BMEP

BIOMEDICAL SCIENCES EXCHANGE PROGRAM

Participants Yearbook

Academic Year 2016/2017

Biomedical Sciences Education Program - BMEP e.V.
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Preface – BMEP Yearbook of the Academic Year 2016/17

Education by Exchange – Exchange by Education

We gladly present the first yearbook of BMEP participants in the reorganized BMEP after Prof Hilmar Stolte's death in 2015. Since 1979, every class of young scientists going abroad made a unique experience, many of them were captured in yearbooks reflecting scientific and personal achievements of their research stay in the US, in Canada, in South Africa or in the UK.

The AY16/17 encountered some special circumstances through several unusual political and natural incidents. It is not only the post-Stolte era, but it has been the year of Donald Trump's election as President of the US, the troubles in Europe after the Brexit vote and a time of fake-news, increasing frequencies of terrorist attacks and natural disasters. Thus, the future development of our planet and our societal structures become even more dependent on a generation of open-minded, highly-educated, international individuals and scientists committed to high principles and values. Such values have always been the guide for the BMEP and its founder, Professor Hilmar Stolte.

Independent of the political environment of the greater society, this yearbook is a summary of individual experiences and achievements of a group of young scientists at the beginning of their academic careers. It is a reflection of their curiosity and ambitions: Supporting these activities in a group of talented individuals in life sciences is the heart of the BMEP.

We hope you will enjoy reading the remarkable experiences of the Academic Year 2016/17 participants.

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Hans-Christoph Pape,
Torsten Doenst

Biomedical Education Program

Karsten Dreinhöfer,
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Helena Anke

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Professor Dr. Michael Ott
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Your personal reaction to the U. S. experience:
It was my first time in the US and on top I directly went to New York. Therefore, it was overwhelming when I arrived and directly got to see many of the tourist attractions such as the beautiful skyline of Manhattan or Times Square in the shuttle on my way from the airport. I was not used to living in such a big city – New York has so many opportunities and things to do! It is a very busy, exciting, loud but beautiful city at the same time. Living at International House, a dorm for interns and students from all over the world, I got to know many people and lifelong friends from lots of different countries. Thanks to that, New York was a great multicultural experience for me where I learned a lot not only about research but also about other cultures and myself.

Greatest Difficulties Encountered:
Definitely the visa with all its paperwork, also the bureaucracy here in the States. Everything took extremely long and I had to ask very often until I got all the needed documents.

Most Humorous Incident:
On my last weekend in the US, my friends and I wanted to make a trip to upstate New York and spend a night in nature. As we planned everything relatively spontaneously and it was the 4th-of-July-weekend, we did not have that many options left when we booked our Airbnb. We finally decided for a nice and cosy-looking caravan in the middle of nowhere with very good reviews. We arrived in the afternoon when the owner had not been there yet, but with the owner's permission we started exploring the area and the caravan from the outside. We could not believe our eyes! Everywhere there were axes lying around, iron chains and at the owner's house wall next to our caravan there was even a skeleton hanging. Inside the caravan there were creepy dolls sitting on the window sills and staring outside. We felt like in these typical horror movies, in which a group of students want to make holidays in a forest and then get killed one after the other by a freak living alone in the middle of nowhere. The owner arrived, opened the caravan for us and it became even worse. It was extremely dirty and full of crap, so that we could not imagine at all to stay overnight at this scary place, although this might have been a little childish and too much cliché. But still - in the end, we literally ran away and ended up in a normal, clean hotel in the next big city. Definitely a weekend I will never forget.

Helpful Hints for Future Students:
Start taking care of your visa as early as possible, at least half a year before leaving! Also, try to get a room in a student dorm or similar accommodations, it is very helpful for finding friends and social activities. Especially in big cities like New York it can be very difficult to get to know people in a bar or on the streets, since you will be working in a laboratory and not going to university classes like other students.

Abstract on Research Topic – Helena Anke

Title: Mechanisms of Hepatic Stellate Cell Activation

Authors: Helena Anke[1,2], Robert Schwabe[1]

Institutions:
[1] Columbia University, Department of Medicine, Institute of Human Nutrition, New York
[2] Hannover Medical School, Hannover

Introduction:
Activation of hepatic stellate cells (HSCs) is a central component of the hepatic wound healing response and promotes the development of liver fibrosis when liver injury is chronic. As the regulation of this process has not been fully understood so far, the aim of my study was to characterize pathways that promote the transformation of HSCs to fibrotic tissue-producing myofibroblasts. In a first project I tested the hypothesis that the transcription regulator YAP contributes to HSC activation in response. Secondly, I was involved in the establishment of an immortalized mouse hepatic stellate cell line since primary HSCs cannot survive in long-term culture and need to be isolated freshly for each experiment. My third project was about the transplantation of HSCs from one mouse to another and to investigate their response to liver injury.

Methods:
Hepatic stellate cells were isolated from BALB/c mice, cultured and then treated with different profibrogenic agonist. The activation of YAP was analysed by Immunofluorescence and by measuring the mRNA expression of YAP target genes via qPCR. Yap-floxed mice were used for HSC isolation to confirm the functional role of YAP. To establish an immortalized HSC line, HSCs were isolated from a triple transgenic ImmortomouseTM that expressed LratCre and Cre reporter tdTomato, incubated at 33°C and treated with Interferon γ. Transplantations were performed through intrasplenic cell injection with subsequent splenectomy. I used tdTomato+ mice as cell donors for lineage tracing and evaluated HSC engraftment via fluorescence in liver sections in untreated and CCl4-treated mice.

Results and Conclusions:
Project 1: I observed upregulation of YAP target genes as well as YAP nuclear translocation following treatment with profibrogenic agonists. Ongoing experiments are determining the upregulation of profibrogenic genes in HSCs that lack YAP.
Project 2: Immortalized LratCre+ HSC were established but have not been characterized yet due to slow growth.
Project 3: HSCs were successfully transplanted into recipient mice and migrated to fibrotic septa following liver injury. Future experiments will investigate whether they activate similarly as endogenous HSCs.
The results show activation of YAP by several profibrogenic stimuli, suggesting a key contribution to liver fibrosis. The immortalized HSC line and HSC transplantation will represent useful tools to further investigate mechanisms of HSC activation and liver fibrogenesis.

Funding:
Helena Anke received funding from DAAD and Columbia University in the City of New York.

Luisa Susan Averdunk

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Christian Stoppe, PhD/PD

Your personal reaction to the U. S. experience:
When thinking back to my time at the Yale School of Medicine, I am still impressed with the American "everything-is-possible" attitude. I found the Americans to be extremely pragmatic, once a good idea comes up, it is tackled and put into practice – the perfect success strategy!
I had the great chance to continue my research project about postoperative acute kidney injury, which I had already begun in Aachen, in the Department of Nephropathology at the Yale School of Medicine. The lab members were extremely supporting and helpful. Thus, I was able to establish an in vivo experiment in a murine model, which had not been possible in our German research group before. This was an extreme benefit for our final published manuscripts in the journal Science translational medicine.
What I enjoyed a lot were the abundant scientific talks at the Yale School of Medicine which were free for everybody and made even more attractive by free lunches ;-). These interdisciplinary talks are a great input and inspiration for my own research.
Another typical American experience I made, was that "Money rules everything" – at least in the research laboratories (but that of course, is an important issue in German laboratories, as well…)
Apart from reasearch and lab work, I had a really great time in New Haven and on the Yale campus. The Yale Office of International Schools offers amusing events (e.g. campus ralley, trips to Boston…) where you can easily make friends. The Yale campus is worth a guided tour and it is great to sit and study in the ancient Yale libraries! Besides, New Haven offers nice restaurants including the best pizza places in the USA (real Italian influenced pizza), the east rock, trips to the lighthouse park etc..
Last but not least, New York is only 1,5 hours away by train, so you can spend great party nights in New York!
Last, I was in the U.S. during the elections – you can imagine what was going on, in Conneticuit - a state that is traditionally dominated by the Democrats, and on a campus of an elite – the atmosphere was ful of despair and frustration…

Greatest Difficulties Encountered:
The Yale university is located in the less famous city, New Haven. New Haven is known for a pretty high crime rate. However, the Yale university is doing everything to provide a save environment for their students. If you consider the advices (e.g. to avoid certain areas, to take controlled routes when you are going by bike in the evening), you can live an untroubled and easy life. You should definitely try to get a housing/room in the East Rock district.

Most Humorous Incident:
I was invited to join a farewell party of one of the professors. For this event, everybody had to wear Mickey Mouse ears – including all professors ;-).

Helpful Hints for Future Students:
- Try out different pizza places, my favourites: BAR, Modern Apizza
- Visit the lighthouse park, east rock during sunset
- Visit New York as often as you can (one way fee via train aproximately 14$)
- Make overnight-trip via Madison, Plymouth to Falmouth (best during Indian Summer) – beautiful!
- Try to make a deal with your mentor in advance, that you do not have to pay the "VAR – visiting assistant in research" fee

Abstract on Research Topic - Luisa Susan Averdunk

Title: The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery

Authors: Luisa Averdunk[1]*, Christian Stoppe[1]*†, Andreas Goetzenich[1], Josefin Soppert[1], Arnaud Marlier[6], Sandra Kraemer[1], Jil Vieten[1], Mark Coburn[1], Ana Kowark[1], Bong-Song Kim[1], Gernot Marx[1], Steffen Rex[2], Akinobu Ochi6, Lin Leng6, Gilbert Moeckel6, Andreas Linkermann3, Omar El Bounkari6, Alexander Zarbock[5], Jürgen Bernhagen[4], Sonja Djudjaj[1], Richard Bucala[6], Peter Boor[1]
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Introduction:
Acute kidney injury (AKI) represents one of the most frequent complications after cardiac surgery and is associated with increased lethality. Macrophage migration inhibitory factor (MIF) is a stress-regulating cytokine that was shown to protect the heart from myocardial ischemia-reperfusion injury. The objective of this study was to determine the role of MIF in the pathogenesis of postoperative AKI.

