Breast cancer cell lines (MCF-7) were cultured in RPMI1640 growth medium enriched with fetal bovine serum, penicillin and streptomycin at 37°C in a humidified atmosphere containing CO2. Then the cells were incubated in adjacent to different concentrations of four organs' extracts. Also for each concentration and each time course study, a control sample was prepared which remained untreated. Doxorubicin was used as positive control in different concentrations and each test was repeated three times. After 72 hours of incubation, alamarBlue was added to cells and 4 hours later, cell viability was measured by alamarBlue (Resazurin) assay. The half maximal inhibitory concentration (IC50) values were calculated by Excel 2013.

Results
alarBlue assay results revealed that the concentrations of leaf, flower and fruit extracts which were capable of killing 50% of the cells (IC50) were not significant in MCF-7 cell line comparing to the control positive; but this value for root extract was 39.88 µg/ml which implied that this part of the plant had a considerable cytotoxic effect.

Conclusion
The aim of this study was to determine the Sophora Pachycarpa’s organ with the most concentration of the cytotoxic compound. Leaf, flower, fruit and root of the plant were investigated for cytotoxic effects by alamarBlue assay and the root of this plant was recognized to be significantly cytotoxic in MCF-7 cell line.
Brain Mesh – A New Neurosurgical Tool for Safe and Precise Cortical Mapping

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Introduction
Standard electrostimulation cortical mapping includes application of electrical current to the explored areas through an electrode and marking of functional zones by paper tags with different symbols. This approach has two disadvantages. First, the electrode is moved randomly. It leads to overlooking of some zones, which causes mapping deficiency, and re-stimulation of others, which can trigger epileptic seizures (the latter occurs in up to 20% of cases). Second, the tags easily shift and close the marked structures. We report a device, invented by the first author, that provides precise cortical mapping without indicated problems, and technique of its application.

Materials & Methods
The device is a Lavsan mesh with square pores of a certain size (specifically, 2.5 × 2.5 mm). It was manufactured by “Lintex” (Saint-Petersburg, Russia). The technique includes mesh application onto the brain cortex and its sequential stimulation through the mesh pores. The functional areas are labeled. Pores corresponding to the lesion are cut out and the lesion is removed through the cutout without removing the mesh. After operation, the mesh is removed. Using this technique, we operated a male patient (25 years, right-handed) with glioma located in the right superior frontal gyrus, near the primary motor cortex. The exposed cortex was initially mapped in a standard “random” fashion and then under guidance of mesh.

Results
The “random” mapping was negative. The mesh allowed to find a motor center of the left deltoid muscle, which took a one pore and was located just behind the tumor. The glioma was completely resected. During all microsurgical manipulations, the mesh stably stayed in place, due to its tight adhesion to the wet cortical surface. The deltoid muscle center was spared, which corresponded to the lack of postoperative functional deficits. There were no intraoperative seizures.

Conclusion
The brain mesh can be successfully used in neurosurgical operations for safe and precise electrostimulation mapping of the brain cortex.
Glutamate metabolism changes and anxiety-like behaviors in rats with experience of maternal deprivation and early weaning: effects of Ebselen

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Introduction
Maternal separation and early weaning (MSEW) is considered as a mature model to assess the behavioral abnormalities including anxiety-like behaviors often apparent in subjects who experience early life neglect. Our previous study revealed that EAAT2, high-affinity glutamate transporter, decreased in the brain of MSEW rats while glutamine synthetase (GS) and glutamate increased. Recent studies reported that Ebselen, an organoselenium compounds, has significant impact on glutamate metabolism in vivo. This study aims to examine if Ebselen can reverse the MSEW-induced changes in glutamate metabolism and concurrent anxiety-like behaviors in rats.

Materials & Methods
Litters on the parturition day deemed as PD0 were randomized into control or MSEW group in which pups were subjected to maternal separation for 4 hours/day during PD2 to PD5, 6 hours/day during PD6 to PD16, and weaning on PD17. In contrast, control pups were housed as usual. On PD21, same gender pups were housed in group (4-5/cage) until behavioral tests. After the last behavioral test, Ebselen was administered to the animals (i.p. 10mg/kg/day) for two weeks. After the second set of the same behavioral tests, the indices of glutamate metabolism such as glutamate, glutamine, EAATs, GS, and glutaminase (Gls) were detected by western blot or HPLC after sacrifice of rats. All data were analyzed by student t test, GLM--repeated measures.

