

Blocked: a clot of red blood cells and fibrin strands (gray) occludes a blood vessel. As this photo taken under a scanning electron microscope shows, the flow of blood is halted. While blood clots are desirable in the event of a trauma, they can also, if triggered by accident, be life-threatening.

## GENOME RESEARCH FOR ENVISAGED NEW THROMBOSIS DRUG

# A new factor

*Research in the lab and on the computer: researchers at Bayer are collaborating closely in an interdisciplinary team to develop new options in thrombosis treatment. One new approach they are looking at is blood coagulation factor XI.*

Thrombosis – the formation of blood clots in the circulatory system – is a life-threatening medical condition, and one that affects a wide range of people. If one of these clots then migrates to the heart, to the brain or the lungs, it can cause infarction, stroke or an embolism. Blood clots are formed by the body's blood coagulation system, a highly complex process cascade that involves more than 30 proteins. This system usually protects us against bleeding by forming a delicate crust over wounds to seal them.

## Higher risk of thrombosis in pregnant women and the elderly

But the delicate interplay between coagulation factors, proteins, messenger substances and blood platelets does not always function perfectly. "Particularly at risk are the elderly and people with accompanying disorders such as diabetes, arteriosclerosis or impaired renal function. And hormonal changes during pregnancy and surgery likewise increase the risk of thrombosis," explains Dr. Volker Laux, Head of Acute Care Research at Bayer HealthCare in Wuppertal. He and his team are therefore looking for new ways to protect specific high-risk groups more effectively against life-threatening thrombosis.

He is therefore collaborating closely with Dr. Kirsten Leineweber, Head of Disease Genomics at Bayer HealthCare in Wuppertal. Her team is investigating human DNA to establish connections between certain genes and diseases. "The more precisely we understand the interplay between individual genetics, throm-



Dialog for the patients: Dr. Kirsten Leineweber, Head of Disease Genomics at Bayer HealthCare, and Dr. Volker Laux, Head of Acute Care Research at Bayer HealthCare, discuss potential variations in the human coagulation system.

bosis and accompanying disorders, the better we will be able to develop more efficient treatments," explains Leineweber. They are therefore scrutinizing the genome for specific risk factors: traits that increase the individual's susceptibility to developing a disease, such as an elevated risk of thrombosis. This involves comparing patients' clinical data. "For example, we analyze whether people who have a specific genetic characteristic – what we call a variation – or specific combinations of variations also have an elevated risk of

a disease," explains Leineweber. "We do this for each of the up to 10 million variations. The computer runs red-hot!" Her team also sifts through the data masses to find links between genetic predispositions and thrombosis.

Findings like these can be used to improve the care of at-risk patients in the future. "The risk profile of a stroke patient indicates reasons why the stroke occurred, such as cardiac arrhythmia. You can then make targeted attempts to avoid these risk factors and prevent a second



Reaching the goal through teamwork: in the Bayer HealthCare laboratory in Wuppertal, Dr. Imke Meyer, Manfred Schumacher, Dr. Volker Laux, Julia Strassburger and Manuela Vögler (left to right) are jointly developing new methods to help patients who have an elevated risk of thrombosis.

stroke," says Leineweber. It is also possible to analyze risk factors for conditions such as weak veins at the same time, because in individuals with susceptible veins, small arteries in the stomach, intestines or brain can burst and bleed into the surrounding tissue. As such, genetic analysis can help to assess both the benefits and the potential risks of therapeutic agents.

Even though novel oral anti-coagulants have improved thrombosis prevention greatly in recent years relative to the previous standard of care, researchers are striving to investigate new mechanisms of action, which may allow further improvements to the benefits and risks compared to existing therapies.

### Computer-based genome analysis supports prevention

Bayer scientists are therefore continuing to investigate new therapeutic options for thrombosis patients. Laux and his team, supported by gene researchers and bioinformatics experts, have already discovered a new target point in the coagulation process. "The complex cascade is controlled by coagulation-promoting and -inhibiting factors. Our current objective is to target coagulation factor XI, or FXI for short," says Laux. In support for this approach was a

risk/benefit analysis that Leineweber and her team contributed to, which looked closely at the genetic data of patients with an inherited factor XI defect. "We could confirm that people with an elevated level of FXI in blood suffered more frequently from stroke, thrombosis and pulmonary embolism than the average," explains Leineweber.

Individuals who do not form FXI, on the other hand, suffered thrombosis considerably less frequently than the general population as a whole. They were not, however, at the same time found to suffer more frequently from spontaneous bleeding. "We hope that targeted inhibition of FXI will enable us to achieve an antithrombotic effect without the risk of spontaneous bleeding," says Laux.

With this information at hand, the scientists have started to conduct research into three different approaches to FXI inhibition. One approach is aimed

Some  
**30** different  
proteins are involved in blood  
coagulation.