Methods and Results:
Sixty patients scheduled for elective conventional cardiac surgery were enclosed in this oberservational study. Perioperative serum and urinary MIF was quantified. After cardiac surgery serum MIF showed a significant increase and patients with high circulating MIF (>median) 12 hours after surgery had a significantly reduced risk of developing AKI (relative risk reduction, 72.7%; 95% confidence interval, 12 to 91.5%; P = 0.03). Besides, perioperative MIF was negatively correlated with the tubular kidney injury marker Neutrophil Gelatinase-Associated Lipocalin in the urine. To mimic postoperative organ failure in vivo, AKI was induced by 30 min of ischemia in wild-type (WT) and Mif knockout (Mif−/−). After six or 24 hours of reperfusion, Mif−/− mice exhibited significantly increased serum creatinine. Immunohistochemical analyses revealed aggravated tubular cell injury, increased number of apoptotic cells (cleaved-caspase 3 positive) and necroptotic (phospho-Mixed Lineage Kinase Domain-Like positive) tubuli in Mif−/− mice. Equivalent results with exacerbated kidney injury in Mif−/− were obtained in a model with rhabdomyolysis, which was induced by glycerol injection. Therpeutic administration of recombinant MIF 30 minutes and 6 hours after ischemia reduced serum creatinine, apoptosis und necroptosis in WT mice. However, MIF augmentation did not ameliorate AKI in Mif-/- mice. For in vitro experiments, primary tubular epithelial cells were isolated and incubated in the setting of hypoxia. Treatment of tubular epithelial cells with recombinant MIF reduced cytotoxicity as measured by lactate dehydrogenase and oxidative stress as measured by glutathione and thiobarbituric acid reactive substances.

Conclusions:
The clinical data from the observational study and the results from the experimental study suggest a renoprotective role of MIF by protecting from renal tubular epithelial cell death which may open future perspectives for perioperative risk stratification and potential therapeutic options. Published in Science Translational Medicine, May 2018.

Funding:
Luisa Averdunk reveived funding for her BMEP time in the U.S. from the DAAD.

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Research Mentors:
Professor Hanns Lochmüller, MD, PhD

Your personal reaction to the UK experience:
When I arrived in Newcastle, I was picked up by an Uber driver with a very strong Geordie accent, such that it took me a while to realize that he is speaking English. However, this accent is not the only thing I got used to and learned to love during my stay in the North East of the UK. I never experienced such a friendly and helpful atmosphere before and at the end of my stay I even adapted quite a bit to this positive way of thinking and used the word "lovely" more than ever. This kindness also surrounded me in the lab, where I started as a complete beginner, who had never used a pipette before, but everyone was patient and willing to help. I will never forget this attitude towards new, foreign people being an important and valuable experience for me. Working together with motivated and open-minded people from all over the world, full of ideas and curiosity, was very inspiring to me and I am grateful that I had the opportunity to be part of this team.

Greatest Difficulties Encountered:
For me, it was sometimes very frustrating that most experiments did not work at the first attempt. Until then, I thought that hard work always leads to success – that is definitely not the case in the lab!
Apart from work it was a great difficulty to find good (meaning "normal") bread. Every day I was already starving at eleven because a white toast in the morning is definitely not enough for me.

Most Humorous Incident:
At the beginning, there were so many funny things happening in the lab because I was simply inexperienced. The first time I had to select female and male fish and put a couple each in a separate tank in order to get the eggs, I was disappointed that my fish couples apparently did not like each other resulting in the lack of any eggs in the tanks. My supervisor pointed out that they might actually come along well, but it is rather difficult for them to lay eggs as they were same-gender. It took me a long time to distinguish between males and big-bellied females, but I eventually figured it out.

Helpful Hints for Future Students:
Newcastle is famous for hen parties and proper nights out, which I did not know before I arrived. So I was quite surprised by all the groups of noisy and well-dressed groups of girls as I found myself to be literally the only one in a bar wearing trousers. But the Quayside nightlife is legendary so I could imagine myself going there for my own hen party one day.
Apart from that, never (!) forget your umbrella, enjoy the view of Newcastle while having a drink at "The Botanist", go to the beach at Tynemouth and just explore and love the rich and friendly character of the North East.

Abstract on Research Topic - Isabell Cordts

Title: Unveiling MYO9A pathophysiology in congenital myasthenic syndrome

Authors: Isabell Cordts, Emily O'Connor, Andreas Roos, Hanns Lochmüller

Institutions:
John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK

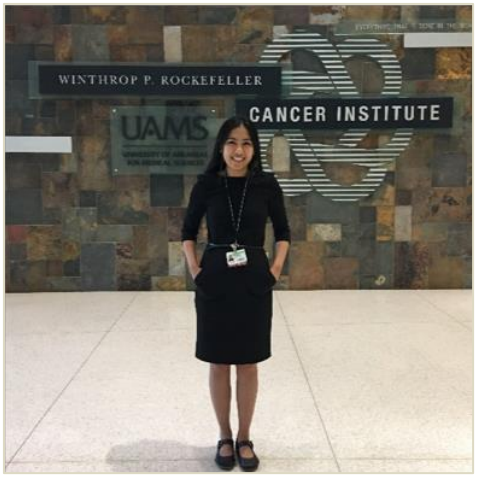
Introduction:
Congenital myasthenic syndrome (CMS) is a group of inherited disorders involving defects in the neuromuscular junction. It is characterized by the clinical feature of fatigable muscular weakness with symptom onset most often at birth or early infancy. Age at onset, severity of muscle weakness and therapy response show a large diversity and depend on the protein involved. CMS constitute a group of genetically heterogenic disorders and causative genes can be broadly categorised as presynaptic, synaptic or postsynaptic. Using whole exome sequencing, mutations in the MYO9A gene, encoding an unconventional myosin, have been recently identified in CMS patients. The aim of our study was to unravel the pathomechanism of MYO9A as a presynaptic CMS gene.

Methods:
Utilising the mouse motor neuron-derived cell-line NSC-34 (wild-type and MYO9A-depleted), the effect of reduced MYO9A expression on the cytoskeleton was investigated, using immunofluorescent and immunoblotting techniques. To investigate the impact of MYO9A mutations on the vesicular transport, we performed (1) a *secretome assay* in order to analyse the effects on secreted proteins from NSC-34 cells, (2) a *transport assay* to assess the transport of newly synthesised proteins to the cell surface and (3) a *recycling assay* to reveal the receptor recycling processes. A systematic and unbiased proteomic analysis of MYO9A-depleted NSC-34 cells was performed to identify dysregulated proteins and allow us to understand the molecular pathways involved in disrupted neuromuscular transmission.

Results and Conclusions:
We identified a disruption of the cytoskeleton in MYO9A-depleted cells, with an upregulation of f-actin and a downregulation of several other structural proteins. In cells depleted for MYO9A, defects in receptor recycling and transport of synthesised proteins to the cell surface were observed. In addition, proteomic data revealed numerous dysregulated proteins. Our data show that defects in MYO9A affect the neuronal cytoskeleton leading to an impaired vesicular transport and thus disrupt the functioning of the neuromuscular junction. The identification and understanding of genetic causes of CMS is essential since the choice of therapy depends on the molecular diagnosis.

Funding:
Isabell Cordts received funding for her BMEP time in the UK from DAAD.

Nova Kristine M. de los Reyes



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Your personal reaction to the U. S. experience:
This was my first time visiting the States, and it has proven to be an eye-opening and valuable experience. Upon arrival in Little Rock, I was warmly welcomed by my housemate, who is also a colleague in the same laboratory. The rest of the lab team also made me feel at home immediately, and it wasn't long before they became my good friends. I also made friends with fellow researchers in other labs at Cancer Institute as well as the neighboring Biomedical and Spine buildings through regular events, such as Science Café and postdoctoral social meetings.

Little Rock is a small, cosy city compared to Frankfurt, but I like it for being an urban city with lots to offer, while keeping that adorable Southern charm. The South offers great comfort food (e.g. Slim Chickens and The Cheesecake Factory), breathtaking natural scenery and warm and friendly local folks. We went for quintessentially American road trips to various parts of the South, and I also traveled to Chicago and Houston to meet relatives and old friends.

I've always been able to thrive best in international settings with people from diverse backgrounds, and my experience at this U.S. laboratory definitely proved that once again. Having little research exposure prior to this lab, I gained relevant experience in academic research, such as writing research grants, conducting animal experiments, writing research papers, presenting data and going out of my academic comfort zone (i.e. I had minimal knowledge of photoacoustics and nanotechnology prior to this experience).

I was also able to meet medical professionals and clinical researchers in UAMS, which allowed me to gain clinical research experience as well. Apart from research work, I learnt how to swim during my free time, how to appreciate the little quirks and idiosyncrasies of American life, and I also gained insight into the healthcare system in the United States.

Greatest Difficulties Encountered:
Acquiring DS-2019 document and applying for US J1 Visa on time. Getting around the city was quite difficult as I didn't own a car nor a driver's license, but there was always a kind friend offering to drive me around.

Most Humorous Incident:
Too many to mention!

Helpful Hints for Future Students:
- Settle immigration and bureaucratic paperwork at least four months prior to your departure.
- Contact your laboratory colleagues or the local international community in advance to get assistance regarding accommodations, tips, etc.
- Try to travel as much as possible, whenever you find the time for it.

Abstract on Research Topic - Nova Kristine M. de los Reyes

Title: *In vivo* detection of sentinel lymph node metastasis in melanoma murine models using label free photoacoustic flow cytometry and multispectral optoacoustic tomography

Authors: Nova Kristine M. de los Reyes

Institutions:
Phillips Classic Laser and Nanomedicine Laboratories, Department of Otolaryngology-Head and Neck Surgery, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Introduction:
Recent trials have shown that sentinel lymph node (SLN) status is the most significant prognostic factor in melanoma patients. Nevertheless, detection of SLN metastasis using minimally invasive SLN biopsy (SLNB) remains controversial. Recent advancements in cancer imaging such as multispectral optoacoustic tomography (MSOT) and photoacoustic flow cytometry (PAFC), have emerged as potential non-invasive, alternative imaging modalities to the current diagnostic standard, SLNB. MSOT has been used to detect SLN metastases ex vivo and in vivo using ICG dye in patients, and for label-free, in vivo detection of micrometastases in conjunction with PET-CT using melanoma murine models. PAFC has been utilized for real-time, label-free, in vivo detection of melanoma circulating tumor cells (CTC) in blood vessels of animal models and patients.
This experimental study aims to 1) demonstrate proof-of-principle that MSOT is capable of accurately detecting primary tumor size progression and assessing SLN status label-free and in vivo in melanoma murine models; 2) show that MSOT and PAFC are complementary methods in detecting SLN metastasis; and 3) investigate if MSOT is able to detect histopathologically verified distant metastases.

