

## Impact Objectives

- Train the next generation of Early Stage Researchers (ESRs), equipping them with the skills to deal with current and future challenges surrounding autoimmune diseases, with a specific focus on TTP (thrombotic thrombocytopenic purpura)
- Develop innovative immuno-profiling technologies and treatment approaches to assist with stratifying and treating patients with TTP
- Utilise the testimonies of TTP patients to gain a better understanding of the real problems TTP sufferers face, and thus work towards more effective personalised medicine for the disease

# Improving predictability for a better quality of life

**Professor Karen Vanhoorelbeke** is the coordinator and **Dr Nick Geukens** is the training manager of the Marie Skłodowska-Curie innovative training network **PROFILE**, a project that should deliver prognostic factors to better predict relapses in patients with a rare blood disorder – thrombotic thrombocytopenic purpura (TTP)



Prof Karen Vanhoorelbeke



Dr Nick Geukens

### What are your respective backgrounds?

**KV:** I am a professor at KU Leuven Campus Kulak Kortrijk, Belgium. I was trained as a biochemist at KU Leuven and obtained my PhD in 1996.

During my postdoc, I started working in the field of thrombosis and haemostasis, working on the role of the plasma protein von Willebrand factor (VWF) and platelet receptors in primary haemostasis and thrombosis.

In 2007, I was appointed as an associate professor and started my own research group. In 2008, my group and five other university labs cofounded PharmAbs, which is a KU Leuven innovation, incubation and valorisation platform for the development of antibody-based therapeutics and diagnostics.

**NG:** I obtained my Master's in Biochemistry from KU Leuven and did my PhD at the same university at the Rega Institute for Biomedical Research. Since 2008, I have been coordinating PharmAbs as Research

and Innovation Manager.

### How did you come to work in the field of thrombotic thrombocytopenic purpura (TTP) and what most interests you about this work?

**KV:** Being an academic research lab, we were performing fundamental research on the role of VWF and ADAMTS13 – also known as VWF-cleaving protease (VWFPC) – in haemostasis (a process that causes bleeding to stop). Since ADAMTS13 deficiency causes TTP, it was logical to also start working in the field of TTP.

In addition, it is a vision of our research group to use our fundamental knowledge to better understand TTP, to develop animal models for the disease, to develop novel treatment strategies and diagnostic assays. In the end, with our fundamental and translational research, we want to contribute to improving the quality of life of TTP patients.

Thanks to the PROFILE project, we learned to identify and focus on the clinical unmet needs of TTP patients. We can now focus part of our research on finding a solution for these clinical unmet needs. We also came into contact with TTP patients and their testimonies are helping us to see the 'real' problems they are facing, which again allows us to better focus on the correct research questions we should study.

### Can you explain the importance of this work

### in real-world terms?

**KV:** In real-world terms, the PROFILE project should deliver prognostic factors to better predict relapses in TTP patients. This will result in a better tailor-made treatment of TTP patients, which will improve their quality of life.

In addition, better treatment strategies are needed (although the current strategies are successful in treating the patients) to replace the current plasma exchange therapy (which is a risk and is cumbersome for the patients) or to replace the current immune modulating strategies (steroids, rituximab), which block the entire immune system.

Through our dissemination, the PROFILE project should also succeed in better informing patients about their disease, help them to better understand their disease and how to deal with it, bring them into contact with other TTP patients and inform them about novel developments in TTP research.

### What is next for the project in the coming five to 10 years?

**NG:** To implement the use of prognostic factors in the clinical follow-up of the patients and to adapt treatment accordingly. This should better predict relapses and decrease the fear of patients not knowing when the disease can set in again.

# Unravelling TTP at the molecular level

**PROFILE** is an innovative training network that is seeking to rectify the shortcomings of current novel diagnostics and therapeutics for autoimmune diseases, with a specific focus on TTP (thrombotic thrombocytopenic purpura)

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease caused by a hereditary or autoimmune deficiency in the blood protease ADAMTS13, for which novel treatment strategies and innovative diagnostic assays are required.

Professor Karen Vanhoorelbeke and Dr Nick Geukens, both based at KU Leuven, Belgium, are responding to this need by coordinating a Marie Skłodowska-Curie innovative training network: Immuno-profile-directed stratification of patients with the autoimmune disorder thrombotic thrombocytopenic purpura (PROFILE). The network is an ongoing Horizon 2020 project that began in October 2015 and is set to finish in September 2019.

Alongside their work on the network, they are also involved in PharmAbs. 'This is an academic innovation and valorisation platform founded by seven professors including Professor Vanhoorelbeke, with the mission to translate fundamental biomedical research into lead products for new medicines or into novel diagnostic solutions,' explains PharmAbs manager Geukens.

### NEXT GENERATION ESR

The objective of the PROFILE network is to train a new generation of innovative PhD students or Early Stage Researchers (ESRs),

equipping them with the skills to deal with current and future challenges and the ability to convert knowledge and ideas into products and services from which society and the economy will benefit. In order to achieve this goal, the network is drawing on expertise from 10 partners in Europe from within academia and industry. Six ESRs will follow this translational training and will be trained in the clinic, in academia and in the non-academic sector.

