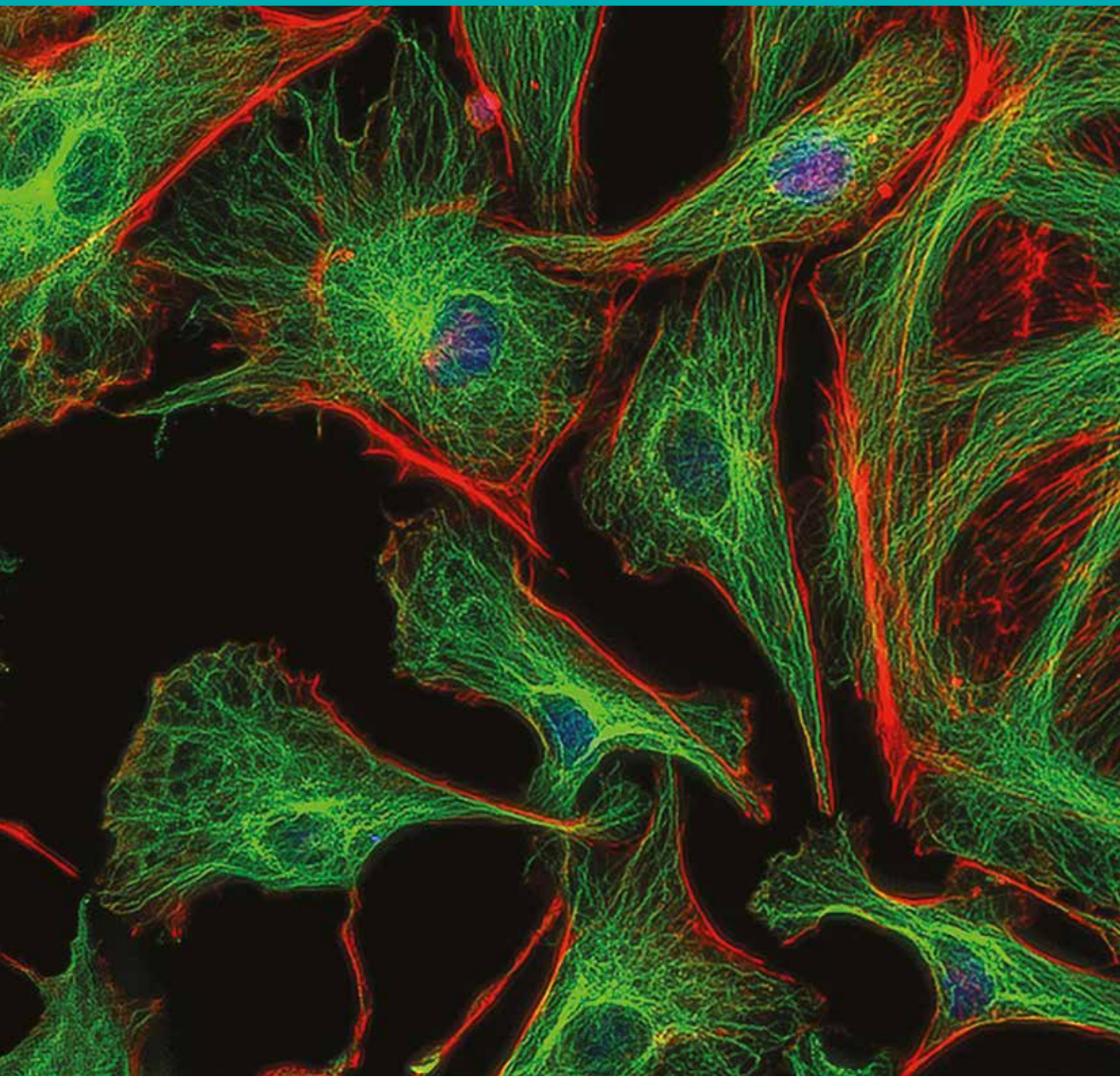
IMPACT

DEVELOPING THE NEXT GENERATION OF PI3K RESEARCHERS



Phd PI3K biology in health & disease

IDIBELL Institut d'Investigació Biomèdica de Bellvitge

http://pi3k-phdproject.eu

Impact Objectives

- Develop and train the next generation of researchers who approach research with ambitious goals and who believe collaboration across Europe is essential to success
- Unite complementary expertise, added value, unique tools and excellent knowledge in a common effort to train talented Early Stage Researchers (ESRs)
- Gain a greater, more in-depth understanding of PI3K isozymes and their physiological functions so as to develop new treatment modalities with PI3K inhibitors and identify new uses for existing PI3K inhibitors

Developing the next generation of PI3K researchers

__Mariona Graupera__, group leader at the __Institut d'Investigació Biomèdica de Bellvitge (IDIBELL)__ in Spain and coordinator of the __Deciphering PI3K biology in health and disease (Phd)__ project explains how the work of the network will help train new researchers

What are the key aims of the Phd project?