Methods:
Left ears of Nu/Nu athymic mouse models (n = 6) were inoculated with B16F10 melanoma mouse cell line. Primary tumor size was measured and clinical lymph node status was assessed weekly for 7 weeks. PAFC monitoring of mouse ear tumor blood vessel was conducted to measure CTC counts, followed by whole body imaging of each mouse including 2 control mice for label-free detection of metastasis using MSOT InVision 256-TF (IThera Medical, Germany) the next day, on a weekly basis. MSOT images were compared with PAFC measurements, then verified with histopathological analysis of primary ear tumor, SLN (submandibular) and distant organs (brain, lungs, liver).

Results and Conclusions:
MSOT is an accurate, non-invasive imaging modality for monitoring primary tumor size progression and assessing SLN pathology status in melanoma murine models. MSOT may be integrated with PAFC to predict emergence of SLN metastasis, by using peaks in CTC count detected by PAFC as a real-time biomarker for in-transit metastasis to distant sites, and then using MSOT to detect SLN micrometastasis. A future clinical prototype combining MSOT and PAFC for simultaneous detection of hematogenous and lymphogenous metastasis could support management decision for clinical nodal observation after primary tumor resection over invasive SLNB in melanoma patients.

Funding:
Nova Kristine M. de los Reyes received funding for her BMEP time in the United States from the DAAD.

Miriam Dibos

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Research Mentors:
Professor Yair Argon, Ph.D.

Your personal reaction to the U. S. experience:
I really enjoyed the time both in my lab and also travelling the country. Everybody in my lab here was treated equally, so it did not matter whether you are a PI, a postdoc, a grad student or an MD PhD. I knew the lab basics when I came here because I got some experience in a German lab before, but the time here helped me a lot to learn how to work independently, to stand by my results, and present and defend them in front of a highly knowledgeable audience.

Greatest Difficulties Encountered:
In my spare time, I played a lot of volleyball and used my bike and public transportation to get to different gyms. If you don't have a car, riding your bike and public transportation (plus taking your bike on the bus/train) can sometimes be very difficult in America. I also felt that most Americans could just not understand how I survive without a car.
Nowadays eating vegetarian in Europe is not a big deal anymore, but eating vegetarian in America sometimes can be very hard. Also, most of my friends here rarely cook.
Using a bike instead of a car and not eating meat made people think that I lived in an "organic bubble".

Most Humorous Incident:
For Christmas, we had booked an Airbnb on a farm in Arizona and our hosts invited us over for Christmas eve. This turned out to be by far the funniest evening in the US for me. This family of die-hard Trump supporters, who were incredibly hospitable and kind, kept telling us the weirdest stories about things they either believed in or had heard of and were convinced of.
This evening vividly summarized how contrary America and Americans can often be. We had a great time but could often only shake our heads in disbelief and laugh at what was talked about that evening.

Helpful Hints for Future Students:
- Everybody who has been trying to get an American visa knows how complicated the whole process is - don't let it discourage you, it will be so worth it!
- Lab work can be very competitive, stand up for yourself and your results, this can be a great learning experience.
- Enjoy your time here, travel and get to know the country and the people. The last year was one of the best years in my life.

Abstract on Research Topic - Miriam Dibos

Title: Clustering of the ER stress sensor IRE1 upon stress

Authors: Miriam Dibos

Institution:
Children's Hospital of Philadelphia, University of Pennsylvania

Introduction:
Endoplasmic Reticulum (ER) stress is triggered physiologically by glucose stimulation of pancreatic ß cells or by antigen-induced differentiation of antibody secreting cells. It is also frequently observed in pathological processes from neurodegeneration, inflammation to uncontrolled cell proliferation that leads to cancer. Secretory and transmembrane proteins enter the ER as unfolded proteins. ER stress occurs when the number of secretory and transmembrane proteins reaches a threshold and the proteins start accumulating. Their accumulation activates 3 coping receptors inside the cell: IRE1, PERK and ATF6. These stress sensors transmit the stress signal from the ER lumen to the cytosol where they activate transcription factors that either induce survival or death of the cell. The luminal domains of IRE1 (inositol-required enzyme 1) dimerize, a signal gets transmitted to the kinase domain, which auto-activates itself by phosphorylation, and afterwards to the RNase domain. The activated RNase domain of IRE1 splices a transcription factor, XBP1, and performs RIDD (regulated IRE1 dependent decay) on selected transcripts. After dimer formation, more and more IRE1 molecules cluster together and are visible as big foci under the microscope. These clusters form within the first hour after beginning of the treatment with an ER stressor, persist over 6 hours and then disperse, even when the cells are under continuous stress. As the activation of IRE1 either triggers cell survival or death, we raised several questions: What are the dynamics of the clustering behavior of IRE1? Is the clustering an autonomous activity of IRE1? And if yes, does it predict the fate of a cell?

Methods:
To image clustering of IRE1 in live cells, we used the leukemia cancer cell line HAP1, whose endogenous IRE1 gene was ablated by CRISPR/Cas 9, and which expressed a GFP-tagged IRE1. Mutated versions of IRE1-GFP were made by Dr. Daniela Ricci. Dr. Daniel Blumenthal and I developed an ImageJ plugin that can identify clusters and measure their size and intensity. To see whether clustering is associated with other activities of IRE1 or can be performed independently from others, the kinase domain of IRE1 was mutated and the clustering further investigated. Cell survival was investigated by tracking cells over 24 hours that become fluorescent when a caspase 3 substrate is cleaved.

Results and Conclusions:
Time-lapse analysis showed that IRE1 initially forms smaller clusters, that then fuse with each other into larger and more intense clusters. Their size seems to be restricted, as they quickly reach their maximum size although their intensity keeps increasing. To further investigate this, we performed bleaching experiments, where different stages of cluster were bleaching and the recovery of their molecules was observed. The bleached IRE1 clusters do not recover within the first minutes. Either the timeframe is too short to see recovery (as it also takes the clusters 1 hour to form) or these clusters actually do not recover. There could be multiple mechanisms behind that: stable protein-protein interaction with other partner proteins, which might limit the cluster size and prevent other IRE1 molecules to enter the cluster, or these clusters are simply so dense that it limits protein exchange. The clustering follows similar kinetics as the splicing of XBP1 and was therefore suggested to be related. A mutation in the RNase domain of IRE1, K907A, abolished both the XBP1 splicing and the RIDD activity whereas the clustering was not only sustained, but was very different from clustering of wild type IRE1: clusters of the inactive IRE1 were 4 times bigger and 10 times brighter, and in addition – persisted and did not resolve. That suggests that clustering is an IRE1 activity distinct from the RNase activity and therefore probably has its own outcome. We used two approaches to investigate whether clustering predicts whether a cell lives or dies: 1) lowering the dose of ER stress and 2) tracking single cells over time. At low concentrations of tunicamycin, a common ER stressor, the clustering was delayed and cell survival was unimpaired. Tracking of 1000 cells over 24 hours in a high dose of tunicamycin showed that 79% of the cells clustered within the first 8 hours but only 33% died after 24 hours and there was no correlation between cell survival and prior clustering. Therefore, at present clustering *per se* is not predictive of cell fate. Current re-analysis is aimed at determining whether different times of formation or dispersal of clusters are more predictive.

Funding: Miriam Dibos received funding for her BMEP time in the U.S. from DAAD and Studienstiftung des Deutschen Volkes

Nadine Gottschalk

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Home Institution:
Charité Universitätsmedizin, Berlin

Host Institution:
Northwestern University Feinberg School of Medicine, Department of Radiology, Chicago, IL

Research Mentor:
Ellen B. Mendelson, M.D., FACR

Your personal reaction to the U. S. experience:
The opportunity to be in Chicago has enabled me to become fluent in American English, both spoken and written, including medical journals. Northwestern's medical and law schools are in the heart of the city a few blocks from Lake Michigan. This huge lake is a wonderful resource for biking, walking, running, and swimming in the summer. I am very comfortable in Chicago, enjoy its many activities including its great symphony orchestra and art museum, the Museum of Contemporary Art, directly across the street of my working place, the Prentice Women's Hospital.

The research stimulation I have received from faculty and residents in Radiology has been enormous! I have been working with my mentors, Drs. Ingolf Karst and Ellen Mendelson on projects related to breast imaging, image-guided percutaneous biopsies, and multi-disciplinary decision-making regarding management of breast cancer patients.

Greatest Difficulties Encountered:
Bureaucratic regulatory requirements for research.

Most Humorous Incident:
During Christmas time many colleagues recommended to go to the Christkindlmarket in Chicago and to visit the ornament store with the Christmas pickle decorations as a nice German tradition. After hearing about the Christmas pickle multiple times I asked a friend of mine and she elaborated it would be a typical German Christmas symbol. She was perplexed that I had never heard about it.
After an internet search, we both learned the Christmas pickle is an American tradition but everybody is believing it originated from Germany.

Helpful Hints for Future Students:
Read detailed guidebooks to the city you will be hosted. It is best to prepare early for your stay, including obtaining Visa, finding housing, and potential social involvement. Plan your time wisely – it will go fast!

Abstract on Research Topic - Nadine Gottschalk

Title: Devising an Extension for a Program for Rapid Assessment of Breast Cancer Screening Quality Measures

Authors: Ingolf Karst, Nadine Gottschalk, Ellen B Mendelson

Institution:
Northwestern University Feinberg School of Medicine, Chicago, IL

Introduction:
Recognizing the need for rapid assessment of quality measures for screening mammography at a time of technologic change (e.g. 2D digital mammography to digital breast tomosynthesis), our goal was to forge an extension to our existing outcome database to help to improve quality of care in breast cancer diagnosis.

Methods:
During my nine month at Northwestern Dr. Karst programmed the database extension which enabled me to enter over 10.000 breast cancer screening mammography cases, which we then analyzed for cancer detection rates, recall rates, positive predictive values (PPV), specificity including statistical significance of these measures.