Results
Behavioral tests revealed anxiety-like behaviors in MSEW group upon the results of open field and elevated plus maze. Compared with control, gls and EAAT2 downregulated in the brain of MSEW group while GS and glutamate increased; glutamine concentration was parallel to control group. (Part of Ebselen will be supplemented in the next future)

Conclusion
The anxiety-like behaviors of rats possibly are attributed to excessive glutamate with experience of MSEW. And glutamate metabolism pool would be a potential target for treatment of anxiety.
PHARMACOLOGICAL BLOCKADE OF THE RECEPTORS OF MELATONIN AND ITS EFFECT ON OVULATORY FUNCTION IN FEMALE RATS UNDER CONDITIONS OF LIGHT DEPRIVATION

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Introduction

Melatonin implements its physiological effects through interaction with specific receptors. Luzindol is the selective blocker of melatonin receptors of type 1 and type 2; it disrupts the synchronization of circadian rhythms which are caused by the action of melatonin.

Materials & Methods

The work was carried out on female rats (n=60). Females born and left in conditions of light deprivation (DD;0-0.5Lux), at the age of 5 months were randomly divided into two experimental groups. In the first group (n=20;DD+luz) the animals received luzindol (N-Acetyl-2-benzyl-tryptamine) at the concentration of 10 mg/l every day, 5 days a week at night with drinking water. In the second group (n=20;DD) female rats received drinking water and served as a comparison group. The third group (n=20;LD) was a control group: animals were in conditions of standard lighting (750Lux;12h light/12h night). The duration of the estrous cycle, the relative number of short, medium and long cycles, and the relative number of animals with irregular cycles were estimated.

Results

The average duration of the cycle extended with age: in LD from 4.8±1.4 days to 7.4±1.7 days; in DD from 4.4±1.4 days to 5.3±1.8 days; in DD+luz from 4.4±1.2 days to 7±1.4 days from the 6th to the 21st month, respectively. In LD group, the number of long estrous cycles increased from the 6th to the 21st month from 3% to 43%; in DD+luz group - from 2% to 43%; in DD group it increased slightly from 10% within 6 months to 20% by the 21st month, short cycles persisted in adulthood. The first irregular cycles in the groups of LD and DD+luz were recorded at the age of 9 months, and by the 21st month - 33% and 36%, respectively. In DD-group the first irregular cycles were observed at the age of 6 months, by the 21st month - 17%.

Conclusion

At the pharmacological blockade of melatonin receptors by luzindol in the conditions of constant darkness, the observed changes in ovulatory function did not differ from those in animals of the control group, which indicates the determining role of melatonin receptors in the regulation of age-related changes in ovulatory function.
Psychiatry

Chair
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Presenters
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Bandyopadhyay, AB (Alapan)
Brink, V.E.
Salmon, C (Caoimhe)
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Assessment of cognitive function in diabetic patients – a case control study


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Introduction
Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, resistance to insulin action, or both. Hyperglycemia causes small vessel diseases and thus affecting the retina, kidneys and the nerves. One of the effects of diabetes that is not quite understood is cognitive dysfunction. Recent advancements in the field of neurology are revealing those effects on the brain.

Materials & Methods
This case control study which aimed to study the cognition function in the participants which included 25 diabetics and 72 non-diabetic controls according to the inclusion criteria, which underwent assessment of cognition by 3MS and personal data was collected from the participants. Twenty three participants were excluded by the exclusion criteria. Age, gender, comorbidities, education, and HbA1C were correlated with the scores. The data was analyzed by Excel version 2013.

Results
A significant decrease in 3MS scores was portrayed by the diabetic group in comparison to the control group (90.111 ± 0.74576 in control group versus 86.2667 ± 1.24007 in diabetic group, P< 0.05). Diabetics of higher age groups scored significantly lower than the control of higher age groups as well (P<0.05). There was a significant relationship between cognitive scores and dyslipidemia in diabetic and control samples (87 ±2.034426 in diabetic group who have dyslipidemia versus 92.5 ± 2.093641 in control group who have dyslipidemia, P< 0.05). Controls that were undergraduate scored significantly higher than the diabetic undergraduates (87.21053 ± 1.308047 in diabetic group 1 versus 90.06154 ± 0.803202 in control group 1, P< 0.05). The correlation with gender as well as HbA1c was not significant (P>0.05).

