

Impact Objectives

- Offer innovative training for Early Stage Researchers (ESRs) in order to provide them with critical aptitude and experience for careers in basic science, clinical investigation and health industry sectors
- Gain a greater understanding of the mechanisms behind non-alcoholic fatty liver disease (NAFLD), to relieve the burden of the disease, from both a health and economic perspective
- Develop and implement strategic communication and educational activities addressing NAFLD awareness, with the aim of informing the general public about NAFLD and promoting healthy lifestyles

Planning for the future

Professor Paulo Oliveira is the Principal Investigator of a project that seeks to provide innovative training for 13 Early Stage Researchers (ESRs) to answer questions related to non-alcoholic fatty liver disease (NAFLD). Here Oliveira offers a brief introduction to himself, some of the challenges the FOIE GRAS project has faced and upcoming dissemination activities



Can you introduce yourself, your key research interests and passions in life and work?

I am currently a Principal Investigator at the Centro de Neurociências e Biologia Celular (CNBC), a research institute at the University of Coimbra, Portugal. I am also an Invited Assistant Professor at the same university. The University of Coimbra is one of the oldest universities in Europe, founded in 1290 by King D. Dinis, and soon became the centre of knowledge in Portugal. Although that role has decreased over the years due to the creation of several other universities in Portugal, my institution still has a unique combination of tradition, combined with advanced research and teaching facilities, resulting in a strong publication record and important contributions to advances in science.

Outside science, I dedicate myself to my two best publications, my two lovely daughters Beatriz and Lara, and to my wife Vilma, also a researcher who is examining the physiology of the menopause.

Although the project is still in development, have any challenges come about so far?

The FOIE GRAS project started in January 2017 and we have finished recruiting the Early Stage Researchers (ESRs) that will be the core of our project. The one major difficulty was the small number of candidates applying for some of the positions, and the fact that some of the host institutions had difficulty finding candidates with sufficient qualifications and experience to meet our requirements. This led to the re-opening of several of the positions (more than once in some cases). Consequently, not all ESRs started their contracts on 1st June as we intended. With non-EU ESRs that were selected for the network, visa applications further delayed the process. Even with the goodwill of all involved researchers, administrations in many European academic institutions can also delay ESR hiring and contract signing.

What impact do you anticipate your studies will have? Who will benefit from the research and how?

We predict our studies will impact multiple levels, from the ESRs own training and career development to different clinical and technological applications. The project, which aggregates world-leading basic and clinical science, industry and scientific communication into a coherent network,

is the core of our research and training programme, resulting in state-of-the-art working conditions and research of high impact that will be exceptionally beneficial to each ESR.

Currently, excellence training for researchers is largely limited to basic science, with little training in clinical innovation to create critical aptitude and experience for careers in clinical investigation and health industry sectors. The FOIE GRAS project addresses this important blind spot and will train researchers of transcending value for universities, hospitals and biotechnological sectors.

Finally, are there any planned publications or workshops coming up that might be of interest to our readers?

Yes, indeed. We are now in the process of beginning to prepare a few review manuscripts on the topic of the project, with some written by the ESRs. I am also editing a book called *Mitochondrial Biology and Experimental Therapeutics*, for the publisher Springer, which will contain topics of interest for the project. We are also holding a network school in the small city of Cantanhede, Portugal which is primarily focused on mitochondrial metabolism.

Reversing the burden of non-alcoholic fatty liver disease

The Bioenergetic Remodelling in the Pathophysiology and Treatment of Non-Alcoholic Fatty Liver Disease (FOIE GRAS) project seeks to answer two critical, yet unanswered questions. It is expected that the findings from the project could lead to reversing the burden of non-alcoholic fatty liver disease, thereby advancing the health and wellbeing of European citizens

Non-alcoholic fatty liver disease (NAFLD) is characterised by fatty infiltrations in the liver that have not been caused by alcohol consumption. Over time, NAFLD can lead to non-alcoholic steatohepatitis (NASH), which is a more serious stage of the disease. It results in an inflamed liver due to the accumulation of fat and represents a significant health burden around the world.

Indeed, guidelines published in 2012 by the World Gastroenterology Organisation, suggest the prevalence of NAFLD has doubled over the last 20 years, with both NAFLD and NASH being closely associated with type 2 diabetes and obesity. Together, they are regarded as the primary cause of liver disease in Western countries. Studies show that in 2013, 29 million people in the European Union suffered from a chronic liver condition. NAFLD is predicted to become the primary cause of liver transplants by 2020 and therefore represents a potential major threat to public health systems in Europe and the world in general.

Thus, NAFLD represents a significant economic and health burden in Europe. Understanding more about the mechanisms behind it is a significant topic of interest for scientists and researchers across Europe.

INTEGRATING EXPERTISE WITH TRAINING

With that in mind, the FOIE GRAS project has been established. Led by the Principal Investigator Professor Paulo Oliveira, this four-year Horizon 2020 project began in January 2017 and focuses on providing innovative training for 13 Early Stage Researchers (ESRs). A crucial aspect of the project is the attempt to answer two critical, and as yet unanswered questions. First, is hepatic bioenergetic remodelling involved in NAFLD pathogenesis, and a target for stratification or therapeutic/lifestyle interventions? Second, is the disruption of the gut-liver axis involved in NAFLD progression?