The aim of the Phd network is to train the next generation of PI3K experts, who consider collaboration across Europe to be essential to their work and who approach their research with ambitious programmes. To this end, the Phd training network has been created to gather the best European academic, clinical and industrial units in PI3K signalling, bringing together complementary expertise, unique tools and excellent knowledge in a common effort to train talented Early Stage Researchers (ESRs).

What impact do you envisage your research will have and who will benefit?

This Innovative Training Network (ITN) aims to have an impact in five areas: ESRs, industry, academia, clinical units and patient organisations. This multidisciplinary and inter-sectorial research training programme will have a tremendous impact on the researchers, as they will acquire full capacities to move towards a new wave of PI3K-targeted therapies. Being composed of basic, translation and clinical units and industrial partners, the Phd network will also impact on the prevention, cure and therapy of diseases with deregulated PI3K activity (cancer, neurodegenerative disease, myopathy, cardiovascular diseases (CVDs) and infections). This will increase the international competitiveness of European research in PI3K research and drug development.

What training opportunities will the project deliver?

The Phd training programme has been designed to strengthen professional skills and enhance the career prospects of the fellows. With this aim, ESRs benefit from local and network-wide training. Local training includes laboratory meetings, journal clubs, taught courses and institutional seminars, while network-wide opportunities include international conferences, secondments and annual two-day workshops.

What is the timescale of the project and what has been achieved to date?

Phd is a four-year project where each of the ESRs will be hired for three years to develop their PhD. All ESRs have been recruited and are actively working on their projects. In November 2016, we had our first annual meeting where the students had the opportunity to present their projects. They also attended a one-day workshop on the latest advances on class II and class III PI3K and a one-day meeting on bioethics, as part of their complementary skills training. In June 2017, the students had the opportunity to attend PHENOMIN 2nd European School for Advanced Mouse Phenogenomics in Strasbourg, France.

How will the results of the project be communicated?

The results will be communicated to the scientific community, but also to a lay audience. To approach the scientific community, ESRs will participate in national and international conferences relevant to the project, where they will present their data orally or in poster format. To approach the public we perform outreach activities, visiting schools and organising open days in the labs. We will also produce a promotional video that will be recorded at the second annual meeting to be held in Cambridge in the UK. The video will then be made available on our website. In addition, fellows will be encouraged to act as Marie Curie Skłodowska Ambassadors and visit schools, universities and community organisations to promote their research in PI3K signalling.

Furthermore, the Phd network has its own twitter account (@pi3k_phd) and a Facebook group (www.facebook.com/groups/2329330138020 55/) where the latest news from both our work and the work of others is reported.

Deciphering the PI3K pathway

The Phosphoinositide 3-kinase (PI3K) pathway is at the core of multiple fundamental biological processes controlling metabolism, protein synthesis, cell growth, survival and migration. A multidisciplinary project led by __Mariona Graupera__ is seeking to develop the next generation of experts in this fast-moving field

Phosphoinositide 3-kinases (PI3Ks) are intracellular signal transducers that regulate many biological functions. Deregulation of PI3K signalling either by excess or deficit has been implicated in numerous diseases. The discovery of mutations in genes encoding PI3K pathway members in human cancer and inflammatory disease has promoted major efforts to target this signalling pathway in cancer and immunity. However, progress in PI3K inhibition in clinical settings must be improved, given that an in-depth understanding of target PI3K isozymes and their physiological functions *in vivo* is still not fully understood. 'Some of the clinical testing has been based on insufficient and sometimes poor preclinical and scientific evidence that almost invariably backfires,' Mariona Graupera, coordinator of the Phd project explains. 'This project seeks to dissect the functions of different PI3K isoforms in distinct tissues and translate this knowledge into new treatment modalities with PI3K inhibitors and to identify new uses for existing PI3K inhibitors.'

A broad spectrum of approaches is needed to accomplish this goal. While individual research laboratories and universities, as well as private companies, excel in investigating PI3K signalling, no European network previously existed to bring together an integrative way of providing a comprehensive research and training programme to understand PI3K biology. The Innovative Training Network (ITN) Phd fills this gap by providing a multidisciplinary, internationally integrated research training programme for talented young researchers to prepare them for leading roles in PI3K research and drug discovery in European industry and academia.

PROJECT PARTNERS

Phd is composed of eight world-leading academic partners, a clinician, an industrial collaborator and two organisations with cross-disciplinary expertise and research capabilities to expand the full spectrum of basic, translational and (pre) clinical research training.

The academic partners, through their leading role in the field of PI3K, provide the potential to establish the new generation of worldwide leaders. They offer different, yet complementary scientific knowledge and technological approaches in: molecular and signalling mechanisms; physiology and pathology; preclinical models, drug development and delivery; and image analysis, transfer and manipulation. They have a long and productive track record of collaboration, which has had a tremendous impact in the signalling field and has highlighted that working together is extremely productive and effective. The clinical unit (VHIO, Barcelona) occupies a worldwide pioneering position in clinical trials of PI3K inhibitors, offering applicability and transferability to the proposal. The SME (Arivis) participating in the project has been carefully selected to overcome limitations in the field of PI3K, in that it is a small-sized company developing software solutions for imaging.