Conclusion
It has been established that diabetes decreases cognitive function. It is important to highlight the importance of testing cognitive function routinely in diabetic patients to control and prevent further complications by early detection and management.
The Pattern of identification of emotions from facial expressions among medical students.

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Introduction
Patients seek empathy from their physicians. Successful identification of emotional expression in patients is of considerable importance to physicians to be able to empathize with them or their families. In addition, recognition of visual cues is important for the diagnosis of many mental disorders like depression. Despite its importance, this aspect remains grossly overlooked in conventional medical training in India. In this study we aim to explore the extent to which the medical students can identify emotions by observing photographs of male and female subjects.

Materials & Methods
A total of 106 medical students (53 male and 53 female), aged 18-25 without any gross mental ailments were shown 24 images of universal facial expressions (anger, sadness, fear, happiness, disgust and surprise) at 100% intensity with an exposure time of 2 seconds for each image. All of the procured images were from the Karolinska Directed Emotional Faces directory. The participants marked their responses after each image was shown. Collected data were analyzed using SPSS (version 19).

Results
On average, the participants identified 75.6% of the emotions. The most correctly identified emotion was happiness (97.4%) while the least was fear. On average, positive emotions (happiness and surprise) were identified more accurately than negative emotions (anger, fear, sadness, disgust). Male participants performed almost similar to women in identifying emotions (77% vs 76.1%). It was also noted that both sexes identified emotions more from the faces of the same sex. Of wrongly identified emotions, Anger was most often mistaken as disgust, disgust as sadness, fear as surprise, sadness as disgust, happiness as surprise, and surprise as fear.

Conclusion
Compared to positive emotions, participants did poorly when identifying negative emotions, which is of significance in a clinical setting when particularly dealing with diseases affecting mental health and broadly in understanding and dealing with distressing emotions associated with physical illness and the reactions of the family members in stressful situations. The misidentification of emotions might shed some light on potential miscommunication based on wrongly identified emotions and the significance of including this aspect in communication training for medical students and others in caring professions who deal with individuals in distress.
Spontaneous discontinuation of distressing auditory verbal hallucinations in a school-based sample of adolescents – a longitudinal study.

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Introduction
Auditory verbal hallucinations (AVH) can be transiently present in both clinical and healthy adolescent populations. It is not yet fully understood why AVH discontinue in some adolescents, while AVH persist in others, increasing the risk of developing psychiatric disorders. The aim of this explorative study is to investigate predictors of spontaneous discontinuation of distressing AVH in a school-based sample of adolescents.

Materials & Methods
1841 adolescents (mean age 12.4 years, 58% female) completed self-report questionnaires at baseline. Included in the current study were 123 adolescents (7%; 63% female) who reported at least mild distressing AVH at baseline and completed the follow-up measurements. Predictors of spontaneous discontinuation of distressing AVH were uncovered with a multivariable logistic regression analysis.

Results
At follow-up, 43 adolescents (35%) reported having experienced distressing AVH during the last 12 months, while 80 adolescents did not. Spontaneous discontinuation of distressing AVH was predicted by having repeated a school grade (OR=5.81, 95% CI=1.76-19.15, p=0.004), less prosocial behaviour (OR=0.68, 95% CI=0.51-0.91, p=0.009), never been scared by seeing a deceased body (OR=0.38, 95% CI=0.16-0.92, p=0.032) and never having used cannabis (OR=0.05, 95% CI=0.01-0.35, p=0.002). No associations between persistence of distressing AVH and delusional experiences, ethnicity, education level or age were found.

Conclusion
Distressing AVH in non-clinical adolescents are mostly transient. It remains difficult to predict discontinuation of distressing AVH in adolescents. The few predictors that were found do not provide leads for preventive measures, except for discouraging cannabis use.
Depression, anxiety and quality of life in a palliative population: 
a comparative study across different settings – community and hospital

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Introduction
Palliative care patients commonly experience fluctuating moods due to the nature of their diagnosis. Management plans focus on keeping physical pain at bay, resulting in the patient’s mental health being overlooked. Understanding adjustment and depressive disorders in this population better may be an important target for improved quality of life.

