Casting new light on thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder, where blood clots develop spontaneously without any previous injuries. We spoke to **PD Monica Schaller, PhD** and **Erika Tarasco, PhD**, who both work in the group of **Prof. Johanna Kremer Hovinga, MD**, a world-renowned expert in the field of TTP, about their research.

A disorder which leads to the spontaneous formation of blood clots, thrombotic thrombocytopenic purpura (TTP) is a serious threat to health. When blood clots form in an uncontrolled fashion, they will attract and activate platelets and form blood clots together with von Willebrand factor (VWF), which obstruct the small vessels. "If the condition is left untreated then the organ becomes ischemic and dysfunctional. The major organs that can be affected are the kidneys, the brain and the heart," explains Dr Monica Schaller. Based at the Department of Hematology at the University Hospital Bern, Dr Schaller is part of a research project which aims to shed new light on both the immune-mediated (iTTP) and hereditary (hTTP) forms of TTP, which share some clinical features. "First of all in both forms there is a reduction in the activity of an enzyme called ADAMTS13," says Erika Tarasco, a post-doctoral fellow at the University Hospital Bern, Inselspital who is also the project manager of the international hereditary TTP registry (HYPERLINK "http://www.ttpregistry.net/"www.ttpregistry.net).

ADAMTS13

This particular enzyme, that was discovered in Professor Kremer Hovinga's laboratory in 1996 (Furlan et al, Blood 1996), plays a crucial role in cleaving VWF, which forms ultra-large multimeres at the origin of the observed blood clotting. In iTTP and hTTP, the ability of ADAMTS13 to cleave VWF is limited. "In hTTP mutations lead to decreased expression of ADAMTS13 or a less functional variant. In iTTP, there are antibodies that block ADAMTS13," outlines Dr Schaller. As an immunologist, the focus of Dr Schaller's research is iTTP. "What kinds of antibodies do those patients have that block ADAMTS13? Characterization of the antibodies (genetically and functionally) might give insights into how inhibition of ADAMTS13 can be prevented. What triggers them?" she says. "Children aren't affected by the immune-mediated form – in general it starts in the third decade – so something must act as an additional trigger. We are trying to figure out how the disease starts and is maintained."

Researchers are using cells from the spleen, which is known to be a major reservoir of antibodies and autoantibodies, to probe deeper in this area. Dr Schaller is analysing material from the spleens of eight patients, which she says opens up a variety of interesting avenues of investigation. "With these spleens we have access to the B-cells that produce the pathogenic antibodies. We can then extract those antibodies with a technique called phage display technology," she explains. Building from these foundations, researchers can then generate antibodies in the lab in a recombinant way. "We use those as tools to select for any molecules that would bind those antibodies," continues Dr Schaller. "In a very broad sense, the idea is to inject small molecules that bind very strongly to those anti-ADAMTS13 antibodies, thus essentially preventing them from binding to ADAMTS13. "

The wider aim here is to essentially restore the function of ADAMTS13 and prevent VWF from growing too long, with Dr Schaller looking at whether small molecules called Designed-Ankyrin-Repeat Proteins (DARPIns) can block these antibodies. This work is at a relatively early stage, and is still a long way from clinical translation. Alongside this work on iTTP, the project's agenda also includes research into hTTP, the two of which have historically been considered to be very similar. "Some of the clinical features that we see with patients are similar. However, there are also aspects in which they differ," says Dr Tarasco. "The two forms of the disease are fairly similar, but I would not say that they are exactly the same."

This is a topic that Dr Tarasco is exploring further in the project, using data from the international hTTP registry, which brings together information on hTTP patients from across this world. The registry was initiated by Prof. Johanna Kremer Hovinga from a collection of several case studies and was officially approved by the ethics committee in 2006.

