EVOluTION

European Vascular Interventions and Therapeutic Innovation Network

MARIE CURIE ACTIONS

The EVOluTION ESRs, London, September 2017

Welcome to the third EVOluTION newsletter.

Our network is fast approaching the half way mark and in May 2018 we will submit our first periodic report to the European Commission. ESRs are now embarking on their secondments and all have completed their first-year assessments, a required milestone in their respective universities.

In 2017, we have organised three EVOluTION events, the last one taking place over 3 days last September in London. You can read more about our London Summer School entitled "The quest for innovative targets on drugs", in Jan's article on page 3.

In addition to pursuing their research, the students have been involved in various dissemination and outreach initiatives. Rebecca has written a very insightful article on her experience talking to high school students. Angelina's article also focuses on dissemination of information and how Society and researchers can benefit from sharing information. Finally, turn to pg 6 to find out more about Ploi's research on how she plans to use nutraceuticals to modulate vitamin K and treat cardiovascular disease.

Upcoming events in 2018

- Annual meeting, workshop and mid- term review meeting: 30th April – 4th May 2018, Maastricht.
- EVOluTION Summer School II: 10th – 14th September 2018, London and Reading.

Save the Date

EVOluTION conference 9th-11th September 2019 Munich.

Summer School Sep 2017

Jan writes about the London Summer School on pg. 3

Outreach

Becky tells us about her experience talking to high school students on pg. 4

Information – highway to horizon

Angelina gives her perspective on sharing research information on pg. 5

EVOluTION Update

Consortium News

One of our Associate Partners, Quintiles, has changed their name and is now known as IQVIA.

To find out more about the company please visit their website https://www.iqvia.com/. IQVIA is currently working closely with the management team to deliver a workshop on clinical trials that will take place during the Summer School in 2018.

ESR News

EVOluTION would like to extend a warm welcome ESR 2, Tipparat Parakaw, who will be joining Amrita Ahluwalia's laboratory at QMUL in early January. Tipparat's project will focus on the therapeutic potential of dietary nitrate in hypertension.

Secondments are now underway and Antonino Cacace has almost completed his placement in London at QMUL and WHRL. He has found his time in London "an intense and fantastic working, living and learning experience". In January, Laura will be moving to Dublin for 3 months to perform lipidomics analyses and Silvia and Monika will be making their way to the Netherlands to spend a few months at the University of Maastricht and Mosamedix.

Outreach and Dissemination

ESRs have attended a number of conferences relevant to their fields of research this year including the Mosa conference in Maastricht, the Berlin Brain and Brain PET 2017 symposium, the Netherlands Society on Biomolecular Modelling (NSBM) fall meeting in Utrecht and the British Pharmacological Society meeting in London.

In August, Chiara attended the fall NorDoc Summit "Health Sciences Across Borders" at the Karolinska Institute (https://www.nordochealth.net/). This interdisciplinary meeting was attended by PhD students from Nordic countries and focused on Nordic research strengths and how to get the most out of their PhD. The two-day interactive summit was designed to give a wider perspective on research, in addition to providing advice on future careers, publishing, innovation and scientific outreach. The event also promoted networking and peer mentoring groups with other PhD students were created. Chiara found the meeting very stimulating both from a research and career point of view, as well as a great networking opportunity.

The facebook and linkedin pages are now run solely by the ESRs and lots of information has been posted such as ESR profiles, relevant research papers and interesting general science articles. A preview of Laura's interview with AntibodyGenie is also available to view, the full interview will be online in early 2018.

EVOluTION –Summer School I 2017

From the 6th – 8th September the third EVOluTION meeting of 2017 took place in London. Contrasting to our previous meetings in Maastricht and Dublin, this meeting was a Summer School entitled *The 'quest' for innovative targets and drugs* and was combined with a Transferable Skills Training module on *Knowledge exploitation: IP and commercial exploitation*. All ESRs keenly anticipated the School and were excited and curious about what would be presented.