Materials & Methods
Patients in the West of Ireland were approached in this ethically approved cross-sectional study. The scales used were Hospital Anxiety and Depression Scale (HADS), the short form of the Adjustment Disorder-New Module scale (ADMN-6) and the EQ-5D to measure quality of life. The HADS focuses on the patient’s recent emotional responses experienced whereas the EQ-5D is a 5-item validated scale which explores functioning in activities of daily living and related quality of life.

Results
Of all patients approached 30 agreed to participate in the study. Adjustment disorder- New module 6 (ADMN-6) highlighted 63.13% of patients whose situation was a burden to them, only 36.84% reported any change to their sleeping habits. 52.63% of patients admit to ‘supressing’ their feelings with others while but only 15.79% of participants say they have withdrawn from their friends and family. The Quality of Life questionnaire reported 42.11% of patients to be moderately depressed. Finally, when asked to rate their current health on a scale, a mean of 56 was obtained.

Conclusion
Working with a sensitive and acutely ill cohort has its challenges. This pilot study will deepen our understanding of the psychological and overall care requirements of palliative care patients. The data collected suggests that end-of-life patients require mental health care to complement their physical management. I aim to provide an understanding of the relationship between stressors and symptoms, and the importance of environment or clinical setting to both symptoms and quality of life. This will result in an improvement of the overall wellbeing of palliative patients, in both community and inpatient based settings.
A Clinical Trial of the Impact of Mindfulness on Quality of Life in Individuals with Parkinson’s disease

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Introduction
Parkinson’s disease (PD) is a disabling neurodegenerative disorder in elderlies. The non-motor symptoms are the most important part that affect patients’ quality of life. The use of mindfulness-related interventions have been considered to improve personal control, stress-management, social interactions and reduce disability in people with PD. This study aimed to evaluate the effect of mindfulness technique on quality of life in patients with PD based on the PD Quality of Life Questionnaire (PDQ-39).

Materials & Methods
In a twelve-month period, 40 patients who referred to outpatient neurology clinic of Imam Reza university-hospital were considered. The patients were randomized into two experiment and control groups (20 patients in each). The PD patients in experiment group attended six sessions of mindfulness training in an 8-week period. The PDQ-39, and PDSI score were calculated before and after the intervention. The change in each item including Mobility (MOB), Activities of daily living (ADL), Emotional well-being (EMO), Stigma (STI), Social support (SOC), Cognition (COG), Communication (COM) and Bodily discomfort (BOD) were assessed at 4-week follow-up and compared to baseline score using paired t-test.

Results
In a 4-week follow up, patents in experiment group had an improved PDSI score compared with control group (p<0.001 vs. p=0.29). The mean PDSI score in experimental group was 33.93±6.2 and 31.85±6.5 before and after the experiment, respectively. A significant decrease in MOB, ADL, EMO, and SOC were noted after intervention in experiment group. The mean MOB score improved from 48.37±6.8 to 47.23±7.5 (95%CI: 0.04–2.2, p=0.04). The mean ADL score changed from 35.17±10.8 to 32.04±11.5 (95%CI: 1.3–4.9, p=0.002). The mean EMO score decreased from 38.92±9.4 to 10.42±2.3 (95%CI:1.7–6.1, p=0.001).

STI, COG, COM and BOD were the items that did not improve significantly after the intervention (p>0.05). The baseline and post-assessment scores of each item did not differ significantly between patients in experiment and control group.

Conclusion
Our findings demonstrated that mindfulness intervention can improve PD symptoms related to motor function and anxiety while, it did not affect communication and sociality in these patients. In the midterm follow up, the intervention yield significant progress in patients’ quality of life, but long-term follow up may be necessary.
Impact of Co-morbid Conditions on the Progress and Outcome of Schizophrenia

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Introduction

Among Schizophrenics, a higher incidence of Cardiovascular Disease (CVD) and associated premature mortality is worrisome. This needs to be tackled with tact. To aid this, the concept of Metabolic Syndrome (MetS), an aggregation of abnormal clinical and metabolic detections, which are predictive markers for CVD, has appeared in Psychiatry. The co-existent state of anti-oxidant dysregulation permits uncontrolled action of free radicals on cell membranes. Such free radical-mediated pathological processes may be the root cause for specific deficits observed in Schizophrenia. This study aims at assessing the proportion of individual disorders of MetS along with Serum Uric Acid levels, a measure of anti-oxidant dysregulation, in Schizophrenics and attempts correlating them with the outcome of Schizophrenia.