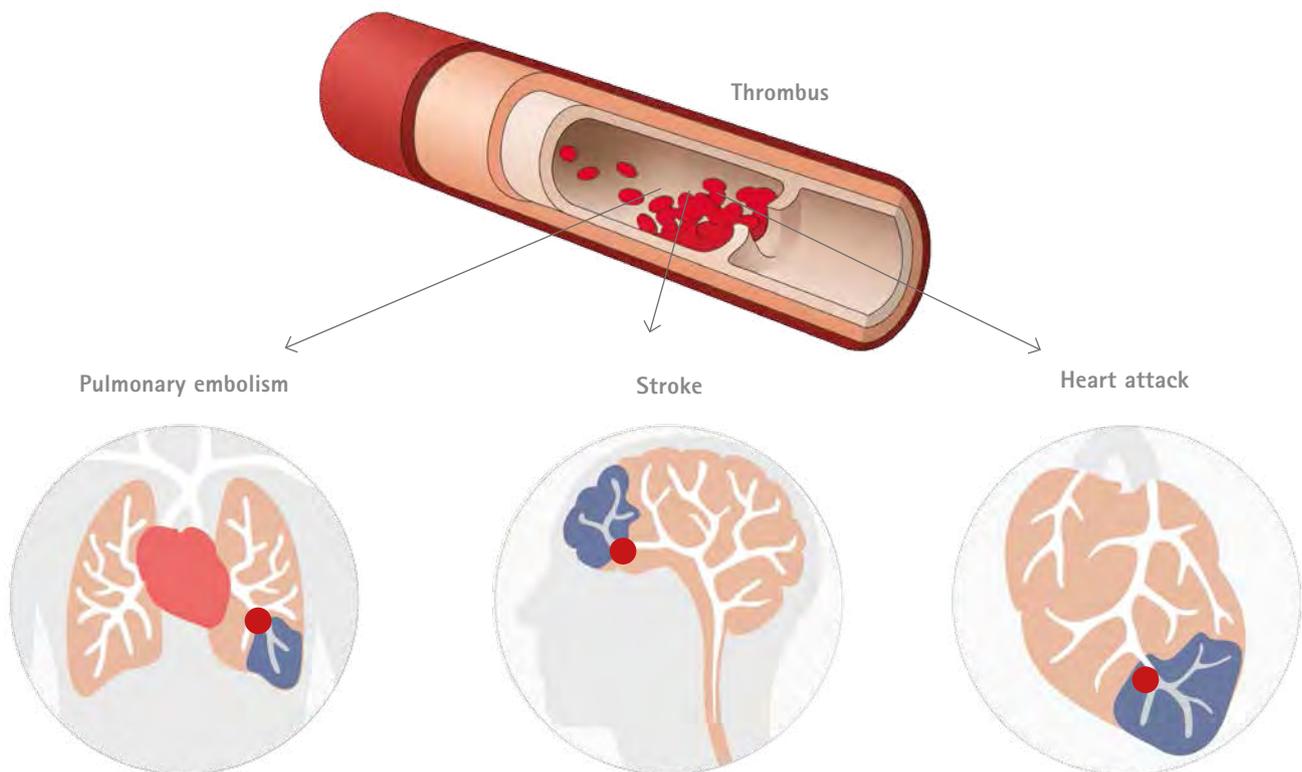
Source: Colman et al.



Small clot, large danger: if a thrombus in a small blood vessel (photo left) detaches and migrates to blood vessels that supply the brain with oxygen, it can cause a stroke. To discover any other clots in good time, neurologists like Dr. Holger Poppert use ultrasound equipment to, for example, precisely examine the carotid vein of their patients.

## Life-threatening clot

Thrombi can be responsible for a number of severe and life-threatening disorders. Different organs can be affected depending on where the thrombus migrates to:



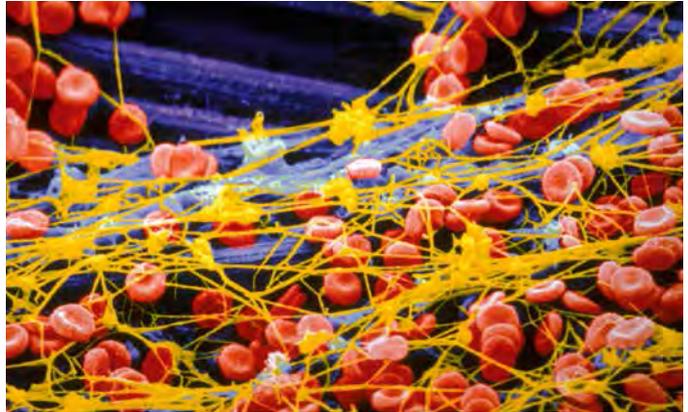
If parts of a **blood clot** in a vein – called venous thromboembolism – become detached, they can migrate to the lungs. This can lead to **pulmonary embolism**, which prevents the blood from taking up oxygen. Every third patient with venous thromboembolism develops pulmonary embolism as well, leading to sudden death in one in four cases.

If a **blood clot** migrates to the brain, it can cause a stroke and thus destruction of brain cells. The consequence can be severe disabilities, which depending on the size of the affected area can also be fatal. In the United States, one person suffers a **stroke** every 40 seconds, and every 4 minutes a patient dies as a result of a stroke.