Results and Conclusions:
We were able to achieve our goal in establishing a relationship between quality measure e.g recall rates and cancer detection rates and introduction of new technology. As a result we are enabling breast imaging radiologists to alter recall rates, limiting their false positives but maintaining/increasing cancer detection rates while transitioning to new technology.

Funding:
Nadine Gottschalk received funding for her BMEP time in the U.S. from DAAD.

Peter Grabitz

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Charité Universitätsmedizin, Berlin

Host Institution:
McGill University, Biomedical Ethics Unit,
Montreal, Canada

Research Mentor:
Jonathan Kimmelman, Ph.D.

Your personal reaction to the Canada experience:
I was thrilled to be able to visit a completely bilingual city. Speaking both French and English became an exciting endeavor and quite often, even though being a foreigner myself, I had the impression that I could build bridges between English and French natives. The experience of living in a city where two different languages co-exist is odd to Germans. This is why I enjoyed it even more. I also enjoyed getting a glimpse of what North American university life is like.

Greatest Difficulties Encountered:
My stay in Montréal was exciting. I joined a highly enthusiastic and incredibly smart team at the Biomedical Ethics Unit at MGill. I worked fairly independently, having my own project and yet I engaged a lot with my colleagues. Montréal, more than any other place, is different in winter than it is in summer. For the first time in my life I felt what it is like when the hair in your nose starts freezing - because it is below -20°C outside.

Most Humorous Incident:
Montréal in winter is cold. Way too cold. And snowy. The people's mentality on the other side is very hands-on. While in most places the whole city shuts down when a few snowflakes fall, people in Montréal couldn't care less about the weather.
I attended "Igloo Fest". In the middle of February, Montreal celebrates an Open Air Festival. Not for a day, not for two, but for 4 consecutive weekends in a row.

Helpful Hints for Future Students:
Explore the city and surroundings to the max. Aside from research, Montréal has a lot to offer: In winter skiing is a great option (great rebates when joining a students‘ club), In summer open air festivals and hikes are great to get out of the city for a bit!

Abstract on Research Topic – Peter Grabitz

Title: The persistence and burden of failing drug development paradigms: An exploratory analysis of VEGF Inhibition in breast cancer

Authors: Peter Grabitz[1], Gaelle Le Moine[2], Benjamin Carlisle[3], Sean Zhang[3], Jonathan Kimmelman[3]

Institutions:
[1] Charité Universitätsmedizin Berlin, Berlin (Germany)
[2] Paris Descartes University, Paris (France)
[3] McGill University, Montreal (Canada)

Introduction:
The success of a drug against a given disease provides grounds for believing that other drugs in the same class may have similar success. In an age of targeted drug development, where trials are planned on the basis of a molecular understanding of disease, it is crucial that research systems efficiently integrate not merely the clinical implications of trial outcomes, but also the implications for a pathophysiological hypothesis. The success rate of oncology drug development is particularly low, as compared to other clinical areas. Dug developers commit substantial resources toward drug development paradigms. Often these commitments bear little fruit in terms of clinical impact, and can impose heavy expense and patient burden. One way such burdens can be mitigated and forestalled is if other efforts in a drug development paradigm build off upstream findings in trials attempting to validate the paradigm.
Our primary objectives were to describe and map the volume and temporal dynamics of trial activities, patient burden, benefit and risk over the lifetime of a cancer drug development paradigm that showed particular perseverance, VEGF-inhibition in breast cancer, and secondly to analyse and explain possible reasons why the research agenda around the drug development paradigm persisted despite contradicting evidence became available.

Methods:
We collected all clinical trials testing VEGF inhibition as treatment for breast cancer. We extracted key information about design, safety, efficacy, outcomes and timing from trial reports. We assessed patient burden using drug-related deaths and adverse events that are Grade 3 or higher. Benefit was assessed through Objective Response Rates (ORR) and, when applicable, Hazard Ratios (HR) described in published reports. We measured patient burden using drug-related deaths and adverse events that are grade 3 or higher (G3-5 AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). For any given report in the VEGF Inhibition paradigm we assessed citation bias by comparing cited earlier reports with overall cite-able earlier reports (based on a one year grace period for non-citation).

Results and Conclusions:
Preliminary results (60% of data analyzed) indicate that in total 4,080 patients receiving a VEGF inhibitor experienced objective tumour response (49.4%, 95%CI 48.3% to 50.4%), and 59 died from drug-related toxicities (0.553%, 95% CI 0.425% to 0.717%). A minimum of 3,419 patients experienced grade 3-4 drug-related serious adverse events (32%, 95% CI 31.1% to 32.9%). Of the total 275 citations in the network 188 occured between studies of the same drug, 87 cited a study investigaing another VEGF inhibitor. This emphasizes to which degree drugdevelopers think in single compounds instead of mechanistic principles. Once data collection is completed further analysis regarding citation bias will be undertaken.

Funding:
Acknowledge that some of the funding for your time in the US/Canada came from DAAD or whatever agency or institution provided any monetary help to you: DAAD

Karen Patricia Hartmann

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Hannover Medical School, Hannover

Host Institution:
Yale University – Department of Immunobiology, New Haven, CT

Research Mentor:
Aaron Michael Ring, M.D., Ph.D.

Your personal reaction to the U. S. experience:
One thing that stood out to me from the very first day was how extremely friendly and helpful Americans are. Starting with the "How are you doing?" that always follows a "Hello", and the "Have a nice day" paired with the sincerity with which people would say it, followed by unknown people offering to lend a hand with e.g. carrying your groceries to the car, or even pay for your purchases because you forgot your wallet at home! Throughout my whole stay, I experienced American people to be very kind and welcoming which made my time abroad very enjoyable.

Further, I am happy to report that I had a fantastic research experience at the Yale Immunobiology Department. The work ethic there was very motivating, and together with an excellent scientific training provided by experts in the field made this institution an outstanding place to conduct research. It was definitely a great opportunity to advance my skills while gaining insights into academic research and training in the U.S.

Finally, I have to admit that I was very impressed by how huge and diverse this country is, even though this is something that you are aware of before you go to the U.S. When I got the chance to travel to different regions, I was stunned by the variety of beautiful landscapes and exciting cities.

Summarizing, I can say that going abroad was a very enriching and valuable experience that helped me grow both personally and professionally. I can only encourage other students to benefit from such an amazing opportunity.

Greatest Difficulties Encountered:
Fortunately, I did not have to encounter greater difficulties. Getting the visa was certainly a lot of work and sometimes quite nerve-racking, but if you start early enough this should not be a major problem.

Most Humorous Incident:
I had great lab mates and made good friends, so there were many humorous incidents. But I cannot think of one in particular.

Helpful Hints for Future Students:
- Get your Social Security number, open an American bank account, and get an American phone number.
- Do couchsurfing or airbnb for the first days of your stay, and look for an apartment once you are there. Make arrangements beforehand, but go see the place personally. Talk to colleagues to find out which areas are recommended to live in. Also, try to find a shared apartment since this helps you make friends and settle in faster.
- Find out as much as possible about your research project and your role in the lab early before you go abroad. Try to align your interests and skills with the assignment you are expected to fulfil.
- Work hard, be dedicated, and accomplish a lot! But do not forget to also take some time to travel the U.S.!
- Maximize your experience in every single way. Try to stay at least six months, if not a whole year.

Abstract on Research Topic - Karen Patricia Hartmann

Title: Cytokine Engineering for Immunotherapy

Author: Karen Patricia Hartmann

Institution:
Department of Immunobiology, Yale University, New Haven, CT

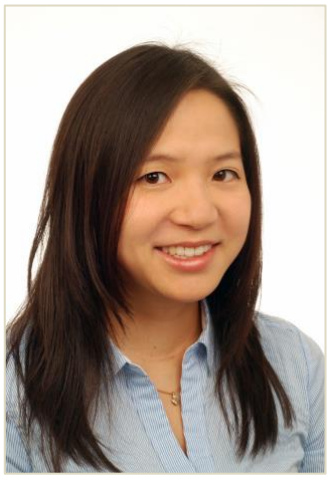
Introduction:
Cytokines are secreted or membrane-bound proteins that serve as intercellular signaling molecules to maintain immune homeostasis. These mediators act by binding to specific cytokine receptors located on the surface of their target cells. Receptor engagement triggers intracellular signaling cascades that regulate gene expression and control biological processes, including immune cell proliferation, activation, differentiation, and migration. Due to their crucial role as immune regulators, cytokines have been studied as potential therapeutic agents to modulate misled or inefficient immune responses causing autoimmune diseases and malignancies. Promising results have been achieved particularly in cancer immunotherapy. However, in spite of their great potential, cytokine-based therapies have been limited by numerous factors - the greatest being receptor pleiotropy and redundancy. One strategy to overcome this impediment is to develop engineered cytokines with altered receptor binding affinities and thus optimized biological activities. Our aim was to use a structure-based approach to engineer an immunostimulatory cytokine with enhanced properties for possible applications in immunotherapy.

Methods:
Directed evolution using yeast surface display in combination with flow cytometric analysis to engineer and select immunostimulatory cytokine variants with enhanced properties. Expression of recombinant cytokine variants in *E.coli* and purification using affinity chromatography, followed by biochemical and biophysical analysis via SEC, SDS-PAGE, and SPR. Functional analysis of recombinant cytokine variants in cell-based signaling assays as well as in *in vitro* experiments via flow cytometry, ELISA, and bead-based multiplex assays. *In vivo* mouse experiments to examine therapeutic potential of selected recombinant cytokine variants.

Results and Conclusions:
Based on the published structure of the cytokine receptor complex, we designed and generated a protein library comprising up to a billion diverse cytokine variants with mutated residues in the receptor binding side. Using yeast surface display, we screened the generated protein library for variants yielding our desired phenotype. Our screen identified four promising variants that were subsequently expressed and purified to assess their biochemical and biophysical properties as well as their biological activity. Our biochemical and biophysical analysis confirmed protein stability and receptor binding alterations favoring enhanced cytokine activity. These results were verified in cell-based signaling assays and in vitro experiments. Further, we observed an increased inflammatory immune response upon systemic administration of our recombinant cytokine variants in in vivo mouse experiments.
In conclusion, using a structure-based approach we were able to increase the immunostimulatory effect of our cytokine of interest by manipulating receptor binding interactions and screening for cytokine variants with enhanced properties.