Materials & Methods

This cross-sectional study was performed in the out-patient department and in-patient wards of the Psychiatry Department at Govt. Wenlock Hospital, and Kasturba Medical College Hospital, Mangalore. With a 95% confidence interval, a sample of 100 Schizophrenics, either previously or newly diagnosed, were assessed. Institutional Ethics Committee approval and Informed Consent were obtained before commencing the study.

Results

We found that Hypertension, constituents of Lipid profile (other than Low-Density Lipoproteins (LDL)), Fasting Blood Sugar, measures of central obesity i.e. waist circumference and waist: hip ratio, and Serum Uric Acid levels had no statistical correlation with Schizophrenia. Conversely, we found that Serum LDL levels were significantly correlated with the Global Development Index (p=0.02) and Body-Mass Index (BMI), with all three indices of the Clinical Global Index (CGI) Scale, i.e. Severity of Illness Scale (p=0.001), Global Improvement Index (p=0.045) and the Efficacy Index (p=0.008).

Conclusion

Schizophrenics having higher LDL levels i.e. belonging to the “Very High” category have the worst Global Improvement as against the “Optimal” category, which had the best. Similarly, Obese patients, as per BMI, have worse prognosis on all three scales, progression of Schizophrenia is more severe, likelihood of improvement is the least and efficacy of treatment is the least, as opposed to the “Normal” BMI category. Hence, it is imperative to take these co-morbidities into account while treating a Schizophrenic. Treating Schizophrenia in isolation may be equivalent to no treatment at all.
EMOTIONAL DISORDERS IN PATIENTS WITH STROKE IN THE ACUTE PERIOD

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Introduction
Emotional disorders after a stroke, along with motor, speech and cognitive impairment, cause significant social maladjustments and reduce the quality of life of patients. Depression develops in 30%, anxiety in 74% of patients with acute stroke.

Materials & Methods
90 patients (48 men and 42 women) with ischemic stroke were examined, 41 of which (45.6%) had a stroke in the left, 30 (33.3%) in the right hemisphere of the brain, and 19 (21.1%) in the cerebellum and brain stem. State (SA) and trait anxiety (TA) were investigated on a scale of Ch. D. Spielberger, adapted by Iu. L. Hanin and depression on the Zung V. scale, adapted by T. N. Balashova.

Results
61 (67.5%) patients had SA of moderate severity, high SA was revealed in 28 (31.3%) and in 1 patient low anxiety. However, TA was more often high in 49 (54.4%), 32 (35.6%) had moderate and 9 (10%) - low TA. At the same time, 55 (61.1%) patients did not suffer from depression, 23 (25.6%) of the examined patients showed mild depression of situational or neurotic genesis, 12 (13.3%) had a sub depressive state, and one patient had a true depression. High levels of SA and TA occurred more often in patients with localised foci in the left hemisphere (60% and 37.1%, respectively). At the same time, patients with ischemic focus in the dominant hemisphere also had depression (48.6%), which correlates with the literature data. The frequency of SA and TA was moderately higher in patients aged up to 44 years, at the same time SA and TA of a high degree was more in affected patients aged 45 to 59 years. The incidence of depression in women was 43.2%, in men 35%, and prevailed in people aged 45 to 59 years.

Conclusion
High rates of emotional disorders were found in patients aged from 45 to 59 years. Depression is observed in patients with stroke in the dominant hemisphere, mostly in women.
Public Health II

Chair

Sander K.R. van Zon PhD

Presenters

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A formative qualitative study exploring the acceptability of deferred consent for emergency research in Malawi

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Introduction

Conducting emergency research in acutely or critically ill adult patients can be challenging because the therapeutic window for intervening may be too short to seek informed consent from the participants prior to their study enrollment. In these circumstances, the application of deferred consent may be an ethical alternative, although there is paucity of locally-relevant data reflecting the knowledge, experiences and attitudes of Institutional Review Board committee members, health workers and representative members of the research community. This study explored the acceptability of deferred consent for research studies of adult emergency care in Malawi.

Materials & Methods

Participants were purposively sampled and invited to participate in in-depth interviews (IDIs) or focus group discussion (FGD), using a semi-structured open-ended interview guide which explored their experiences of deferred consent, perceived potential benefits and risks of deferred consent and ethical considerations for its implementation. The sample for the IDIs comprised 6 health care workers working at an emergency centre and 5 research ethics committee members, whereas the sample for the FGD comprised 12 community representatives. Sample size was determined through the concept of saturation in qualitative research. Transcripts underwent thematic analysis using NVivo 11 software and all members of the research team agreed on the coding framework.

