EVOluTION

European Vascular Interventions and Therapeutic Innovation Network

Welcome to the fifth EVOluTION newsletter

In this issue, we explore some of the initiatives and training activities EVOluTION students have been involved in over the past six months.

Chiara Moretti tells us about her experience as a volunteer for the open house of the KI Biomedicum – a brand new research facility in Stockholm, where she is now based (pg. 3). The Biomedicum was completed in May 2018, and as part of the opening launch an open day was held where members of the public were able to take a tour of the labs, meet with the scientists and hear about the latest research stemming from the Institute.

You can read a full update on the second and final EVOluTION Summer School that took place in London in September, written by Sanne Maas (pg. 4).

Turn to page 5 to read about Laura Menke's thoughts on career options after your PhD and her time working for QConsult, a QMUL based scheme that enables graduate students to get first hand consultancy training by completing a project for businesses based in London.

Finally, in our Scientific Bites section, Tipparat Parakaw has written a summary of her research investigating the effect of Xanthine oxidoreductase on platelet activity in cardiovascular disease.

Upcoming events in 2019

- Annual meeting 2019, 20th-21st May 2019, Coimbra, Portugal.
- Final conference 9th-11th September 2019, Seeon, Germany.
- Transferable skills training VII 12th – 13th September 2019, Munich, Germany.

Stockholm

Chiara

KI Biomedicum Open House

London

Sanne

Summer School II

London

Laura

Career options after your PhD

London

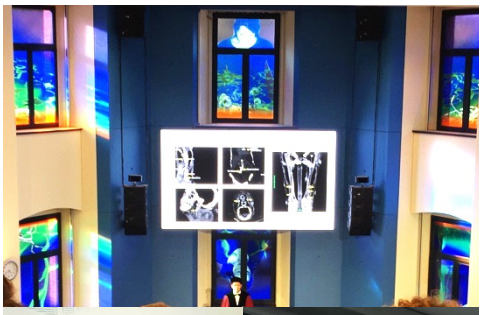
Tipparat

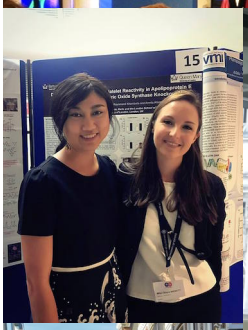
Scientific Bites

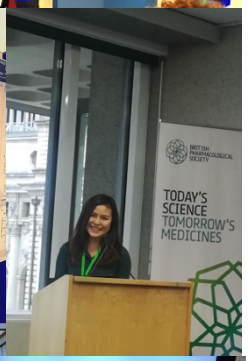
EVOluTION Update

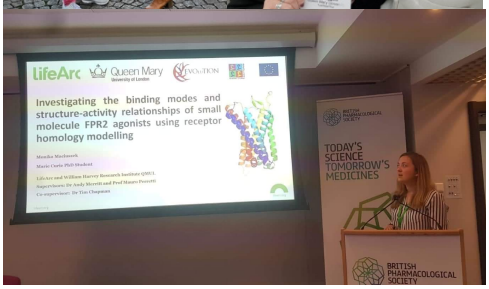
Consortium News

- We congratulate Leon Schurgers who was officially inaugurated as Professor at the University of Maastricht on the 12th of October 2018.
- Following the mid-term review in May 2018, the EVOluTION periodic report was approved and the second installment of funding for all beneficiaries has been received and distributed.
- Our existing Project Manager, Dr Annabelle Scott, will be leaving the programme at the end of January. We are currently recruiting for a new Project Manager and will inform you of her replacement once the post has been filled. We thank Annabelle for her top-class management of the programme and wish her success for the future.









Outreach and Dissemination

The students are now embarking on the final year of their PhDs and have had some fantastic opportunities to present their work. Tipparat Parakaw and Chiara Moretti attended the the *10th International Conference on the Biology, Chemistry and Therapeutic Applications of Nitric Oxide*, held in Oxford between the 16th-20th September 2018. Congratulations to Chiara, who won the oral presentation prize! Sanne Maas gave an oral presentation at a retreat on *Trafficking of Immune Cells in Inflammation, Development and Disease*, organised by LMU in Günzburg, Germany on the 5-7th November 2018. Silvia Oggero was awarded a poster prize at the *Netherlands Society of Extracellular Vesicles* (9th November 2018) and Angelina Pavlic was awarded the young Investigator Award for outstanding scientific achievements after her presentation at *European Congress on Thrombosis and Haemostasis* in Marseille (24-26th October 2018). She also presented a poster at the *Netherlands Society on Biomolecular Modelling* in Utrecht on the 16th of November 2018. Finally, Silvia Oggero, Laura Menke, Monika Maciuszek and Ploi Petsophonsakul recently attended *the British Society of Pharmacology Annual Meeting* in London (18th- 20th December 2018) where they gave talks and presented posters.