Funding:
Karen Patricia Hartmann received funding for her BMEP time in the U.S. from BMEP/DAAD.

Ngoc-Nhi C. Luu



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Eberhard Karls Universität, Tübingen

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Research Mentors:
Professor Albert S. Edge, Ph.D.

Your personal reaction to the U. S. experience:
Though arriving in Boston for my third stay felt more like a 'coming home' experience, it was clearly different this time. A long-term stay ahead of me was promising an intensive, educational time as a full-time researcher, an essential step for me to move forward towards a more independent work and life style. For that purpose, the lab I could join was perfectly equipped. As one of the leading labs in the field it offered not only unique expertise and skills to learn from but also exceptional interaction including lectures and seminars with other labs of the big laboratory consortium at MEEI. But also outside the lab, I experienced Boston as a very international, interactive and lively city. It may be true that the city is not representative for the U.S., but it's for sure one of the cities which makes it easy for Europeans to blend in and make yourself a second home.

Greatest Difficulties Encountered:
Similar to the experience of others, I found the huge amount of paperwork to prepare challenging and time-consuming. This includes travelling to the embassy, organizing flight and housing for an arrival day which should match a day ideally after receiving visa and necessary forms in your mailbox. Difficult but important was also to get over 'normal research frustration' and to keep on going, with reserving some time for personal recreation in between. For me, the gym of the institution was a good way to load up some energy.

Most Humorous Incident:
Coming to the U.S. and get to know 'local Bostonians' turned out to be more difficult than expected, especially in a lab which is so international that it just has one slot for an American guy (currently from Texas) out of 15 lab member slots which are filled with people from China, Taiwan, Japan, India, Australia, Israel, Italy, France and Germany. Leaving the home continent for the U.S. was apparently needed for getting closer to French people for the first time and having just one single American/Texan guy in the lab who is representing "Murica" for me. More than that, leaving the home country was apparently also needed for me to feel more German than ever before. Here, I especially refer to my experiences during the UEFA European Championship far from home. I started to drink (undiluted!) beer for the first time and was desperately trying to get a companion and a place which was actually broadcasting the German matches. To be fair, my stay in Boston was hitting an exceptional time for Europe which you should better spend home, but I have never thought that I would miss (German!) beer, soccer, public viewing and Béla Réthy so much!

Helpful Hints for Future Students:
Craigslist gave me a hard time in separating honest and fake housing offers, I eventually got the best housing recommendation from the student coordinator of MEEI.
Boston is such a compact city so that you don't need a car nor a T-pass for public transport (depends on housing though), a bike and maybe a bike basket is all you need for getting everywhere. Just don't forget helmet, lights and the fact that Bostonians can't drive but are good in stealing bikes or parts of it! For an everyday ride to work the hospital offers a secured bike cage for parking.
Groceries are extremely expensive here. I got by with Haymarket once a week, which is one of America's oldest open air market offering fresh, affordable vegetables, fruits and fish. Even meat you can get in the same run at the Halal supermarket with access right from the Haymarket. Check the quality by natural instinct and you will be covered for at least a week with some of the lowest price in whole New England.
http://www.haymarketboston.org/market-tips/

Abstract on Research Topic - Ngoc-Nhi C. Luu

Title: Development of a therapeutic strategy for auditory nerve replacement

Authors: Ngoc-Nhi C. Luu, Judith S. Kempfle, Albert S. Edge

Institutions:
Tillotson Cell Biology Unit of the Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Introduction:
Degeneration of the auditory nerve is an important cause of sensorineural hearing loss in patients with auditory neuropathy or genetically inherited tumors involving the 8th cranial nerve (neurofibromatosis type 2, NF2). As auditory neurons do not regenerate spontaneously, our regeneration therapies focus on restoration of hearing by regenerating auditory neurons from glial cells that remain after the loss of spiral ganglion neurons.
One of the major players for self-renewal of neurons is the HMG domain transcription factor Sox2. As a key stem cell gene, it is expressed at high levels in embryonic and neural stem cells and maintains proliferation in progenitors during development and in the adult mouse.
We hypothesized that glial cells of the spiral ganglion have a similar capacity for regeneration as CNS glia and function as stem cell pool for spiral ganglion neurons. We assessed neural regeneration using neurospheres generated from a transgenic mouse model in which we could manipulate Plp-expressing glial cells in the spiral ganglion to up- or downregulate Sox2.

Methods:
Spiral ganglion stem cells were isolated from cochleae of neonatal Plp-Cre-ER; Sox2flox/flox mice or from Plp-Cre-ER; Sox2TetO/+ mice. Single cell suspensions of spiral ganglion tissue were cultured with growth factors to obtain proliferative spheres. Neurosphere formation was then quantified by immunohistochemistry after 2 passages. Under differentiation-promoting conditions, plated neurospheres were quantified after 9 days in vitro and analyzed for neural progenitor and more mature neural marker expression by quantitative RT-PCR and immunohistochemistry.
For downregulation of Sox2, 4OH-Tamoxifen was added to the culture medium continuously during proliferation or differentiation to induce the CreER recombinase in Plp-expressing (+) cells. For upregulation of Sox2, Tamoxifen was added to activate the Tetracycline transactivator protein (rtTA). In a second step, Doxycycline was used to upregulate the Tetracycline operator (tetO) and thus the gene of interest, here Sox2. Both drugs were applied during proliferation or during the first 3 days of differentiation. Lineage tracing of Plp-expressing neural stem cells was performed by immunohistochemical colocalization with tdTomato.

Results and Conclusions:
Quantitative RT-PCR revealed that Sox2 expression in Plp+ neurospheres was successfully altered between 24 - 48 h after induction from Sox2 +/-, Sox2 -/- and Sox2tetO, compared to control.
In our Sox2 loss of function model (Sox2 -/-), Plp+ progenitors from spiral ganglion neurospheres failed to expand during proliferation stage. When Sox2 expression was decreased in differentiating Plp+ prognitors, neurogenesis into TuJ+ neurons was greatly reduced.
Overexpression of Sox2 in Plp+ neurospheres increased proliferation of Plp+ progenitors at 3 days in vitro, and differentiation subsequently increased the number of early neurons derived from Plp+ progenitors. After 9 days of differentiation, the early neurons co-expressed Sox2+ with neuronal marker Tuj+.
Downregulation of Sox2 in Plp1-positive neurospheres failed to initiate neurogenesis upon differentiation. Transient overexpression of Sox2 led to neurogenesis from Plp1- positive progenitors in vitro. This study could contribute to understand the role of Sox2 in glial precursor cells and its ability to convert progenitor cells into neurons in the inner ear. Endogenous glial cells for neural regeneration after damage offer a novel tool for hearing restoration in situ.

Funding:
Ngoc-Nhi C. Luu received funding for her BMEP time in the U.S. from the DAAD.

Anna Masseli

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Host Institution:
Mount Desert Island Biological Laboratory, Salisbury Cove, ME

Research Mentors:
Professor Hermann Haller, M.D.

Your personal reaction to the U. S. experience:
Mount Desert Island lies right in front of Maine's coast and is well known for the beautiful Arcadia National Park, which is covering most of its surface. When I arrived in the middle of August Mount Desert Island was very busy with a lot of tourists coming in, looking for the perfect place to hike, rock climb or just to visit Bar Harbor as a quick stop on their ongoing cruise. I was very lucky to enjoy not only summer with its endless opportunities for outdoor activities, but also the Indian Fall and winter in Maine. Around the same time I arrived in Maine, a couple of young research assistants started working at MDIBL. So when winter came, my group of friends were busy planning weekend ski trips and snowshoeing in Arcadia. While Mount Desert Island can be a bit empty in winter time, I experienced its people to be very welcoming, friendly and open-minded. My lab colleagues were extremely generous in sharing their knowledge and experience. They supported me in every aspect of my research project, investing time and effort in answering questions and teaching me new techniques. Offering excellent tutorship and research opportunities, as well as amazing people, MDIBL was both personal and professional a unique experience which I am very grateful for.

Greatest Difficulties Encountered:
The greatest difficulties I certainly encountered before setting foot in the United States, while I was soliciting my visa. It takes longer than you think to gather all the documents in order to be considered for a visa.

Most Humorous Incident:
One of my friends decided to apply for med school. We had already talked about some of the schools she was considering. So when she told me that she got invited to an interview, I asked her to which school. She told me about the very "tough" school. It was not until later that I found out that the very "tough" university was actually Tufts University.

Helpful Hints for Future Students:
Start applying for your visa early enough, because it will take its time.

Abstract on Research Topic – Anna Masseli

Title: The role of Sulfatase1 and Sulfatase2 in the function of the glomerular filtration barrier

Author: Anna Masseli

Institution:
Mount Desert Island Biological Laboratory, Salisbury Cove, ME, USA

Introduction:
Sulfatase 1 (Sulf1) and Sulfatase 2 (Sulf2) are 6-O-endosulfateses that by modifying the sulfation pattern of heparan sulfate are considered to change its properties as co-receptor to the Vascular Endothelial Grow Factor (Vegf), affecting angiogenesis and the function of the glomerular filtration barrier.
While in Sulf1 knockdown zebrafish there has been shown severe vascular patterning defects, there is little known about the role of Sulf2 in the development of blood vessels and its effects on the glomerulus in Zebrafish. And though Sulf1 knockdown is discussed to change Vegf-signaling, it remains unclear and controversial how the signaling is affected.

Methods:
The Sulf1/Sulf2 knockdown were performed in zebrafish (Danio rerio) using splicing-morpholinos. The antisense oligonucleotides bind to the pre-mRNA at the exon-intron border and thereby block the splicing of the pre-mRNA to the mature mRNA. The morpholino was injected into 1-4 cell zebrafish embryos.
The zebrafish larvae were monitored for the development of edema and proteinuria over 120 hours post fertilization (hpf) as indicators for the renal function of the zebrafish. The edema was classified on the basis of the phenotype into the groups P1 (no edema) to P4 (very severe edema). For the proteinuria assay transgenic fish lines were used, which express green fluorescent protein (GFP) attached to fatty acid binding protein (Fabp). The loss of this high molecular fusion-protein through the urine can be measured through the loss of fluorescence in the eye of the zebrafish larvae. Images of the eye were taken at 72, 96, 120 hpf and analyzed using Image J. Knockdown fish and control fish were embedded at 120hpf for electron microscopy. For the in vivo confocal imaging of the vasculature Fabp-GFP and Flk-mcherry double transgenic fish were used. Through the red fluorescence labelled promotor of the VEGF-receptor (flk) the development of the blood vessels can be examined. Samples of control and knockdown fish were collected for further analysis of altered VEGF-signaling.