Results

Participants’ experiences of deferred consent were mostly of clinical and hardly research context. Views on the acceptability of deferred consent varied among the participants, with perceived benefits and risks identified. Perceived benefits included potential scientific benefit while potential risks included abuse/misuse. However, many participants felt that deferred consent would be acceptable provided community engagement efforts were made to address ethical concerns and the regulatory framework was sufficiently robust to provide governance and oversight to studies employing deferred consent.

Conclusion

Deferred consent in emergency research in Malawi may be acceptable provided the community is appropriately engaged and regulatory mechanisms are in place to make its implementation ethically acceptable.
Introduction
Smoking is the second leading risk factor for both deaths and disability-adjusted life-years (DALYs). It accounted for seven million deaths in 2017, 12.7% of all deaths globally. In addition, smoking was considered to be responsible for 182 million DALYs, 7.3% of all DALYs globally. Although smoking is a risk factor for six of the eight leading causes of death, prevention of smoking as a modifiable risk factor has received improper attention. In addition, 98% of all smokers begin smoking in adolescence and young adulthood. Therefore, the objective of this study was to determine the current smoking prevalence among a nationwide representative sample of Iranian adults aged 18 to 30 in 2017.

Materials & Methods
This cross-sectional study was conducted in 2017 in the 31 provinces of Iran. Iranian adults aged 18 to 30 were invited to participate in the study. Multistage cluster sampling method was used for selecting participants. Data were collected through face to face interviews using the transcultural adaption of STEPs questionnaire developed by World Health Organization.

Results
As many as 7047, 3780 (53.6%) women and 3267 (46.4%) men, participated in the study. The mean (SD) age of participants was 25.2 (3.4) for women and 25.3 (3.4) for men. The prevalence of current smoking was significantly higher among men than women: 311(9.5%) vs. 11(0.3%): $X^2=345.2$, $p<0.001$. The mean (SD) number of daily smoked cigarettes was 16.8 (12.7) among women and 12.1 (8.7) among men. The onset age of smoking was 19.2 (5.4) among women and 17.3 (3.8) among men. As many as 1142 (30.2%) women and 1325 (40.6%) men reported that they had been exposed to second-hand smoke in the previous month. Among participants who were smokers, 123(38.2%) reported they had been advised by healthcare professionals to quit smoking. The prevalence of current smoking was significantly higher among participants with education levels below high school diploma than those with high school diploma or higher: 7.8% vs. 3.4%: $X^2=91.1$, $p<0.001$.

Conclusion
The current smoking prevalence was higher among men than women. Therefore, necessary measures need to be taken to improve knowledge, proper attitudes, and practices regarding smoking.
Is your stressful lifestyle associated with severe pre-menstrual depression?

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Introduction
The association of stress with chronic illnesses such as diabetes, cardiovascular diseases, etc has been well documented. In addition to these chronic consequences of stress, there could also be a cyclical pattern of impact on women's mental health. This can manifest in the form of worsening pre-menstrual symptoms, such as depression. The aim of the study was to find out if there is any correlation between severity of depression symptoms in the premenstrual phase and the pre-existing stress levels in women belonging to the age group 18-22 years.

Materials & Methods
A prospective cohort study was carried out with 123 female students, who met the appropriate inclusion criteria. They were asked to track their menstrual cycles using “period tracking” software applications for the past 6 months. Women with diagnosed psychological illnesses and those using hormonal contraceptives were excluded from the study. In the first month of the study, Perceived Stress Scale(PSS) questionnaire was used to determine the psychological stress levels. It takes into account the feelings and thoughts associated with psychological stress in the preceding four weeks. In the following month, Beck Depression Inventory(BDI) was used to assess the severity of depression symptoms in pre-menstrual/luteal phase of the menstrual cycle. Spearmans Rho correlation test was used to find the strength of association between the severity of premenstrual depression symptoms and pre-existing stress levels.

Results
The Spearmans coefficient was calculated to be 0.52911. (p<0.01 for a confidence interval of 99%). This indicates a moderate strength of association between stress and pre-menstrual depression.