In a **heart attack**, a **clot** blocks a coronary artery. The result: not enough oxygen and nutrients are supplied to part of the heart muscle. This can likewise be life-threatening in many cases: 15 percent of patients die as a result of a heart attack. In the United States, one person suffers a heart attack every 43 seconds, with one in five heart attacks initially remaining undetected.

## Liquid becomes solid

*If a blood vessel is injured, certain cells called blood platelets collect in the area of the wound and seal it preliminarily. At the same time, a chain reaction is launched which leads to blood coagulation. A delicate molecular web grows over the injured tissue in which blood platelets and other cells form a thrombus which closes the wound. In healthy individuals, a finely regulated balance between coagulation-promoting and coagulation-inhibiting factors ensures that blood clots do not occur at the wrong place – and that they dissolve again once the wound has been sealed. If this balance is impaired, thrombi can also grow in blood vessels and block them.*



Molecular art: when an injury occurs in the blood vessel of a healthy person, a fine, temporary net of blood cells, platelets and protein molecules forms to preliminarily seal off the wound.



Open up: life-threatening thrombi that occlude long sections of major blood vessels have to be surgically removed. Thrombectomy is a relatively conservative way of restoring the patency of blood vessels. Doctors use X-rays to visualize the blood vessels.

## “New therapeutic option”

research spoke to Dr. Andras Gruber, CEO of Aronora Inc., about the future of antithrombotic therapy. Aronora focuses on developing new antithrombotics and is collaborating with Bayer.



**Andras  
Gruber**



### Why is the thrombotic factor XI a promising target?

Targeting FXI could offer even more protection against unwanted bleeding than any of the antithrombotic drugs currently on the market.

### Why is that?

Inherited FXI deficiency, which is a prevalent condition in certain human populations, causes only a mild defect in bleeding control in a small percentage of these individuals. Most live without any known related disease condition or bleeding problem. Accordingly, it has been reasonable to argue that preventing or inhibiting FXI activity or activation might show beneficial effects for patients. Preclinical studies performed in laboratory animals do, in fact, provide strong support to this hypothesis.

### You also develop antibodies in collaboration with Bayer.

A longer-acting FXI inhibitory antibody would in my view be most likely to represent a new and extremely effective approach. Antibodies are usually selective for their target, but they can be very different from each other, as they target specific and different parts of a FXI molecule. The clinical safety profile of FXI inhibitory antibodies may therefore be different. So, antibodies could open new markets in the cardiovascular emergency arena: stroke, heart attack, and consumptive coagulopathy.

### What is your experience collaborating with Bayer?

Working for several years with the Bayer team in Wuppertal, San Francisco and Berkeley has been a very good personal and educational experience on the antibody development side. I also met many other excellent scientists and clinicians at Bayer and learned a lot about antithrombotic development.

at preventing the formation of FXI in the liver. The investigational agent is an antisense drug, which was discovered and developed by scientists at the U.S.-based partner company Isis Pharmaceuticals and is currently undergoing Phase II clinical testing in patients with end-stage renal disease on hemodialysis. Bayer and Isis have entered into an exclusive license agreement on its development and commercialization.

### Coagulation FXI inhibition: three therapeutic options being tested

The blueprint for FXI is contained in the genetic material of the cells and is transcribed as required. The antisense drug binds specifically to the RNA that will be translated into FXI protein. The binding of the antisense drug to the RNA signals a cellular process by which the RNA is degraded, thereby inhibiting FXI production. “Weekly doses of the antisense drug can sustain substantially lower concentrations

of FXI in the blood, providing the potential for long-term treatment,” explains Laux.

In the second approach to FXI inhibition Bayer scientists are working together with experts from the U.S. biotech company Aronora in Oregon, which is also a tenant in the Bayer CoLaborator in San Francisco. For example, they have developed a specific antibody that targets the activated form of FXI, so-called factor XIa or FXIa. The FXIa antibody showed very promising results in preclinical studies. “Even at very high doses of the antibody, we haven’t seen any bleeding so far,” sums up Laux. Based upon these encouraging findings, the antibody has recently been progressed into Phase I clinical testing.

In addition to the antisense drug and the FXI antibody, Bayer’s scientists are also working on the discovery of small chemical active substance molecules as a potential third therapeutic option to inhibit FXI. In contrast to the biological large molecules, which will have to be ad-

ministered via subcutaneous or intravenous injection, a small chemical molecule inhibitor would offer the chance of oral administration. After showing promising early results in preclinical studies a first small molecule drug candidate has recently been advanced into clinical Phase I development.

Genetic data analysis of patients with an inherited FXI defect formed the basis for Bayer researchers to investigate FXI as a new target point in the coagulation process. Three different therapeutic approaches of FXI inhibition are now in clinical development and will have to prove their worth in patients. As Leineweber summarizes, “Cardiogenomics is a promising new field of pharmaceutical research. We hope to discover even more therapeutic target options for cardiovascular diseases in the future.”



[www.research.bayer.com/thrombosis](http://www.research.bayer.com/thrombosis)  
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