ELISAGenie has released the full interview on Laura about her insights on starting a PhD, her background and being a STEM ambassador - https://www.elisagenie.com/blog/labchats-with-laura-menke/.

On October 13th Angelina was involved in **World Thrombosis Day**. With her colleagues, Angelina raised awareness on thrombosis, complications and clinical aspects to a broad population on the streets of Maastricht. Lectures were also presented to the general public by medical specialists in the field. In addition, she promoted the fundamental research that is ongoing at CARIM and the important collaborations that the University of Maastricht has developed with the hospital.

Biomedicum Open House

An outreach opportunity that I will never forget

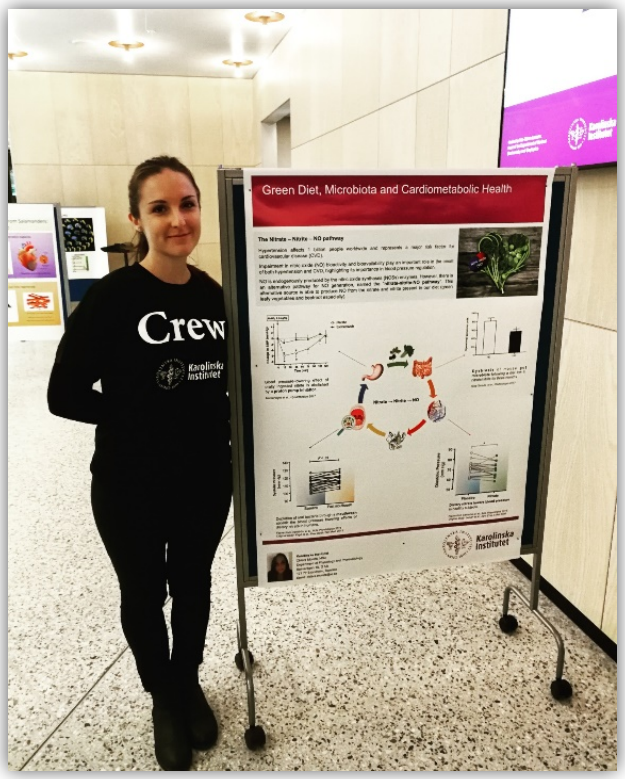
On the 29th of September, I had the great opportunity to volunteer for the Open House Biomedicum event. Biomedicum has been the new home for all the pre-clinical researchers at the Karolinska Institutet, since May 2018. This brand new, state of the art research facility has been attracting Sweden´s interest and curiosity since the beginning of its construction in 2013. For this reason, we were all very happy and excited to open our new home to the entire city of Stockholm and invite everyone to breathe science as we do here every day.

It was a full day of great cooperation among PhD students, PostDocs, researchers and technical staff. The event opened with a very interesting lecture about stem cells and regenerative medicine: a topic that very much attracts the public´s attention nowadays. From children to their parents and grandparents, more than 250 people gathered to learn more about how stem cells work, ethical aspects related to their use in healthcare and future directions for new therapies.

After this exciting moment, everyone had the chance to explore the large Biomedicum hall, where we had set up a series of activities for adults and kids. Within a few minutes, a long queue appeared at the "test your lungs" station where doctors from Karolinska University Hospital and researchers from the Karolisnka Institutet were on hand to explain what lung and respiratory diseases are, and what therapeutic opportunities are available. Several people took the chance to test their lungs with a simple and quick breathing test.

Many young researchers and PhD students had the opportunity to guide the audience through their main research focus. We set up several exhibitions and games for children: some could try a microscope for the first time and see how the tissues and cells forming our body look like. Many families gathered around our biotic games table or the DNA exposition table, where researchers gave insights on the molecule of life. Finally, most of the younger attendees headed to the "experimental station" where they could be a researcher for a day!

It was a pleasure indeed for me to help set up the exposition tables and welcome the young and elderly to the event, but especially introduce them to my daily life. In fact, being an EVOluTION ESR, made me



understand how important outreach and science dissemination are. For this reason, I decided to bring a simple poster, which most people could understand, summarizing my research. It was a great inspiration and extremely fun to talk to anyone who wanted to know more about what myself and my group works on every day! Not only did I get the chance to disseminate and transmit to others what I have been learning so far during my PhD but this experience

reminded me how important our role is in society as researchers, how many people can and will benefit from our findings and that, for this, we should never stop going out from our labs and research groups and communicating with the general public.