PROFILE is working to develop innovative immuno-profiling technologies and treatment approaches to assist with stratifying and treating patients with TTP. In the disease, thrombi form in small blood vessels throughout the body, limiting or blocking the flow of oxygen to the organs, which can lead to serious health problems. Vanhoorelbeke explains more: 'In TTP, the haemostatic system is more active, leading to increased formation of a special kind of thrombi mainly consisting of platelets. These thrombi block the normal blood flow through the organs of the human body, leading to severe organ failure. TTP is a life-threatening disease and urgent and adequate treatment is essential,' she highlights. 'The disease can be either congenital (inherited), or acquired (autoimmune). Only around five per cent of individuals present with inherited TTP, with around 95 per cent of an autoimmune nature – acquired TTP (aTTP).

Patient stratification is necessary in order to develop personalised medicine approaches for the disease. This requires a detailed understanding of TTP at the molecular level, as well as the implementation of a solid set of innovative biomarkers. 'We are aiming to identify biomarkers (antibodies or T-cell epitopes) to highlight prognostic factors for aTTP,' explains Vanhoorelbeke. 'The relapse rate of patients suffering from aTTP is high and the time course of relapses is unpredictable. Hence, there is an unmet need to identify reliable prognostic factors to predict relapses in aTTP patients. This will improve the follow-up and treatment of aTTP patients and eventually their quality of life.'

### AN INVESTED TEAM

Existing treatments for TTP are costly, invasive and involve a complex regime, with plasma infusion used in cases of congenital TTP and plasma exchange used in patients with aTTP, in combination with immune system modulators. The team is investing in developing innovative therapies for TTP, as Vanhoorelbeke reveals: 'We are aiming to obtain recombinant ADAMTS13 variants that can be used to treat patients, instead of the cumbersome plasma exchange therapy. We are also developing small molecules or anti-idiotypic antibodies that inhibit the binding of the anti-ADAMTS13 autoantibodies to ADAMTS13,' she says.

**PROFILE is working to develop innovative immuno-profiling technologies and treatment approaches to assist with stratifying and treating patients with TTP**

'In this way we can specifically interfere with the immune component of the disease, instead of blocking the whole immune system of the patient.'

The members of the PROFILE consortium are: Vanhoorelbeke (coordinator), Geukens (training manager) and Wim Maes (project manager) from KU Leuven; Jan Voorberg (scientific manager) from Stichting Sanquin Bloedvoorziening; Gerry Nicolaes and Chris Reutelingsperger from Pharmatarget; Rob Fijnheer from the TTP Contact Group; and Carin Smand and Robin Doeswijk from the European Haematology Association (EHA), which are all based in the Netherlands. The rest of the team includes: Kaia Palm from Protobios and Andres Männik (IP manager) from Icosagen AS, both based in Estonia; Paul Coppo and Agnès Veyradier from Assistance Publique-Hopitaux de Paris (AP-HP) in France; Marta Palicio from Biokit in Spain; and Liselotte Brix from Immudex in Denmark. Vanhoorelbeke highlights the importance of these various collaborations: 'The academic centres, KU Leuven, Sanquin and AP-HP are world-leading experts on aTTP. SME's Protobios, Icosagen, Pharmatarget and Immudex are highly skilled and specialised immuno-profiling experts and experts in developing small molecules and recombinant proteins as novel therapies. Biokit is a world leading diagnostic company. Dissemination of results emanating from the PROFILE consortium to patients, clinicians and other societal interest groups is ensured by the inclusion of EHA as a partner,' she explains. A patient TTP contact group is also involved in the work to ensure an in-depth involvement of patients in the project. 'This is crucial for dissemination and communication and for looking at the scientific questions from a patient point of view,' Vanhoorelbeke highlights.

#### A POSITIVE IMPACT FOR PATIENTS

When it comes to training the ESRs, the researchers are learning to study clinical needs, identify new biomarkers, develop new diagnostic tests, validate and commercialise these tests in order to stratify patient groups for development of personalised medicine,

with programmes in both academic and non-academic sectors. 'In addition, the PROFILE ESRs will be trained in a broad set of soft skills, including communication skills (verbal and written), management skills and entrepreneurial and productive development skills,' says Vanhoorelbeke. 'Researchers combining this set of expertise and skills are scarce, which lies at the root of the shortcomings of current novel diagnostics and therapeutics for autoimmune diseases.'

The network hopes to have a positive impact on patients as Geukens explains: 'Immuno-profiling will allow for the stratification and subsequent development of personalised medicine for patients suffering from this clinically heterogeneous and rare autoimmune disorder,' he states. 'In view of the increasing prevalence of autoimmune diseases in Europe, the expertise and "human capital" delivered by the PROFILE training network is expected to have a huge impact on quality of life and healthcare costs in Europe.' According to Geukens, the immediate benefit of the network is a better understanding of the significance of different steps needed in developing personalised medicine. 'Achieving this goal requires a translational approach both for the science and training programme. The project discovers and validates novel biomarkers and develops novel personalised therapeutic modalities for patients suffering from this autoimmune disorder tailored to the industrial knowledge needs,' he states. 'The PROFILE network is providing multidisciplinary training across sectors to a new generation of researchers that will know how to identify a clinical need, how to validate their research, how to transfer technology and knowledge to the industry, how to manage intellectual property rights and how to act as competent managers.'

#### TOWARDS A CURE?

Future plans for the researchers involve investing in novel therapies that reach TTP patients: 'The novel therapies should improve the quality of life of the patients and hopefully really cure the disease (for example, gene therapy for TTP),' Geukens concludes.

## Project Insights

### FUNDING

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### COLLABORATORS

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