The first day of the School started bright and early when we caught the shuttle bus to our meeting location in Stevenage, where the headquarters of LifeArc are based. Debbie Taylor and Andy Merritt welcomed us all at LifeArc and we began with the first of four very interesting sessions on antibody therapeutics and small molecule drug discovery presented by Andy and David Matthews. In the second session Kerstin Papenfuss and David Jones talked about the identification and validation of targets for drug discovery. These two sessions were very informative and helpful and again highlighted what a great opportunity it is for us to be part of the EVOluTION network.

One of the advantages of this multi-organisational network is that we are exposed not only to the academic institutions but are also able to be involved and observe the industrial aspects of science. Thus, the subsequent tour through the laboratories with Monika as our guide gave us valuable insight into daily life and work at LifeArc.

In the afternoon session, Keith Ansell, Pete Coombs and Arek Oleksy presented different screening

approaches for new lead discoveries that are commonly used at LifeArc. Chido Mpamhanga, Tim Chapman and Preeti Bakrania then gave us our last session with an interesting overview on hit-to-lead and lead optimisation. At this point I wish to extend my thanks to all the presenters and people of LifeArc for such an instructive day. Back in London some of us used the remaining time in the evening to discover the city from above at the Skygarden. I think all of us could recommend this place for its incredible views of London.

For the second day, we switched the location to the historic Charterhouse Square campus of QMUL in Smithfield in London. This day was mainly focused on lead discovery and varied approaches to identify diversified targets. Several of the speakers were working in the industrial sector in companies such as GlaxoSmithKline, LifeArc and IQVIA, thus made for some very interesting talks. Andy Merritt and Jeff Jerman (LifeArc) started the day with presentations on promising targets for drug discovery. In the plenary lecture, John Wallace (Antibe Therapeutics) gave a fascinating and lively insight on the different steps involved in drug development and the trials and tribulations that he has encountered. Emily Bureau (LifeArc) and Mark Stubbs (ICR) then talked about phenotypic approaches and screens of lead discovery before Mike Barnes (QMUL), David Tough (GSK) and Mark Caulfield (QMUL and Chief Scientist of associate partner Genomics England; https://www.genomicsengland.co.uk) illustrated and discussed genetic approaches and ways for target discovery. In the last talk of the day Elizabeth Allen (IQVIA) gave a comprehensive introduction to

pharmacokinetics. 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 for the transferable skills training on *Knowledge exploitation: IP and Commercial exploitation*.

On Friday, Paula Alessandro and Beatrice Lana (Queen May Innovation) started with a great introduction to intellectual property laws which was for all of us a new and exciting field. Paul Briscoe and Michael Newton, both working for the patent and trade mark firm Kilburn & Strode (EVOluTION associate partner; http://www.kilburnstrode.com), then continued with instructive talks about intellectual property protection, management and exploitation. The last presentation was led by Georgia Gliki (LifeArc's Senior Business Manager) who informed us about the complete process in the development and commercialisation of a diagnostic test in a case study. Although the last day was less scientific, it was definitely just as interesting and important for us.

Overall, we had a great experience in. None of us has ever been in contact with this important part of science but getting such a great input and so many insights and tips on lead discovery, validation and intellectual property will be helpful for our further scientific research and surely also helpful at later stages of our career. Finally, also a very big thanks to all the speakers during these three days and special thanks Debbie and Andy for organising such an impressive event.

Article by Jan Nagenborg

The world of science: A small glimpse

During a regular working day, I received a request from a high school outside of Munich asking if I would be willing to give a "peek behind the scenes" talk on a career in science and the daily challenges I am confronted with. I accepted the invitation without thinking twice about it and realised later that the hardest part was about to begin. Preparing a talk for a non-scientific audience is quite a challenge, but preparing a talk for young adults to attract their attention is even more difficult. After many twists and turns I was eventually ready on the day of my visit to the school. I began by introducing the different ways that one can pursue for a career in science. For me this was an important aspect to address as the students will have to decide in what direction they want to go in one year.