Article by Chiara Moretti, ESR9

Summer School II

Sanne writes about the EVOluTION Summer School in London

The EVOluTION Summer School II 2018 took place on the 10th and 11th of September at the historic Charterhouse Square campus of QMUL in Smithfield, London. This Summer School was entitled "Hello! 'Any drug there'? Preclinical and Clinical innovation for next decade therapeutics" and was combined with transferable skills training. All ESRs were excited and curious about what would be presented. The first day of the Summer School started with two transferable skills training sessions given by Prof. Nick Goulding and Dr. Sarah Barnes. Prof. Goulding started this Summer School with an interactive session on ethics and research governance. His talk was entitled 'Researchers behaving badly – why it matters' and posed some very interesting questions when thinking about how we should conduct our research. Dr. Sarah Barnes followed with a session covering public engagement and fundraising. She highlighted how to engage with people from outside of academia and she addressed public engagement and patient involvement. After lunch, we continued two sessions concerning "Are large data sets delivering their promise?" and "Nature's experiments: how human genetics can guide target selection". In session one, Dr Stefano Piero talked about data integration and the

subsequent benefit for the patient by linking health, -omics and biobanking data with the use of a novel software programme. The session continued with a plenary lecture given by Prof. Clare Turnbull. She introduced us to genetic susceptibility for cancer prevention, since she is using next-generation sequencing technologies to identify novel cancer predisposition genes. After these enlightening talks, it was time for session two. Dr. Eirini Marouli gave a fascinating talk on the 83 new genetic variants influencing human height. Prof. David Van Heel spoke about the East London Genes and Health project and the benefit of studying the natural occurrence of human knockouts. Our final speaker for the day was Dr. Damian Smedley from our associate partner Genomics England. He gave an overview of the 100 000 genomes project and the international mouse phenotyping consortium.

On the second day, the morning session was devoted to clinical drug development and pre-clinical testing. This session was led by UCB, our associate partner. The session consisted of 5 very fascinating talks regarding different types of in vitro assays (Dr Adrian Moore), the 3 Rs (replace, reduce and refine) in animal research (Dr Gareth Davies), in vivo pharmacology (Dr Adrian Moore), modeling and simulation (Dr Mark Penney) and the morning session concluded with a talk by Dr Gill Holdsworth on the development of one of UCB's flagship projects on Sclerostin. The afternoon session focused on unbiased technologies for new target identification with respect to transcriptomics (Dr Myles Lewis), phosphoproteomics (Dr Pedro Cutillas) and the session ended with a fascinating talk by Prof Chris

Thiemermann on drug repurposing of the antimalarial drug Artesunate for use in trauma care. The summer school concluded with an ESR journal club, which after spending the whole day in the university building was held in a pub. Later that evening presenters and attendees of the London meeting had a nice dinner together. This was a perfect opportunity to talk and discuss the topics that we had recently heard during the past two days of Summer School and also to network with the presenters.

Overall, this Summer School was a great experience. It was very interesting to get an introduction to preclinical and clinical innovation for next decade therapeutics. Finally, also a very big thanks to all the speakers during these two days and a special thanks to Annabelle and Mauro for organising such an impressive event.

Article by Sanne Maas, ESR7

What's next – expanding your horizons

Laura recounts her time on the QConsult programme

In a month, I will be starting the last year of my PhD. I cannot believe it has already been 2 years and with the final year poses the question that we all have been dreading since the start - what's next? I have been working in the lab since I started my Bachelor in 2011 and have not done much else since then, neither did I want to. As part of EVOluTION, I had the chance to gain some insights into the other side of biomedical research besides academia; industry. Following workshops from LifeArc, UCB Pharma and IQVIA, I knew I wanted to get out of the lab and learn more about potential jobs that integrate economy, business and science.

Easier said than done. As PhD students, it is expected that we generate data, write reports, present at conferences and repeat. I am lucky to have a supervisor who understands my wish to try something new and to be part of QMUL, which offers a variety of career workshops for PhD students. One of the programmes offered includes the QConsult researcher scheme that allows students to step into the role of a consultant and solve a mini consultancy project for a London-based business. For 6 weeks, I worked together with a law student, an aquatic ecologist and a biochemist. We investigated the link between unfulfilling work and mental health issues for our client, who offers a platform and workshops for people who are stuck in the wrong career. Even though it was quite similar to what you do as a researcher, scanning articles for unique data, writing an article and presenting the findings, this project was more challenging than expected. For one, it was the first time in a long time that I had to work in a team. We were all coming from different backgrounds and therefore had different ways of approaching our task which lead to confusion and sometimes delays.