Conclusion
Women with a higher level of perceived stress were found to have more severe pre-menstrual depression symptoms compared to those who had a lower level of perceived stress. Though correlation does not establish a causal relationship between stress and pre-menstrual depression, the finding of a positive association warrants further research into this topic. The results could be the basis for initiating stress reducing exercises in women. This will not only improve the quality of life, but may also reduce the burden of pre-menstrual syndrome on women's mental health.
Predictors of severe hypoglycemia in adults with type 1 diabetes with focus on questionnaire-assessed impaired awareness of hypoglycemia.

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Introduction
Recognizing prodromal symptoms of hypoglycemia is crucial for patients using insulin to self-treat and thus prevent severe hypoglycemia. In those with type 1 diabetes (T1DM) this ability often deteriorates leading to impaired awareness of hypoglycemia (IAH). In clinical practice IAH can only be recognized by question-based tests. However, the value of those questionnaires in predicting occurrence of severe hypoglycemia in modern cohorts of patients has not been defined.

Materials & Methods
A total of 449 outpatients attending diabetes clinic in 2017 completed two standardized questionnaires to determine presence of IAH (by Clarke and Gold). Participants also reported any episodes of severe hypoglycemia (in their understanding) experienced in the preceding year. Afterwards, confirmed episode was defined as an event involving loss of consciousness; situations reported as “strong confusion” or “need of another’s help” were discarded as subjective. During the visit, routine measurements were performed: weight, height, glycated hemoglobin (HbA1c) and insulin doses were recorded. Retrospectively, mean HbA1c was calculated for all available measurements from the last year. Mean and standard deviation of glycemia were calculated from data downloaded from patients’ glucose meters. Patients who were using any type of continuous glucose monitoring or provided incomplete data were excluded from the study.

Results
The analysis included 393 patients [median age 26.4 years old (25-75%:21.2-31.4); median diabetes duration 14.3 years (25-75%:9.9-19.3), median HbA1c 7.5 (25-75%:7.8-8.2%), 58.5% treated with continuous subcutaneous insulin infusion (CSII)]. Confirmed severe hypoglycemia was reported by 6.6%, another 22.1% reported subjectively-perceived episodes. Those who experienced severe hypoglycemia presented higher prevalence of IAH according to Clarke (13.1% vs 3.4%, p=0.0008) but not Gold questionnaire (8.1% vs 5.8%, p=0.4000). Multivariate logistic regression revealed that both standard deviation of glycemia (OR=1.016, 95%CI:1.001-1.036, p=0.038) and IAH recognized by Clarke criteria (OR=3.584, 95%CI:1.509-8.512, p=0.004) were independent predictors of severe hypoglycemia, after accounting for model of treatment and age.

Conclusion
IAH identified by Clarke survey predisposes to hypoglycemia-associated loss of consciousness more than impaired awareness determined by Gold questionnaire.
Acceptability of Video Observed Treatment vs. Direct Observed Treatment for Tuberculosis: A Comparative Analysis Between South and Central India

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Introduction
Direct Observed Treatment (DOT) is a requirement in the management of Tuberculosis (TB) globally. With the transition from alternate day treatment to daily treatment in India, monitoring treatment adherence through DOT is a logistic challenge. The pervasiveness of mobile phones in India therefore provides a unique opportunity to address this challenge remotely.

This study was therefore designed to study and compare the acceptability of mobile phones for antitubercular treatment support in two distinct regions of India.

Materials & Methods
This was a cross-sectional exploratory study that enrolled 351 patients with tuberculosis, of whom 185 were from Bangalore, Karnataka, South India and 166 from Ujjain, Madhya Pradesh, Central India. Trained research assistants administered a pretested questionnaire comprising demographics, phone usage patterns and acceptability of mobile phone technology for treatment adherence in tuberculosis. The results were statistically analysed.

Results
The mean age of the 351 participants was 32±13.58 years of whom 140 (40%) were women. Of the participants, 121 (66%) were urban, 145 (78%) had >4 years of education. A significantly greater number of participants at Bangalore had >4 years of education; were from a rural residence; were newly diagnosed TB patients and were in the intensive phase of treatment. There were no other significant differences in mobile usage patterns between the two sites, except using the mobile camera. Overall, 218 (62.1%) preferred vDOT over DOT due to the time and money it saved. Of those who preferred DOT, 70 (53%) did not know how to record videos, nine (7%) preferred personal contact with medical staff, while eight (6%) feared breach of confidentiality and disease disclosure thereof. Most of those who preferred vDOT were from the Bangalore site.