Results and Conclusions:
The development edema phenotyping and the loss of fluorescence in proteinuria assays indicate strongly that both Sulf1 and Sulf2 knockdown zebrafish have impaired renal functions. In Sulf2 knockdown zebrafish the proteinuria diminishes over time while in Sulf1 knockdown zebrafish the proteinuria is consistent over the examined period of time. The vasculature imaging shows evidence that angiogenesis during the larvae stadium in Sulf2 knockdown fish is affected more severely than in Sulf1 knockdown fish, indicating that Sulf2 is most important during larvae development.
Electron microscopy and experiments on the Vegf-signaling in Sulf1 knockdown zebrafish are still ongoing.

Funding:
Anna Masseli received funding for her BMEP time in the U.S. from DAAD.

Tilman Müller

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Host Institution:
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Northwestern University Chicago, IL

Research Mentor:
Professor Daniel Batlle, M.D., FACP

Your personal reaction to the U. S. experience:
Chicago definitely matched my expectations. I found a big and very diverse city with an easy-going and friendly population. From skyscrapers to very nice suburban neighborhoods, beaches and cool events, Chicago has it all, for sure I can't say that I was bored. Everyone is really into sports and you see a lot of people wearing shirts or hats of their favorite team. Especially Baseball is highly celebrated here, which resulted in a big party throughout the whole city, when the Cubs won the World Series for the first time in over 100 years.
Working in the labs of Northwestern University was a great experience. My lab was on the 10th floor in a building near the lake and had an astonishing view on Navy Pier, perfect scenery for a quick mental break. I also went to a lot of lectures and clinical case conferences in the hospital, which all had a very laid-back atmosphere.
I am taking home a lot of memories as well as friends and thank BMEP for making all this possible.

Greatest Difficulties Encountered:
Probably grocery shopping, especially good bread was really hard to find. None of the brands for e.g. cheese were familiar to me, so I had to go for try and error and of course I went to Wholefoods the first time without knowing how expensive everything is there. Fortunately, I found an ALDI later!

Most Humorous Incident:
There were numerous little stories or misunderstandings leading to funny situations. One of my favorite memories is about a night of card games with some friends.
At some point I tried to explain to them how you play Skat. I barely made it past the point of bidding (which is indeed quite complicated, but necessary so you can start with the actual game), when the others just commented that this is exactly how they imagined a German card game to be like.

Helpful Hints for Future Students:
Rent an apartment through Airbnb for the first month or two and start looking for a shared flat once you are in the States, if finding one while in Germany proves to be difficult as it was in my case. Most of the people (e.g. on craigslist) will want to meet the applicants first.
Americans are very friendly and helpful especially towards tourists, so play the tourist card from time to time for an extra bright smile and good local advice.

Abstract on Research Topic – Tilman Müller

Title: Characterization of the Apelinergic System in Mouse Kidney

Authors: Tilman Müller, Anastasia Z. Kalea, Jan Wysocki, Minghao Ye, Daniel Batlle

Institution:
Department of Medicine, Division of Nephrology and Hypertension, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

Introduction:
Apelin is the endogenous ligand for the G-protein coupled receptor APJ, that is widely expressed in various organs including heart, lung, kidney, liver, brain, adipose tissue, gastrointestinal tract and human plasma. Since its discovery in 1998 many studies showed beneficial effects of apelin especially for the heart and blood pressure. Apelin is the most potent stimulator of cardiac contractility and exerts an anti-remodelling and anti-apoptotic effect on heart cells, whereas lowered concentrations of circulating Apelin are associated with an increased risk of hypertension.
In mouse models of type 1 diabetes mellitus, Apelin was found to antagonize pathological effects on kidneys such as kidney and glomerular hypertrophy, renal inflammation as well as albuminuria. Yet the evidence on how the Apelinergic system might contribute to these effects is incomplete. The aim of this study was to localize and characterize apelinergic system components in the kidneys and examine signaling pathways in kidney cells with abundant apelin receptor expression.

Methods:
Obese db/db mice were used as a model of type 2 diabetes, their lean littermates (db/m) served as nondiabetic controls. Kidneys and hearts from 8 weeks old female mice (C57BLKS background) were halved. One half was used for protein and RNA analysis, the other was fixed with 10% buffered formalin phosphate, paraffin embedded and sections were stained with rabbit-anti-apelin and -anti-APJ. Hematoxylin was used as for counterstaining. Antibodies to cell-type specific markers were used to stain podocytes, endothelial cells, and mesangial cells. Confocal microscopy was performed using a Zeiss LSM 510.
Apelin protein levels were measured by ELISA directed against the C-terminus of apelin. Conditionally immortalized mouse podocytes were cultured, stimulated with apelin and activation of cell signaling proteins were detected by Western Blot using antibodies to their phosphorylated forms.

Results and Conclusions:
In conclusion, the present study shows that in the kidney glomerulus the apelin receptor is preferentially localized in podocytes, which showed a transient change in the phosphorylation status of the signaling proteins, AKT, ERK, and p70S6K, 15 min after stimulation with Pyr 1Apelin-13. In podocytes, APJ mRNA was downregulated in high glucose, when compared to normal glucose conditions and exposure to angiotensin II led to a further significant decrease in APJ mRNA levels while the apoptotic effect of high glucose on podocytes can be reversed by stimulation of APJ by one of its main ligands Apelin-13. In diabetic db/db mice kidney, APJ and preproapelin expression is markedly decreased at the mRNA level and protein level. Altogether our findings suggest a role for APJ downregulation in the development of DKD. The half-life of apelin-13 and other apelins is short (minutes) but with the development of apelin agonists with prolonged half-life (Juhl et al. 2016; Huang et al. 2018), the podocyte apelinergic system may become a good target for the treatment of DKD. Published December, 6th 2018 (doi: 10.14814/phy2.13939).

Funding:
Tilman Müller received funding for his BMEP time in the U.S. from DAAD.

Patrick Rhodius

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Host Institution:
Wound Healing & Tissue Engineering Lab,
Department of Surgery, Harvard Medical School, Boston

Research Mentors:
Professor Dennis P. Orgill, M.D., Ph.D.

Your personal reaction to the U. S. experience:
I am most grateful for the amazing opportunity to gain a profound insight into U.S. research culture as part of my medical studies and for thereby promoting my personal development. This was my first stay in the U.S. and when I arrived at Boston, I was impressed primarily by the exceptionally privileged academic environment, but also by the vibrant beauty of the city, with its bright Charles River Bay and shimmery golden skyline at sunset.
My first day was marked by an individual guided tour around the hospital and Longwood Medical Area, which was complemented by a warm welcome at the lab meeting.
The whole team was very professional and just great, we often went to different places for lunch and met after work. I was fortunate enough to meet some of the most fascinating inspiring people, who I now call friends.
Being given the excellent opportunity to work at HMS facilities, attending Plastic Surgery Grand Rounds, exploring research in the beautiful environment of Boston/Cambridge and above all making both scientific and interpersonal progress has been a perfectly unique experience.

Greatest Difficulties Encountered:
Acquiring a DS-2019 visa and clearance from the Department of Homeland Security remains a nerve-racking cause. Finding affordable accommodation can turn out to be quite difficult while you are still in Germany. Try to get some university support and do not sign off any rental contract before actually seeing the place. Suburban neighborhoods are seriously dangerous and cannot be recommended.

Most Humorous Incident:
Far too many to make an easy choice! The Plastic Surgery Department's Christmas holiday celebration and the McCloy Viennese Ball at Harvard certainly stuck out as two of the most magnificent memories.

Helpful Hints for Future Students:
- Start planning ahead regarding visa application at least 4 months in advance.
- Pack a warm coat and water-resistant boots, especially if you are going to stay for the northern hemisphere winter.
- Explore a rich variety of downtown clubs/bars. Pick up social activities with fellow students such as Harvard Ballroom Dance!
- Take some time for weekend trips to New York City and Washington D.C.

Abstract on Research Topic - Patrick Rhodius

Title: Moderate-Intensity Intermittent External Volume Expansion Optimizes the Soft-Tissue Response in a Murine Model

Authors: Patrick Rhodius, Giorgio Giatsidis, Anthony Haddad, Luca Lancerotto, Hajime Matsumine, Dennis P. Orgill

Institution:
Tissue Engineering and Wound Healing Laboratory, Department of Plastic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston

Introduction:
Intermittent external volume expansion using suction enhances the vascular network of soft tissues, possibly increasing fat graft survival. However, the optimal kinetics of application have not been determined. Based on their previous experience, the authors hypothesized that moderate-intensity intermittent external volume expansion application may further enhance both the angiogenic and adipogenic potential.

Methods:
Fifty 12-week-old wild-type mice were assigned to five experimental groups (n = 10 per group) and underwent five different intermittent applications of external volume expansion (i.e., single-application control, low-intensity, moderate-intensity, and two groups of high-intensity). Five days after the final stimulation, skin biopsy specimens were obtained from stimulated and contralateral nonstimulated areas. Microscopic sections were analyzed for angiogenesis, skin remodeling, and adipogenesis.

Results and Conclusions:
Moderate-intensity intermittent stimulation (0.5 hour, 6 times/day for 5 days at -25 mmHg suction) almost doubled cutaneous vascular density (1.9-fold increase), induced skin thickening (1.9-fold increase), and expanded the subcutaneous tissue (2.3-fold increase) compared with control. External volume expansion kinetics did not affect tissue inflammation at 5 days after treatment. High-intensity intermittent stimulations also increased the density of blood vessels (1.6-fold increase compared with controls) but caused tissue damage, whereas low-intensity external volume expansion did not induce significant changes.
Application of moderate-intensity intermittent external volume expansion optimizes induction of angiogenesis and adipogenesis in soft tissues without tissue damage, holding potential for time-effective recipient-site preconditioning before fat grafting.

Funding:
Patrick Rhodius received funding for his BMEP time 2016-2017 in the U.S. from DAAD.