One of the particularly exciting aspects of the project is that it combines strong scientific expertise with integrated and complementary training. Specific factors include translational research, clinical practice, technology commercialisation and public outreach. Partnering with industry is seen as crucial to the success of the project, where microBiology and Mediagnost help provide experience on commercialising the findings from FOIE GRAS, while the affiliated patient organisation, APDP-ERC, will provide important training related to societal

awareness topics. Agilent, which acquired Seahorse Biosciences, will provide training regarding metabolic technological platforms.

However, perhaps the most unique aspect of FOIE GRAS is its keen focus on training ESRs. 'ESR training utilises network-wide workshops and secondments to foster translation of basic research to clinical applications and SME creation,' explains Oliveira. 'This diverse yet integrated skill set enhances the employment prospects of the trained researchers in both academic and non-academic sectors.' Importantly, the FOIE GRAS network embraces the Marie Skłodowska-Curie ETN action in training ESRs with transferable skills. In doing so, Oliveira and his team hope to boost the individual ESRs' career development and long-term opportunities, as well as maintaining a level of interest in NAFLD research.

WIDESPREAD COLLABORATION FOR WIDE-RANGING SUCCESS

It is the team's belief that NAFLD pathogenesis and progression involves nutrient, inflammatory and oxidative stress factors that directly or indirectly impair metabolic activity and energy generation in the liver. Thus, successfully characterising the underlying mechanisms or metabolic

and gut-liver axis dysfunction, identifying biomarkers that inform metabolic status, and designing interventions for restoration of normal metabolic activity in NAFLD patients, are the main goals of this project.

To address these goals, there needs to be a clear focus on the need for collaboration, not only because it is vital that new methods and training move away from current practice; but also because collaboration helps foster this new form of approach. 'At present, the typical training in the field of liver diseases is limited to specific aspects, usually not

isolated mitochondrial fractions, as well as high-precision respirometry, there are also provisions for nuclear magnetic resonance facilities, microscopy and genomics/proteomics.

Alongside the technologies that will be employed, Oliveira is keen that the ESRs are imbued with some societal qualities that are essential for effective research. 'We will help the 13 individuals by getting them to work alongside patients, clinicians and industry,' explains Oliveira. 'An important objective of one of the 13 ESR projects is to develop and

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providing interaction with basic, clinical and industrial fields. Generally, academic and non-academic sectors work separately to provide their own direction to ESRs, with collaborative opportunities being bound to a narrow scope,' explains Oliveira. 'FOIE GRAS introduces a well-balanced, pan-European structure to support the career development and training of researchers. FOIE GRAS partners consistently match the proposed research topics across academic and non-academic sectors in Europe and have a record of previous successful collaborations between themselves.'

Indeed, the supervisors and co-supervisors involved in the project are all renowned researchers in their particular areas of expertise, and have substantial experience in heading national and international research projects. This puts them in a perfect position to effectively manage the respective areas of study and ensure the project remains focused on independent, but entirely complementary investigations.

RIGHT TOOLS FOR THE JOB

While bringing 13 ESRs together to work towards producing improved understanding and clinical outcomes for NAFLD is of great importance, it is equally important that these individuals are given the tools they need to flourish and advance in their careers. Accordingly, FOIE GRAS provides access to top facilities and modern equipment, often through partnering with various industries. In addition, it provides a mean for metabolic analyses in cells in culture and

implement strategic communication and educational activities addressing NAFLD awareness, which targets the general public and aims to inform and promote healthy lifestyles.'

SOWING THE SEEDS OF SUCCESS

Given the project only began in January 2017, and the time it took to identify the 13 ESRs who would form part of FOIE GRAS, there have been no true scientific results as yet. However, there has been evidence of progress to date, even at this early stage. Building bridges between different research groups is no mean feat, while bringing various people together to discuss science – as well as identifying and hiring the best researchers for the job – are essential seeds for the successful germination of the FOIE GRAS project.

Ultimately, Oliveira and his colleagues hope to clearly identify and validate the biomarkers involved in NAFLD, which will naturally lead to accurate diagnosis, effective treatments and effective tools to monitor disease response. Together, these will help improve support for medical practice. Of equal importance is putting together an educational package that will encourage individuals to lead healthier lifestyles, modify their behaviours and significantly reduce the burden that NAFLD currently represents. As the science behind understanding NAFLD improves, so will the understanding of individuals. And with 13 ESRs becoming well-versed in every aspect of NAFLD, it is reasonable to expect an even brighter future for those individuals and NAFLD patients.

Project Insights

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Professor Paulo Oliveira completed his PhD in Cellular Biology in 2003 at University of Coimbra, Portugal. He is currently head of the Mitochondrial, Metabolism and Disease Workgroup and the Principal Investigator at the MitoXT: Mitochondrial Toxicology and Experimental Therapeutics, both at CNBC. His main research interests involve the role of mitochondrial biology in metabolic diseases and cancer, drug-induced mitochondrial dysfunction, and the development of mitochondrial-targeted molecules that can delay metabolic disruption during different pathologies.



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