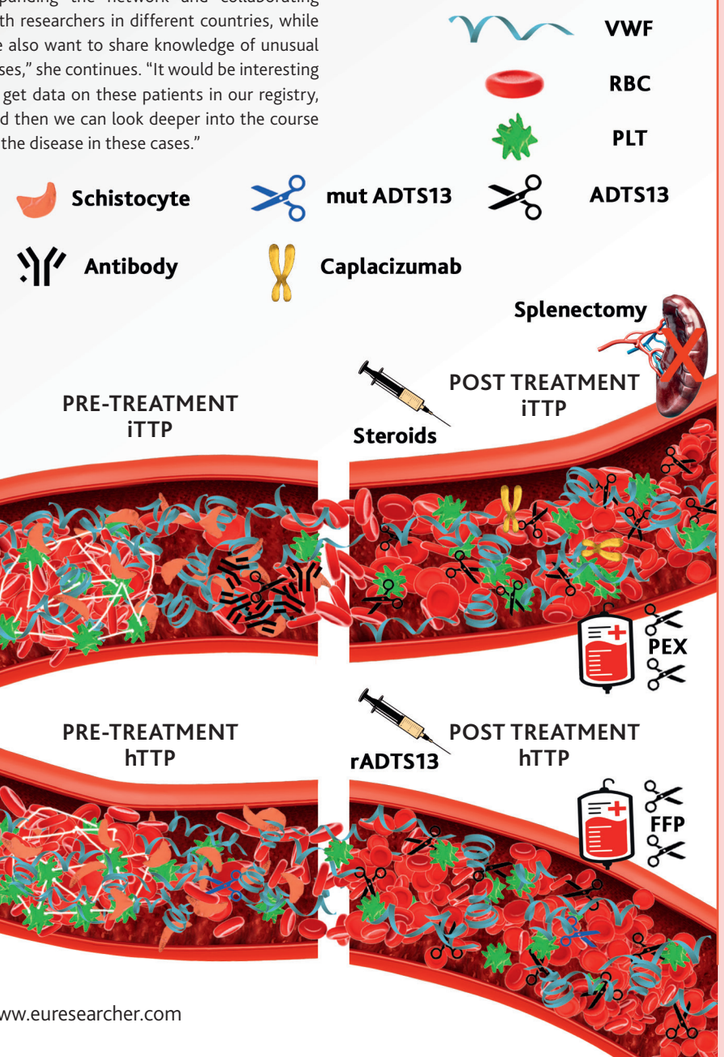
How can we raise awareness for this rare disease to **optimize treatment** and **develop new therapy approaches** for the **iTTP and hTTP? Antibody-targeted therapies** would be **highly desirable** for **iTTP.**

TTP is a rare and complex disease, so Prof Kremer Hovinga and Dr Tarasco say it's important to share information. "Our laboratory is one of the major reference centres on TTP in the world, so we are part of a network," they explain. This kind of network can help physicians – some of whom may not have seen many patients with TTP – to diagnose it rapidly when they do come across a case, while the registry is also a valuable research resource. "Hereditary TTP is a very heterogeneous disease," says Dr Tarasco. "We see some patients who have been diagnosed, had one episode, and then are subsequently fine - with or without treatment. We also see patients who are regularly sick. They are constantly having blood-clotting episodes, requiring additional treatment."

The main treatment option for both forms available at the moment is plasma exchange, for which a patient typically needs to travel to hospital. If a patient feels fine and is not experiencing symptoms they might ask whether the inconvenience is really necessary, so preventing over-treatment is also an important issue. "We hope that the clinical trial studies on recombinant ADAMTS13 will lead to greater possibilities for patients to have home treatment," says Dr Tarasco. More data on TTP would help researchers probe deeper into the disease, and Dr Tarasco says she and her colleagues are keen to widen the network in future. "We are interested in expanding the network and collaborating with researchers in different countries, while we also want to share knowledge of unusual cases," she continues. "It would be interesting to get data on these patients in our registry, and then we can look deeper into the course of the disease in these cases."

Rare disease

This remains an extremely rare condition, yet there has been an increase in the number of cases over the last 10 years which is largely due to heightened awareness of the disease among clinical professionals. Even so, Dr Tarasco believes it is important to raise awareness of the disease still further, which would improve the treatment prospects of patients. "Often it's only in the later stages, when all the other possible microangiopathies have been excluded, that somebody will raise the possibility that a patient has TTP," she says. By measuring levels of ADAMTS13 activity, Prof. Kremer Hovinga and her group can help diagnose cases of TTP. "For hTTP we do this nearly free of charge for the countries that would like to collaborate with us and become part of the registry. Then we can strengthen the network and plant the seeds of future collaboration," she continues.



THROMBOTIC THROMBOCYTOPENIC PURPURA - ROLE OF ADAMTS13 AND LONG-TERM OUTCOME

Project Objectives
Research at Professor Dr Kremer Hovinga's lab is centered on underlying the mechanisms behind immune-mediated and hereditary TTP.

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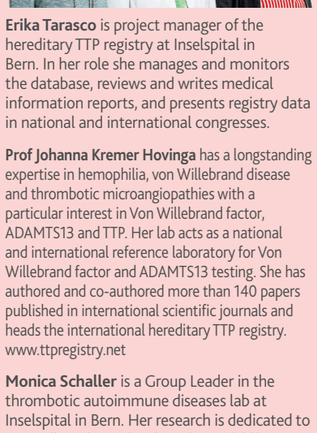

Erika Tarasco is project manager of the hereditary TTP registry at Inselspital in Bern. In her role she manages and monitors the database, reviews and writes medical information reports, and presents registry data in national and international congresses.

Prof Johanna Kremer Hovinga has a longstanding expertise in hemophilia, von Willebrand disease and thrombotic microangiopathies with a particular interest in Von Willebrand factor, ADAMTS13 and TTP. Her lab acts as a national and international reference laboratory for Von Willebrand factor and ADAMTS13 testing. She has authored and co-authored more than 140 papers published in international scientific journals and heads the international hereditary TTP registry. www.ttpregistry.net

Monica Schaller is a Group Leader in the thrombotic autoimmune diseases lab at Inselspital in Bern. Her research is dedicated to unravelling the pathophysiology of different autoimmune diseases, including TTP.

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