In the end, we successfully finished the project to the satisfaction of our client. I learned some important life lessons, such as to not get frustrated if something does not work out right away and trust in the abilities of other people. Additionally, I learned how important it is to try something new and step out of your comfort

zone because it allows you to re-evaluate your strengths, and more important your weaknesses. That can be scary, but also exciting. I know now that consultancy is something that I would consider as a future career, but I still have a year to learn about other roles. I will take every opportunity I can get to challenge myself and expand my horizons to find my path.

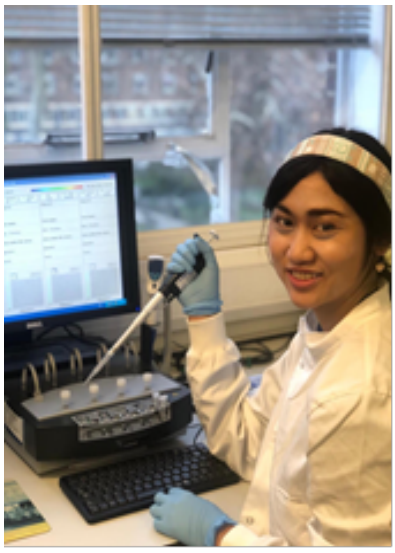
Article by Laura Menke, ESR3

Scientific Bites

Tipparat Parakaw ESR 2

XOR: the missing link in platelet hyperactivity and cardiovascular disease?

When we think about platelets, it is well known that they help our body form clots at sites of vascular injury and maintain the integrity of the vasculature. Without platelets, we would have severe bleeding which would cause death. Less is known, however, on how platelet hyperactivation can contribute to pathologic thrombosis and other diseases, including ischemic stroke, chronic atherosclerosis, myocardial infarction (MI), congestive heart failure (CHF), diabetes mellitus, renal disease and pulmonary arterial hypertension (PAH) (Sangkuhl et al, PMID: 20938371). The most recent cohort study this year with 2831 participants revealed evidence that individuals who were hyperresponsive to Adenosine diphosphate (ADP), a platelet stimulant, showed higher risk of stroke, MI, and cardiovascular death (Puurunen et al. PMID: 29502103). Therefore, finding an approach to inhibit platelet hyperactivity is potentially one of the most pivotal strategies to reduce the risk of cardiovascular diseases.



Interestingly, inorganic nitrate rich in green leafy

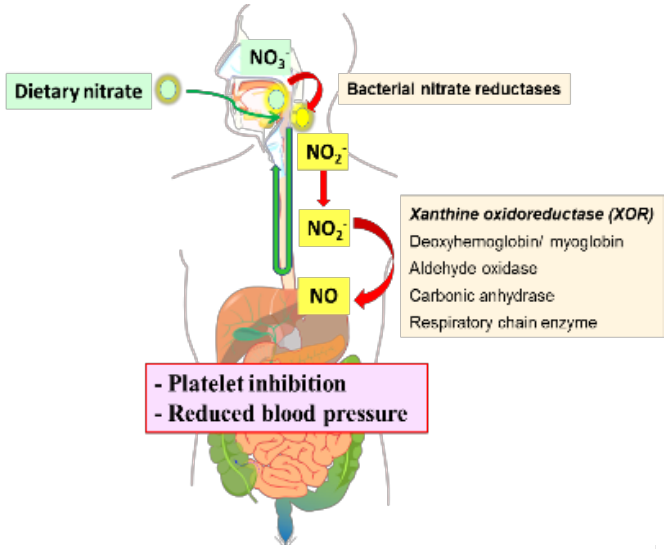


Figure 1. The Nitrate bioconversion pathway.

vegetables (especially spinach and beetroot) has been shown to exert a substantial benefit upon platelet regulation (Webb et al. PMID: 18250365, Velmurugan et al. PMID: 26607938). The benefits on cardiovascular function have been attributed to the bioconversion of inorganic nitrate to nitrite and then from nitrite to nitric oxide (NO) which decreases platelet aggregation and blood pressure (Figure 1). The first step in this chemical pathway is the conversion of nitrate (NO_3^-) to nitrite (NO_2^-) by commensal bacteria in the oral cavity. The second part of this pathway is a mammalian response. Several distinct molecular pathways have been shown to facilitate the reduction of nitrite to nitric oxide including heme-based nitrite reductases, molybdopterin reductases, and nitrite anhydrases. Xanthine oxidoreductase (XOR) is possibly the most important nitrite reductase enzyme which reduces nitrite to NO particularly in the settings of cardiovascular disease and endothelial dysfunction.

