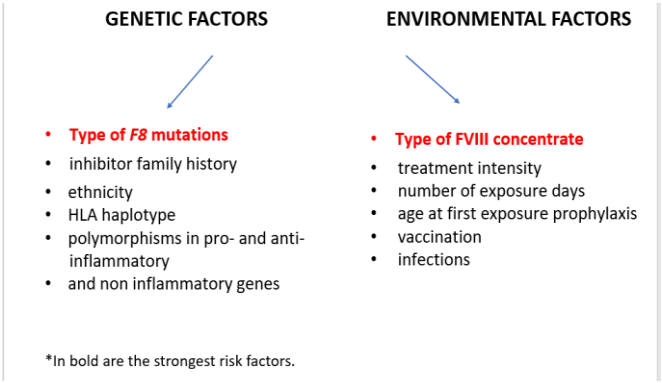
Inhibitors in their **ENTIRE**ty: presenting the European Network on Inhibitor Research Group

By Raia Mihaylova, EHC Communications Officer

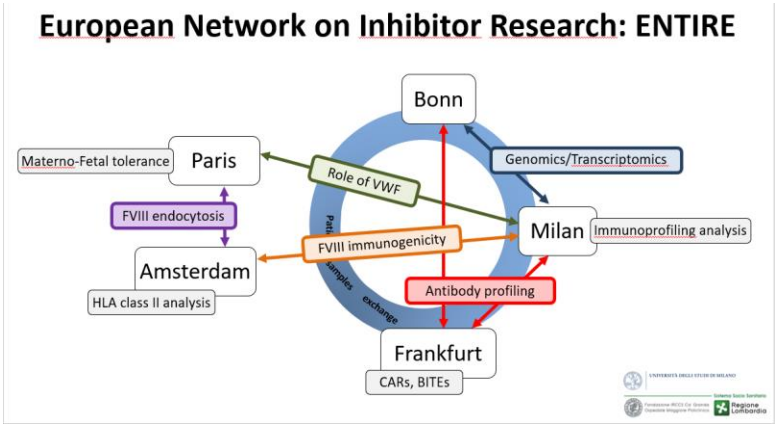
When speaking of novel haemophilia agents, there is a re-occurring phrase often used to describe their effect – "changing the haemophilia landscape." Extended half-life products have already led to significant improvements and together with other emerging novel therapies, are allowing patients to reduce the number of weekly injections while increasing protection from bleeds, as well as decreasing joint damage and pain.



Information taken from Professor Flora Peyvandi's presentation at the 2018 Inhibitor Conference in Milan.

If the definition of a landscape in this case is "*the distinctive features of a sphere of activity*," there is one attribute that has stubbornly stuck throughout the years – inhibitor development and the unknowns around it. A complex complication, inhibitor development results from interaction between the genetic and environmental risk factors of patients. It is interesting to note that in the case of haemophilia A, it is not that certain patients develop an immune response to their factor VIII treatment (FVIII) and others don't, but rather the other way around – all haemophilia A patients have an immune response to FVIII but 70-95 per cent of them will develop tolerance. So why don't the remaining patients?

As an answer to that question, Professor Flora Peyvandi from the Angelo Bianchi Bonomi Haemophilia and Thrombosis Center in Milan, and member of the EHC Medical Advisory Group, formed a multidisciplinary team to address the complex interplay between patients' genetic and environmental-related risk factors, and to try to prevent inhibitor development and develop innovative protocols for inhibitor eradication in patients with haemophilia A. The European Network on Inhibitor Research, or ENTIRE, brings together leading experts from various fields and universities, each specialising on concrete research. This will allow



Slide from Professor Flora Peyvandi's presentation at the 2018 Inhibitor Conference in Milan.

for the exchange of different human biological samples between the group, which are collected during a biopsy or surgery and are preserved by researchers to study the specifics and progression of a disease. The ENTIRE studies cover and focus on the role of the von Willebrand factor (vWF), FVIII immunogenicity, antibody profiling and genomics/transcriptomics analyses.

"*This is the first European network that tries to empower the biological sample collection among centres and to bring together expertise and knowledge at European level in order to understand the pathophysiology, to predict, and to eradicate the inhibitor in haemophilia*," explains Prof Peyvandi.

The ENTIRE group includes **Sebastien Lacroix-Desmazes** from France; **Christoph Königs** and **Johannes Oldenburg** from Germany; and **Frits Rosendaal** and **Jan Voorberg** from the Netherlands.

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When asked about his vision for ENTIRE, Prof Rosendaal credits the diversity of the group as what is needed to really tackle the multi-causal factors behind inhibitor development:

"*The inhibitor problem is currently the major complication of haemophilia treatment, and its incidence has only gone up over the last decades. I hope that by bringing together experts with quite different backgrounds, based in biochemistry, immunology, genetics and epidemiology, we can come to truly translational research that will lead first to better understanding, and then to improved prevention and treatment.*"

As to the philosophy behind it, Dr Sébastien Lacroix-Desmazes shares that by fostering the development of common research projects, the group aims to understand the etiology of the development of inhibitor antibodies to FVIII from both a patients' and a products' perspective, and to imagine and validate novel strategies to induce long-term tolerance to therapeutic factor VIII:

"The ENTIRE research group is a European initiative from leading academic research teams working on the immunogenicity of therapeutic pro-coagulant factor VIII in patients with haemophilia A. The inclusion in the ENTIRE research group of basic scientists and clinicians creates a multidisciplinary group ideal for intellectual discussions and exchange of ideas and biological material; it promotes synergy between fundamental science and translational research. Importantly, the group brings together a large array of complementary technologies and know-how, including the use of preclinical models and access to patients' biological samples. The creation of the ENTIRE research group will give visibility to research on factor VIII at the European and world-wide levels. The ENTIRE research group aims at influencing decision makers at the National and European levels, and at attracting the interest of funding bodies from both the academic and private sectors."

With years of slow advancement in understanding inhibitor development, the establishment of the ENTIRE research group offers hope where it was lacking before. Together with the improvements brought by novel therapies, there is potential to visualise a fully changed landscape with the new attribute being a high quality of life for all patients with haemophilia (and inhibitors).