Jeannette Tang

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Home Institution:
Charité Universitätsmedizin, Berlin

Host Institution:
Northwestern University, Chicago, IL, USA

Research Mentors:
Daniel Batlle, M.D.

Your personal reaction to the U. S. experience:
Chicago – What a place. I am extremely grateful to have lived in this beautiful city and experienced its many different facets. On the obvious side there is the city's unique history that gave way to its magnificent architecture, rich cultural diversity and communities. The cosmopolitan buzz is mixed with Midwestern authenticity, resulting in an atmosphere that feels deeply American. Being here when Donald Trump became president and the Chicago Cubs won the World Series – the last time they won was 1906 – gave insights into the American psyche during times of deep despair and great joy. I attended equally as many sports games as I did protest marches. I met people from all walks of life and learned about their hopes, dreams and ambitions.
The people I worked with in the lab were very supportive, helpful and friendly from the get-go. They were wonderfully international and unique, a fact I am very appreciative of. Going to work was fun and invigorating. Even at times of high pressure (the week before an important deadline), we managed to all work together well.
From work to life outside of work, I will always look back on this year as a profoundly formative experience in my life, both professionally and personally.

Greatest Difficulties Encountered:
The greatest difficulty was by far visa related. There were a lot of unforeseeable obstacles that delayed the beginning of my stay by almost a month and required me to return to Germany halfway through the year to apply for a new visa. In the end, it worked out but it cost a lot of money and nerves.

Most Humorous Incident:
There were countless humorous incidents throughout the year! Off the top of my head, I went to Chinatown with a group of Venezuelan people for Lunar New Year and we ended up having lunch at a dim sum restaurant. They were very conservative and cautious in what they wanted to order. Naturally, I felt compelled to help them see light and break free from their debilitating culinary constraints, and I ordered daring, "advanced" dishes, such as chicken feet and turnip cake. Unfortunately, the particular chicken feet dish that was served in that restaurant was really… bad. My promises that usually, chicken feet taste much much better were met with disbelief and raised eyebrows. We never went out eating together again.

Helpful Hints for Future Students:
Take care of paperwork early. Don't panic, it will work out in the end. Everything will be new, unfamiliar and sometimes scary. Be curious and confident. Talk to people. Live with locals. Go out and explore, explore, explore! Go travelling!

Abstract on Research Topic – Jeanette Tang

Title: On the Significance of Urinary Renin in Diabetic Kidney Disease: A Critical Role of Impaired Reabsorption

Authors: Jeannette Tang, Jan Wysocki, Johannes Rein, Minghao Ye, Maryam Afkarian, Daniel Batlle

Institutions:
Division of Nephrology/Hypertension, Northwestern University, Feinberg School of Medicine, Chicago, IL; Department of Internal Medicine, University of California, Davis, CA

Introduction:
Increased expression of renin in the kidney collecting tubule of rodents made diabetic by streptozotocin (STZ) has been well demonstrated but whether this site is the main source of urinary renin is unknown. We wanted to examine the origin and significance of urinary renin in diabetic kidney disease (DKD).

Methods:
Total and active renin was evaluated in urines from people with longstanding type 1 diabetes of more than 25 years, with (n=36) or without DKD (n=38) (eGFR 101 vs. 39 mL/min/1.73m2; $p<0.001$). Mice given STZ (n=15) or vehicle (n=8) 20 weeks prior to study were also studied. To examine the role of filtration and tubular reabsorption on urinary renin, human active renin was measured in urines from non-diabetic mice infused with human recombinant renin (hrRenin) (n=8), a combination of lysine and hrRenin (n=5) and non-infused controls (n=15).

Results and Conclusions:
In people with DKD, total renin was markedly increased compared to people without DKD (82 vs. 49 pg/mg Cr; $p=0.023$). Active renin was also significantly increased in people with DKD compared to people without DKD (3.2 vs. 1.3 pg/mg Cr; $p<0.001$). In mice with STZ-induced DKD a significant increase in renin was found compared to controls (1093±319 vs. 64±18 pg/mg Cr; $p=0.0001$). Urines of mice infused with a combination of lysine (a blocker of proximal tubular protein reabsorption) and hrRenin had markedly higher urinary human active renin than those of controls (179±129 vs. 1.6±0.4 pg/mg Cr; $p=0.001$). The values were also markedly higher than those of mice infused with hrRenin only (4.4±1.1 pg/mg Cr; $p=0.003$). The effect of lysine was also evaluated in regard to endogenous mouse renin. Urinary mouse renin in mice infused with lysine (n=5) was markedly increased compared to non-infused controls (n=18) (22360±8673 vs. 346±82 pg/mg Cr; $p=0.001$).
In humans with DKD, urine concentrations of both total and active renin are increased. In mice with STZ-induced DKD, urine total renin is also markedly increased. The data further demonstrate that renin is both filterable and reabsorbable in normal mice. At the time of writing, experiments are being conducted to investigate whether the increase of urinary renin seen in DKD can be attributed to increased renin filtration coupled with its impaired reabsorption or increased tubular production.

Funding:
Jeannette Tang received funding for her BMEP time in the U.S. from DAAD

Peter Truckenmüller

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Host Institution:
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Research Mentors:
Professor Michael G. Kaplitt, M.D., Ph.D.
Professor Roberta Marongiu, Ph.D.

Your personal reaction to the U. S. experience:
New York City may not be representative of America but constitutes a separate world formed by a bit of each part of the planet. Even within my circle of friends I found people from every ethnicity and style. Due to this variety, I got to know a lot of different people with different views and everyone could express him- or herself in any unique way. Since there are a lot of like-minded people who come to New York City to pursue their goals you will not feel like a stranger but like being part of the city and contributing to what distinguishes New York from other cities.

Greatest Difficulties Encountered:
Although New York City is considered a melting pot, the size and the pace of the city can make it difficult to socialize and find new friends. If your budget does not already force you to live in a shared apartment, this might be very helpful – especially in the beginning. I found great roommates who integrated me into their activities and social lives. However, I have been advised that such a great dynamic with roommates is an exception so take your time looking for a place to stay. But once you connect with people you will find the most amazing friends.

Most Humorous Incident:
For Thanksgiving friends and I fried a turkey that we attached to a chain in a huge pot of boiling oil on the rooftop overlooking the skyline of Manhattan. That was definitely a funny moment.

Helpful Hints for Future Students:
New York offers endless opportunities of watching art and performances, attending parades, free events, parties or cultural celebrations beyond the regular experiences and activities. In order not to miss out, I recommend to frequently check out ´Time Out New York´ or ´pulsd NYC´. These online guides let you know about upcoming events every day. You should buy tickets in advance since some of the events sell out pretty fast.

Peter and his co-workers on his last day out in the City

Abstract on Research Topic - Peter Truckenmueller

Title: Chemogenetic Inhibition of the Subthalamic Nucleus improves motor function in the Parkinsonian Rat Model

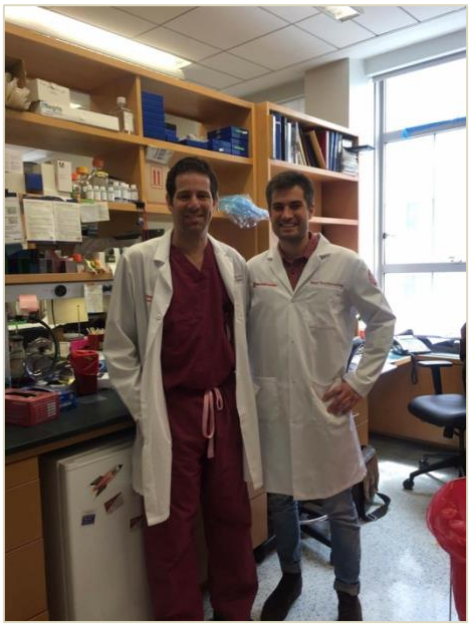
Author: Peter Truckenmueller

Institutions:
Laboratory of Molecular Neurosurgery, Department of Neurological Surgery,
Weill Cornell Medical College, New York

Introduction:
Parkinson´s disease (PD) is a neurodegenerative disease with the loss of Dopaminergic cells in the nigrostriatal system leading to movement disorders. The symptoms are caused by an altered neuronal activity of the basal ganglia circuitry with a higher activity of the subthalamic nucleus (STN). Deep Brain Stimulation (DBS) of the STN has been shown to relieve motor symptoms in patients with PD restoring the balance of the basal ganglia. However, the underlying mechanism of the implanted electrode is still controversial but inhibition is considered to be part of the effect. Here, we used chemogenetics, a neuronal perturbation tool using an engineered chloride-selective Ligand-Gated Ion Channel (LGIC), to inhibited the neuronal firing of the STN in unilaterally lesioned, parkinsonian rats. The chemogenetic approach is fairly new and allows for control of neuronal activity without implanting an electrode and fibers that restrict the animal´s movement and experimental flexibility as in case of DBS and optogenetics.

Methods:
After unilateral 6-OHDA lesioning of the medial forebrain bundle in Sprague Dawley Rats in order to create PD on one side of the brain, we stereotactically injected Adeno-associated virus serotype 1/2 encoding either for the chemogenetic LGIC to inhibit the subthalamic neurons upon ligand application or for mCherry as a negative control into the STN on the lesioned side of the brain. Both vectors were under control of the Synapsin promoter. After enough time to guarantee a sufficient expression in the transducted neurons, pontaneous and drug driven rotational behaviour was used to assess the effect of the inhibition of the STN.

Results and Conclusions:
Since the rats are lesioned unilaterally, the healthy side of the brain shows a higher output of the basal ganglia circuitry with higher motor activity causing ipsilateral spontaneous rotations. These spontaneous rotations can be counted and used as a marker for the severity of the motor disorder. Application of he LGIC ligand in both groups leads to reduced ipsilateral spontaneous rotations in the group treated with the chemogenetic channel compared to the baseline without ligand whereas the number of rotations remains the ame in the control group. This indicates that chemogenetic inhibition of the STN in the lesioned side of the brain restores the balance of the basal ganglia circuitry approximating the level of the healthy side. Some of the rats even rotated to the contralateral side. The result could be confirmed in drug driven rotations. The lesioned side of the brain is deprived of Dopamine and therefore highly sensitive to Dopamine agonists. Thus, the lesioned side responds to Apomorphine, a dopamine agonist, with higher output than the healthy side and causes contralateral rotations instead of ipsilateral rotations as in case of the spontaneous rotations. Dopamine agonists are used in the treatment of Parkinson patients and lead to an inhibition of the hyperactive STN. The inhibition of the STN in the chemogenetic group potentiates the effect of Apomorphine and increases the drug driven contralateral rotations in the chemogenetic group whereas the number of rotations remains again the same in the control group. Both the decreased spontaneous ipsilateral rotations and the increased drug driven contralateral rotations indicate that the inhibition of the STN compensates for the loss of Dopamine in the lesioned, parkinsonian side of the brain. Further we showed that the chemogenetic approach is a great tool to manipulate neuronal circuitry and might be used as a feasible gene therapy in the STN of parkinsonian patients.