My PhD study aims to explore the functions of XOR in long-term dietary nitrate intake by using a genetic mouse model assessing cardiovascular function in wild type (control), *Xdh* heterozygous, and *Xdh* knockout mice, which is a gene coding for the XOR enzyme. My work will focus on assessing platelet function under cardiovascular disease scenarios where the conventional pathways for endogenous NO generation are impaired by using various techniques such as platelet aggregometery flow cytometry, intravital microscopy, tail bleeding, and chemiluminescence. This project will identify

whether the enzyme XOR is key for anti-platelet activity in a cardiovascular disease scenario as well as determine whether targeting this pathway might be useful in therapeutics. I really hope that the exploration of this study will potentially bring to light a new drug target through the use of dietary nitrate supplementation as a therapeutic agent for the treatment of cardiovascular diseases, particularly platelet hyperactivation

Article by Tipparat Parakaw, ESR2

UPCOMING CONFERENCES

The International Society of Extracellular vesicles Annual Meeting, 24-28th April 2019, Kyoto, Japan https://www.isev.org/

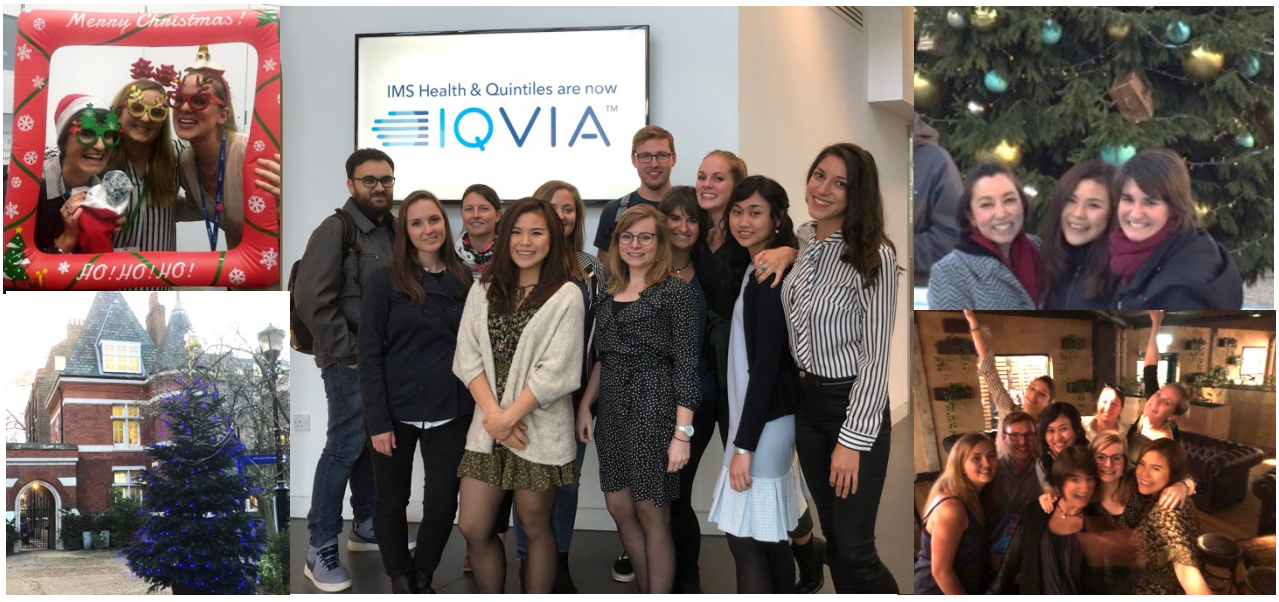
Experimental biology, 6-9th April, Orlando, Florida. http://experimentalbiology.org/2019/home.aspx

Annual meeting of the European Society for Clinical Investigation, May 22nd -24th 2019 Coimbra, Portugal. https://esci2019.com/welcome/

EVOLUTION PUBLICATIONS

Asymmetric synthesis and biological evaluation of imidazole- and oxazole-containing synthetic lipoxin A4 mimetics (sLXms). de Gaetano M, Butler E, Gahan K, Zanetti A, Marai M, Chen J, **Cacace A**, Hams E, Maingot C, McLoughlin A, **Brennan E**, Leroy X, Loscher CE, Fallon P, **Perretti M, Godson C**, Guiry PJ. Eur J Med Chem. 2018 Oct 23;162:80-108.

Organ-Specific Mechanisms of Transendothelial Neutrophil Migration in the Lung, Liver, Kidney, and Aorta. **Maas S.L.**, **Soehnlein O.**, and Viola J. R. Front. Immunol., 27 November 2018.



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