Conclusion
While mobile communication and vDOT are acceptable for adherence support in TB, its coverage will likely depend on its design, mobile ownership, and the data security and confidentiality that it promises. The choice of the technology for the health system should depend on these factors along with its aim i.e., adherence support, adherence monitoring or a combination of both, along with its ability to document ‘a dose taken or swallowed’. A necessity for most healthcare programmes globally.
Screening of risk factors for prediction of pre-eclampsia in early pregnancy- A Retrospective Record based Case Control Study in Coastal South India

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Introduction

Preeclampsia contributes to 76,000 of the maternal deaths annually. Assessment of each risk factor individually could estimate a woman's risk of pre-eclampsia and her eligibility for heightened surveillance and prophylactic aspirin administration. After all, no woman should die during pregnancy & childbirth.

Materials & Methods

A Retrospective Record based Case Control Study of 164 cases & 166 controls admitted in the hospital over 2 years in the same gestational age were evaluated with the help of a pretested data sheet in relation to risk factors associated with current pregnancy status such as nulliparity, advanced maternal age, chronic hypertension, pre-pregnancy diabetes mellitus, chronic kidney disease, SLE, assisted reproduction, multiple pregnancy & past obstetric performance such as history of pre-eclampsia, history of placental abruption, fetal growth restriction and stillbirth. Data was analysed using Statistical Package for Social Sciences Version 16.0. Chi square test for comparing the qualitative data between cases and controls was done and P value < 0.05 was considered as statistically significant.

Results

With respect to current pregnancy status, chronic hypertension (P value = 0.000) & multiple pregnancy (P value= 0.03) had well-known association with pre-eclampsia. Patients with history of FGR (P value = 0.023) & pre-eclampsia (P value = 0.000) were more prone to develop pre-eclampsia than the controls with respect to their past obstetric performance. Reverse significance was found with pre-pregnancy DM; its incidence being more in non-pre-eclamptic patients (11.4%) than preeclampsia patients (5.5%). No significant differences between cases and controls were found with respect to nulliparity, advanced maternal age, ART, history of placental abruption and stillbirth.

Conclusion

This study gave us an insight into the risk factors that could be used for screening patients who are more prone to developing pre-eclampsia so that their assessment can be done at the woman’s first antenatal visit itself & started on low dose Aspirin from 12 weeks of gestation for better outcomes.
A pre-post implementation study of improving informed consent for caesarean section in a low-resource setting.

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Introduction
Several reports have recognised weaknesses in the informed consent process for caesarean section (CS). This study aims to improve the quality of informed consent for CS in a low-resource setting by implementing health worker targeted interventions; a standardised checklist, combined with a six-step guidance and communication training.

Materials & Methods
A pre-post implementation study was done to improve completeness of the informed consent process, women's recollection of the indication and their recollection of associated risks. Women giving birth by CS were interviewed 48 to 72 hours postoperatively using a questionnaire. Completeness was defined as inclusion of five components of informed consent. Each individual component was compared between pre- and postintervention using a Chi-squared test. Components were also combined and analysed as part of a completeness score using an independent sample t-test. Risk recollection was measured by the number of common risks chosen out of a list and was compared using an independent t-test as well. Additional simple bootstrapped independent sample t-test was performed.

Results
A total of 160 patients were included; 80 prior to implementation and 80 after. In the pre-intervention group, the informed consent process showed dissatisfying inclusion of all but one component; indication was mentioned in 96.3% of the consultations, explanation of the procedure in 55%, associated risks in 31.3%, implications for future pregnancies in 53.7% and verbal consent enquiry was included in 83.8%. Post-intervention, the consultations which included risks related to CS increased from 31.3% to 58.8% (p<0.05). The mean overall completeness score increased from 3.20/5 to 3.79/5 (p=0.04). The percentage of patients recollecting the indication for their CS increased from 70% to 82.5% (p=0.063). The mean number of common risks recollected increased from 1.39/3 to 1.64/3 (p=0.048). Simple bootstrapped t-test did not provide different outcomes.

Conclusion
These low-cost facility-based interventions improved completeness of the informed consent process and resulted in better recollection of information. This is an important pillar of respectful maternity care.
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