MULTIDISCIPLINARY NETWORK

The Phd training network has been designed to deal with limitations in current clinical trials, starting from basic science to impact on drug development and finally back to the clinic. 'The scientific objectives of the network are being addressed through a variety of research activities broken down into five work packages (WPs),' Graupera adds. 'These are omics, imaging PI3Ks and their lipid products, physiological functions, disease context and molecular medicine. The research involved in each WP is lead by a PI (Principal Investigator) who supervises the execution of the tasks. These five WPs are divided into 15 different sub-projects, each one with specific aims and developed by one of the 15 recruited ESRs. The individual projects of each fellow are integrated into the overall research training programme, shown by belonging to one work package, but exhibiting overlapping research activities between different work packages' Graupera explains.

Fellows benefit from training, tools and scientific advice from all collaborators, and

have the opportunity to study PI3Ks from multiple angles, ranging from biochemical and imaging analysis to their roles and implications in physiology and disease. All ESRs are involved in network meetings, laboratory courses, single-topic conferences and network workshops, management courses and secondments to other laboratories within the network.

EARLY BENEFITS

One of the students already benefiting from the project is Christina Courrèges, who began her PhD in October 2016 in the lab of Klaus Okkenhaug at the Babraham Institute, UK. 'I began my scientific career in 2010, studying biology at the University of Bonn, Germany,' Courrèges explains. 'During my bachelor degree, I spent two semesters at the University of Ottawa, Canada, where I became fascinated by the field of Immunology. It was then an obvious decision to continue with a Master's in Cancer Biology at the University of Heidelberg, Germany, before joining my current research group at the Babraham Institute.'

the first Phd Workshop/Annual Meeting in November 2016 in London, UK. I also attended the second European Advanced School for Mouse PhenoGenomics in France in June 2017, providing me with a deeper and thoughtful understanding of the use of mice as a research tool.'

FUTURE FOCUS

The potential of PI3K inhibitors in disease has yet to be fulfilled due to gaps in the understanding of the cellular roles of the PI3K isoforms. The Phd network has been created with this objective. It is composed of basic, translational and clinical units together with an SME with the common goal of impacting on the prevention, cure and therapy of diseases with deregulated PI3K activity – all EU health priorities. The interdisciplinary collaboration of these high quality pioneer groups in the field of PI3K will train young scientists to become the new European experts in this fast-moving field. Some may consider that focusing on one signalling pathway – PI3K – may be too narrow a scientific approach for an interdisciplinary training programme.

> *"The potential of PI3K inhibitors in disease has yet to be fulfilled due to gaps in the understanding of the cellular and organismal roles of the PI3K isoforms"*

In her PhD project, Courrèges is exploring the role of the class III PI3-kinase Vps34 in T cell immunity. Vps34 is highly conserved from yeast to mammals and is a key mediator of endocytosis, receptor trafficking and autophagy in various cell types. Meanwhile, its role in T cell immunity is poorly understood and her work aims to understand the involvement of Vps34 in regulatory T cell and cytotoxic T lymphocyte function and homeostasis.

'I find my project fascinating and highly interesting, mainly because it will contribute to characterise the role of Vps34 in T cell immunity and place these results in the context of infection and immune-mediated tumour cell rejection,' Courrèges continues. 'I am very grateful for the chance to work on such a challenging and interesting scientific question. Thanks to close supervision from Klaus and the day-to-day support of colleagues, I have been able to quickly grasp the key questions of the project and I am currently working on my first manuscript,' highlights Courrèges. 'In the realm of the programme, I was able to take part in

However, this pathway is of fundamental importance in an unexpectedly large number of different biological processes in health and in disease. This has made the PI3K pathway a goldmine of new therapeutic agents and a clear priority in drug development strategy around the world. Therefore, the close collaboration amongst member groups will grant ESR fellows the opportunity to face the association of PI3Ks and disease from an integrative and interdisciplinary angle, in a process that starts from science and resolves into drug discovery, promoting translational medicine and ultimately supporting clinical trials and patient treatment improvement. This is crucial to move towards a new generation of PI3K inhibitors and to learn how to treat diseases ranging from cancer and inflammation to congenital myopathy.

Project Insights

FUNDING

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 675392.

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Mariona Graupera is group leader at the Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Spain. She obtained her PhD in Biochemistry from the University of Barcelona, Spain, focusing on the pathobiology of endothelial cells in liver cirrhosis. She carried out postdoctoral studies with Bart Vanhaesebroeck in London in the UK, where she was involved in characterising the physiological role of class I PI3K isoforms and unravelling the importance of being selective in angiogenesis during development. In 2009, she joined the Angiogenesis Unit at IDIBELL and she set up her own lab focused on the role of PI3K signalling in angiogenesis in health and disease.

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