New approach prevents thrombosis without increasing the risk of bleeding

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This is an electron microsscopy image of a throbmus attached to the oxygenator membranes. Credit: Kjell Hultenby, Karolinska Institutet

In collaboration with an international team, researchers at Karolinska Institutet in Sweden have developed an antibody, 3F7, which blocks a

protein that is active in the coagulation system factor XII. Inhibition of factor XII makes it possible to prevent thrombosis in blood vessels without increasing the risk of bleeding in clinical settings.

Thrombosis is caused by blood clotting; clots can block blood flow in one or more blood vessels and so cause thrombotic diseases such as stroke, myocardial infarction or pulmonary embolism. Today, thrombosis is prevented or treated by means of anticoagulants. There is a broad variety of anticoagulant drugs, such as warfarin (a vitamin K inhibitor), the novel oral anticoagulants (dabigatran or rivaroxaban) and drugs of the heparin group. All of these agents target different components of the blood coagulation system to prevent blood from clotting and thus to interfere with thrombosis. However, all these drugs also entail an increased risk of bleeding in patients that partially offsets their beneficial effects.

The blocking of coagulation factor XII (F XII) functions differently compared to traditional anticoagulants. It has been known for long time that humans that are deficient in FXII do not bleed excessively and because of that FXII was believed to have no function for blood coagulation in patients. In 2005, Thomas Renné and his research team discovered that mice lacking F XII could have neither a stroke nor pulmonary embolism, even though they had normal bleeding patterns.

"Since then, our goal has been to find an effective way to block F XII. Now, we have developed an antibody that blocks F XII in human blood, mice and rabbits", says Thomas Renné. "This provides protection against thrombosis without increasing the risk of bleeding."

Together with the doctoral student Magnus Larsson, the researchers developed and tested the antibody, called 3F7, in rabbits during an ECMO treatment. ECMO is an advanced heart-lung machine used in life-threatening conditions especially in infants. Contact with the plastic

tubing causes the blood to clot, so patients are routinely administered with anticoagulants (heparin). However due to the heparin anticoagulation patients bleed excessively and a substantial number even dies from these bleedings.

In the study, thrombosis in rabbits on ECMO receiving 3F7 decreased was as low as rabbits receiving heparin, but the risk of bleeding with 3F7 was minimal, whereas heparin-treatment led to bleeding.

"Blocking F XII appears to be an effective strategy against thrombus formation, and we have shown this in experiments on rabbits in a clinically relevant context", says Thomas Renné. "There is a great need for a treatment that reduces the clot risk in emergency situations, such as during ECMO treatment and many others such as cardiovascular surgery. We plan to test the antibody in a phase I study. It is possible that the antibody also blocks inflammation mediated by F XII, an interesting area for future studies."

More information: 'A Factor XIIa Inhibitory Antibody Provides Thromboprotection in Extracorporeal Circulation Without Increasing Bleeding Risk', Magnus Larsson, Veronika Rayzman, Msarc W. Nolte, Katrin F. Nickel, Jenny Björkqvist, Anne Jämsä, Matthew P. Hardy, Marion Fries, Stefan Schmidbauer, Patricia Hedenqvist, Michael Broomé, Ingo Pragst, Gerhard Dickneite, Michael J. Wilson, Andrew D. Nash, Con Panousis and Thomas Renné, *Science Translational Medicine*, 5 February 2014 Vol 6 Issue 222 222ra17

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