The following topic we discussed was regarding animal experiments and the mainly negative press from the media, which as a result has had an effect on society's poor attitude to research involving animals. Thus, it was important for me to particularly emphasise that these procedures are necessary and are currently very strictly controlled and regulated. I firstly gave an insight into the process of applying for animal experiments and secondly how the animals are treated. To avoid the students getting bored I brought some illustrative material such as some short movies, a cage and the clothes one has to wear when entering the animal facility. Of course, they would have loved to see real animals as well, however due to the strict laws it was not possible to bring them, but at least they were kept entertained trying on the lab coats and playing around with different tools. I realised that it was very astonishing for the students to see how strictly regulated everything is if you are carrying out animal experiments in comparison to having pets, where the housing and care is not regulated that much. To make the atmosphere of the talk even more relaxed I involved the audience by asking questions, which was very successful. The students were also not aware of how expensive it is to carry out a project, how difficult it is to get funding from the government or

grants and what has to be considered during the planning process.

In the final part of my presentation I was asked about my PhD project. Hence, I included a short inside view on what is done at the Institute of Dementia and Stroke Research. The students were really interested and there were some good questions, they also showed a lot of interest regarding my work in the laboratory.

Although I was at first a bit worried about giving a talk to such a young audience, I can say that I was surprised how attentive and fascinated they were. This experience has been very rewarding and has motivated me to be more involved in outreach. Therefore, if the opportunity arose again it would definitely be a pleasure for me to introduce the amazing world of science to another group of students.

Article by Rebecca Sienel

Information- highway to horizon

In this fascinating commentary, Angelina reflects on information exchange that takes place on a daily basis across the world and also within our network. She has written this article with some artistic licence to illustrate how information usage and development fits into a horizon both metaphorically and literally.

A horizon is defined as an imaginary line that connects the sky and earth, it is a line that crosses country borders, but can also mean the limit of a person's knowledge, experience or interest. Horizon 2020, the EU framework programme for research and innovation, promises to create more breakthroughs and discoveries by taking great ideas from the lab to the market. I believe that the science funded in this scheme will undoubtedly be of infinite value to science and the wider community, and therefore "expand horizons" and open up the views of humanity. However, to achieve this goal it is imperative that the information gathered and exchanged is valid and of the highest quality.

The same information can be both powerful and weak, depending on who is using it, depending on the impact the information has, and the chance for that impact to touch the whole population. We are living in a highspeed information exchange era, relying on statistical predictions and computer algorithms. This has both benefits and drawbacks, however with a sharp state of mind, we can control the information flow and let the benefit outweigh any disadvantages. As human beings, information is the gold standard for our existence, and as scientists information could be a gold standard for eternity. It is the one and unique currency for all countries in the world, but the interpretation and manipulation of information differs depending on the individual itself and the environment that promotes or hinders information dissemination. Information can be an accurate and precise manifestation of reality, but it could also be a veil of illusion, and therefore lead to disturbance of world coordinates. Proper preservation and establishment of information is one of the fundamental protocols for good science and essential

for the development of the human race in spiritual, intellectual and biological terms. Particularly as researchers, our results rely on the raw information inherited from previous experiments in elucidation to our scientific question. We also receive information from our supervisors, collaborators and contributors. Whatever flow the information takes, information exchange is highly dependent on validity.

Nowadays, information exchange is continually occurring, however we have to be aware that it is at the same time a highly sophisticated tool that the human race possesses. If properly formed, truthful, and unique, information is worth distributing. Seen from different perspectives and seeded into discussion, information can be displayed in the best version of itself and that way reach a wider population over time. Thus, one of the most productive ways to proceed and reach this point in science and everyday life is to form a good network. The Marie Sklodowska Curie Actions Innovative Training Networks that are part of the Horizon2020 programme are a prime example of how excellent networks can be developed that span multiple disciplines. Through collaborative enterprises between academia and industry, where information exchange is driving our acceleration of scientific knowledge, these networks are developing a new generation of researchers with entrepreneurial drive and a wide range of transferable skills and research expertise.

It is evident that although information exchange may be a transparent fossil of our time, it is an essential dimension to the world we are living in.