Miriam Weiss

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Center for Cerebrovascular Research (CCR)
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Research Mentors:
Professor Hua Su, M.D.
Professor Michael T. Lawton, M.D.

Your personal reaction to the U. S. experience:
I first became familiar with living in the US during a high school year in small town Washington State. San Francisco life differed tremendously from that with its openness, creativity, spirit of innovation, and political activity. Having half of all new people outside the medical facilities tell you they are running a start-up became completely normal. There is a vibe to the city that is extremely motivating and inspiring. The city and surroundings are breathtaking so the quality of free time more than made up for what it lacked in quantity.

Greatest Difficulties Encountered:
Coming back to Germany after a time with so much professional and personal thrill.
On site, finding a place may prove difficult but I got lucky. Have no illusions about stellar prices for small rooms.

Most Humorous Incident:
I encountered some mad Uber drivers. Once I saw people beating Trump Piñatas in Mexicotown and once I saw someone walking around with a living cat on their head – San Francisco has them all.

Helpful Hints for Future Students:
More of a general but never too old advice: Don't be afraid to show motivation, work hard and ask for what you seek in return. It may just be within reach and you may be getting the most profound experiences and greatest chances out of it.

Abstract on Research Topic - Miriam Weiss

Title: Alk1 Deficiency in Bone Marrow-Derived Endothelial Cells may be Sufficient to Cause Brain Arteriovenous Malformations in Mice

Authors: Miriam Weiss, Qiang Li, Man Luo, Wan Zhu, Rui Zhang, Li Ma, Sen Wang, Michael T. Lawton, Hua Su

Institutions:
Department of Anesthesia and Perioperative Care, University of California, San Francisco
Department of Neurological Surgery, University of California, San Francisco

Introduction:
The exact pathophysiology of brain arteriovenous malformations (bAVM) remains unclear up to date. Haploinsufficiency of Eng (HHT1) or Alk1 (HHT2) causes AVMs in multiple organs, including the brain. Recent evidence in animal models showed that endothelial cells may have a significant impact on bAVM formation. This study investigates the role of Alk1 knock out in bone marrow derived endothelial cells (BMDEC) on AVM formation in a mouse model.

Methods:
We used wild type mice and mice with an inducible Alk1 knock out coupled to endothelial cell gene expression in a Cre-LoxP model. Wild type mice were irradiated at a lethal dose and rescued by bone marrow transplantation from the genetically altered mice. After a resting period, the mice were injected with an adeno-associated viral vector expressing vascular endothelial growth factor into the basal ganglia, and tamoxifen to induce the Alk1 knockout. After a second resting period, the mice were terminated, vessel density and occurrence of vessel dysplasia determined and specific immunostaining of endothelial and immune cells was performed. Control groups were established.

Results and Conclusions:
We detected increased vessel formation and dysplasia in the test group. These preliminary findings show that the impact of BMDECs alone may be significant enough for bAVM formation.

Funding:
Miriam Weiss received funding for her BMEP time in the U.S. from DAAD.

Note:
The above stated project represents the main project. Further projects included:

- Role of macrophages and microglia in bAVM pathogenesis (mouse model)
- CRISPR/Cas9 mediated Alk1 mutation to induce bAVM formation (mouse model)
- Validation of the BEHAVIOR score for cerebral infarction after subarachnoid hemorrhage
- Risk of Aneurysm Residual Regrowth, Recurrence, and De Novo Aneurysm Formation after Microsurgical Clip Occlusion Based on Follow-up with Catheter Angiography (published in World Neurosurgery)

Laura M. Wienecke

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Hannover Medical School, Hannover

Host Institution:
National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London (UK)

Research Mentors:
Professor Johann Bauersachs, MD
Professor Sian E. Harding, PhD

Your personal reaction to the UK experience:
Regarding my work in the lab at Imperial, I experienced a very open and communicative atmosphere with extremely fruitful discussions and lab meetings, promoting the exchange of ideas and experiences within the group. As already reported by many others, the hierarchical structures and the Professor-Student relations are different compared to Germany. During my first weeks, I was really astonished by the respect my professors showed for me and by the mutual appreciation between both, students and professors in general.

Most British people and all people I met so far are very kind, respectful and polite. It almost sounds like a cliché, but I have to remark that the extreme British politeness and the fear of being rude are interfering with my beloved straightforwardness as usually practiced in Germany. Hence, constructive criticism, for example, was rarely practiced in my surrounding. Regardless the situation, whether on the hockey pitch or after a presentation in front of the lab, my seeking for suggestions of improvement seemed to be unusual and only ended up in a courteous "well played" or "well done".

I very much appreciated the pleasant British culture in terms of sports, the British accent, the atmospheric pub culture and the mostly elegant attire and behaviour. On the other hand, I witnessed an eventful time of political chaos and disasters. Especially London, with its enormous contraries left a deep impression. The massive gap between the poor and the rich living in co-existence, but beyond any reach, has never been so apparent to me. London thereby offers loads of wonderful places, markets, events, cultural and academic options and it definitely is a paradise - for prosperous people.

After moving you have to rebuild your social life and leisure time activities. College societies and clubs provide brilliant opportunities to get in touch with other students.

I played for the women's 1st team of Imperial Medics Hockey Club, joined the Cricket Club in summer (to get the full British experience) and had German food at socials with the German Society. For me, the clubs opened the door to authentic College life, parties, formal dinners, events, College league matches and most importantly, established many, hopefully long-lasting friendships.

Greatest Difficulties Encountered:
It should be pointed out that being responsible for everything concerning your new research project and life abroad is an important lesson to learn. Next to cycling in London, the most challenging task was muddling through the jungle of forms by NHS bureaucracy with the attempt to get permission for a short clinical observership.

Most Humorous Incident:
During my stay, I had countless marvellous moments hard to reproduce on the little space remaining on this page. When looking for accommodation before coming to London, Imperial Student Hub directly refused my application for a vacancy in their halls of residence, just to offer me a place a few weeks later after I just arrived. I finally got the most beautiful luxury room in a top floor flat with a panoramic view over central London.

Helpful Hints for Future Students:
My precocious advice: Do not work for "positive" research results, otherwise disappointment will hit you hard. Work for the "truth" and good quality of your data! Overall, enjoy yourself during your stay abroad, socialise and visit as much as you can.

Abstract on Research Topic - Laura M. Wienecke

Title: The role of Takotsubo Syndrome associated miR-16 and miR-26a on adult and pluripotent stem cell-derived cardiomyocyte contractility

Authors: Laura M. Wienecke[1,2,3], Liam Couch[1], Thomas Thum[1,3], Cesare M.N Terracciano[1], Sian E. Harding[1]

Institutions:
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[3] Institute of Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School, Hannover

Introduction:
Takotsubo Syndrome (TTS) is an acute, but often reversible, type of severe heart failure, caused by emotional or physical stress. Initially, the symptoms resemble an acute myocardial infarction (MI). The distinction need echocardiography or ventriculography, to reveal the typical pattern of TTS: apical akinesia and basal hypercontractility of the ventricle. Specific blood microRNA levels (elevated miR-16 and miR-26a) have been discovered as markers distinguishing TTS from both, MI and healthy controls. However, the aetiology of this disease is still under investigation. The effects of miR-16 and miR-26a on apical and basal cardiomyocytes (CMs) as well as on human induced pluripotent stem cell (iPSCs) CMs have never been investigated.

Methods:
Adult, male Sprague-Dawley rat CMs, separately isolated from the left ventricular apex and base were transfected with pre-miR-16, pre-miR-26a or pre-miR negative control using Lipofectamine 3000. After 48 hours, fractional shortening was measured under field stimulation (0.5 Hz, 0.5ms, 50V), using an IonOptix system. Cells were treated 1h prior to recording with 1mmol methyl-β-cyclodextrin or PBS as control. Experiments were performed and analysed blinded to all conditions.
IMR-90 iPSCs were differentiated into iPSC-CMs and enriched by metabolic selection. At day 31 following differentiation, iPSC-CMs were transfected and 48 hours afterwards, optical mapping was performed. Fluo-4 calcium transients and Fluo-Volt action potentials were recorded under perfusion and field stimulation (1&2 Hz, 5ms, 20V).

Results and Conclusions:
We showed that miR-16, previously found to be elevated in TTS patients, decreased the fractional shortening of apical rat CMs significantly (control vs. miR-16, 4.57±0.52 % vs. 2.76±0.28 %, n= 35/7 [cells/rats], p=0.005; control vs. miR-26a, 4.57±0.52 % vs. 3.77±0.42 %, n= 30/6, ns). Basal CMs from the same hearts had unchanged contractility after transfection with the pre-miRs.
In iPSC-CMs none of the miRs showed any effect on calcium handling or action potentials. This could be due to the immature state of iPSC-CMs and the different spatial arrangement of signalling components. A key difference between apical and basal cardiomyocytes seems to be the compartmentation of βARs through caveolae. Cyclodextrin is known to remove and internalize cholesterol rich parts, such as caveolae, from the cell membrane. Indeed, treatment with cyclodextrin restored contractility and abolished the effect of miR-16 in apical CMs (miR-16+PBS vs. miR-16+cyclodextrin, 2.76±0.28 % vs. 4.12±0.47 %; n= 35/7; p=0.02). Cyclodextrin had no significant effect on contractility of the apical pre-miR control and miR-26a cells, neither on basal CMs. The observed apex-base difference in adult cells strengthens the hypothesis about the apical-specific coupling underlying TTS aetiology. Furthermore, we could demonstrate that this effect seems to be dependent on caveolae.

Funding:
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