Article by Angelina Pavlic

Scientific Bites

Ploi Petsophonsakul ESR11

Nutraceuticals modulating the vascular vitamin K-system

A great deal of scientific literature to date has been devoted to describing cardiovascular disease (CVD) associated with endothelial dysfunction, lipid infiltration, and inflammation. However, very little is known about how vascular smooth muscle cells (VSMCs) influence CVD. VSMCs are the major cell type found in the vessel wall. They are essential for good performance of the vasculature and maintain appropriate blood flow. VSMCs are also involved in many vascular diseases such as atherosclerosis and aneurysm formation. In these pathologies, VSMCs play an important role in remodeling of the vessel wall. A contractile VSMC can switch its phenotype to become synthetic and express abundant vesicle proteins which then further mediate vascular remodeling. A VSMC synthesised vitamin K dependent protein (VKDP) which regulates VSMC phenotypic switching is called matrix Gla protein (MGP). MGP maintains the contractile phenotype of VSMCs and supports vascular elasticity. MGP binds to BMP-2 and inhibits downstream regulation of VSMC switching towards an osteochondrogenic phenotype which induces calcification. It also prevents mineralization of vesicles produced by VSMCs.

Vitamin K2 supports cardiovascular health by activating VSMC derived MGP to inhibit phenotypic switching and vascular calcification. In addition, vitamin K2 also an effect on non-canonical pathways such as inhibition of oxidative stress and supporting ATP synthesis. I am particularly interested in the vitamin K metabolism in aneurysm. An aneurysm is

an enlargement of the artery caused by weakness in the aortic wall. It is characterised by pronounced oxidative stress, VSMC phenotypic switching and VSMC apoptosis, thus leading to extracellular matrix degradation and weakening of the arterial vessel wall. Moreover, aortic stiffening and/or calcification generates aortic wall stress which potentially accelerates the dilatation of the vessel wall and thereby contribute to aneurysm growth. The sequential pathophysiology of aneurysm formation is unclear, however VSMCs have increasingly been recognized as an important contributor to the disease. The goal of this project is to optimize vascular homeostasis by delivery of vitamin K-analogues, specifically in prevention and treatment of vascular calcification by harnessing the protective endogenous vitamin K cycle of VSMCs. The research project focuses on vitamin K metabolism in VSMCs in aneurysm. I will investigate the role of vitamin K-dependent mechanisms in VSMCs, in particular related to oxidative stress, metabolic activity, phenotypic switching, senescence, and apoptosis.

My research approach includes both in vitro and in vivo studies. Human primary VSMCs from healthy donors and from patients suffering from aneurysms will be used for in vitro analysis. In preclinical experiments, animal models of vascular remodeling, apoptosis and calcification in relation to aneurysm formation will be used. Our animal models include apoE:sm22hDTr KI mice (VSMC apoptosis), smtn-/- mice (vascular remodeling), and warfarin diets (calcification). In addition, human tissue, plasma and serum samples from the biobank of aneurysm patients at Maastricht UMC+ will be accessed. These human samples will allow us to investigate the pathologies of disease at the histological level.

EVOLUTION PUBLICATIONS

European Journal of Pharmacology, Dec 5 2017; 816: 14-24. Jan Nagenborg, Pieter Goossens, Erik A.L. Biessen, Marjo M.P.C. Donners, Heterogeneity of atherosclerotic plaque macrophage origin, phenotype and functions: Implications for treatment.

UPCOMING CONFERENCES

- Keystone Symposium: The Resolution of Inflammation in Health and Disease. **March 24th – 28th, 2018**, Royal Dublin Society, Dublin, Ireland. Scientific Organizers: Catherine Godson, Ira Tabas and Mauro Perretti, http://www.keystonesymposia.org/18C6
- Experimental Biology 2018, **April 21st-25th 2018,** in San Diego. http://experimentalbiology.org/2017/Home.aspx
- WCP2018, 18th World Congress of basic and clinical pharmacology. **July 1st- 6th 2018**, in Kyoto http://www.wcp2018.org/

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