And yet another biological from Biberach

Boehringer Ingelheim is an important contract manufacturer of biopharmaceuticals that also produces proprietary drugs. The company's last propriety biotech drug (tenecteplase) received marketing authorisation in 2001. The company has now placed another proprietary biopharmaceutical (idarucizumab) on the European and American markets and has a proprietary pipeline of monoclonal antibodies in late clinical development phases. We spoke with Dr. Joanne van Ryn, a Canadian pharmacologist who has been doing research at Boehringer Ingelheim's company site in Biberach for over 20 years. Her research focuses on thrombosis, haemostasis and coagulation. She is involved in the scientific monitoring of dabigatran (Pradaxa), an oral anticoagulant that, in 2008, was granted marketing authorisation for the prevention of venous thromboembolism following orthopaedic surgery. Van Ryn works in Boehringer's "Product and Pipeline Scientific Support" department.

Whose idea was it to develop a reversal agent for dabigatran?

The scientific monitoring of drugs that have been granted marketing authorisation means that I need to attend many scientific conferences to gain full understanding of an active ingredient. At a conference I attended in 2008, I came across a poster that focused on ways to specifically neutralise an anticoagulant.

Pradaxa was granted marketing authorisation in 2008, Praxbind was recently placed on the market. It appears that the antidote was not developed at the same time as the anticoagulant, but much later. Is this right?

Nobody really thought about an antidote for the new anticoagulants. Other anticoagulants have also received marketing authorisation without a reversal agent. Scientific studies have shown that dabigatran is more effective than warfarin, which is another anticoagulant. It also has a very positive safety profile. The data were so convincing that nobody considered the need to develop an antidote. This is a view still shared by the authorities.

Was there any medical necessity for developing an antidote and, if not, why did you decide to develop one?

There was no real need to develop an antidote. Clinical studies showed that the results obtained with Pradaxa were as good or even better than those obtained with warfarin. There will always be situations, for example a car accident, where there is an urgent medical need for an antidote. Such

Dr. Joanne van Ryn came up with the idea of developing an antidote.
© Boehringer Ingelheim

cases are very rare though. But when they happen, an antidote such as Praxbind completes the drug offer.

It is more a matter of perception than an actual need, and is more psychological than anything else. The FDA had a rather lively debate about the fact that doctors were reluctant to prescribe new anticoagulants although the data were better than those of the substance to which they were being compared. That said, one needs to keep in many that many people with atrial fibrillation are not protected against strokes because they are afraid of anticoagulants and do not want to take them.

How does Pradaxa work?

New anticoagulants such as Pradaxa have a much shorter half-life than warfarin, an anticoagulant which acts indirectly on coagulation factors. It may take up to four or five days for the body to produce normal levels of coagulation factors again. New coagulation inhibitors have a direct effect and have half-lives of eight to twelve hours, so that after just one day their effect is usually fairly limited.

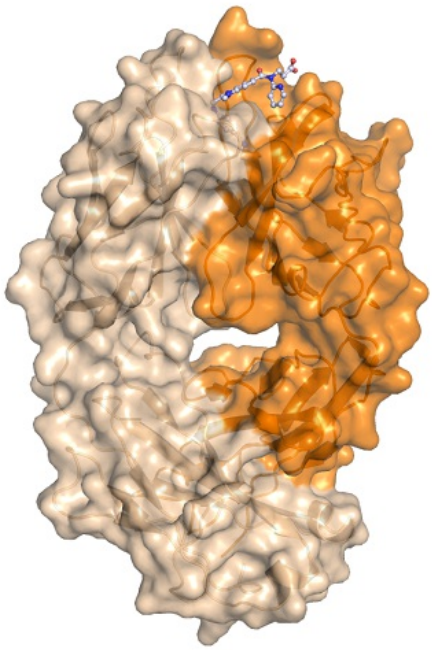
In principle, bleeding caused by new anticoagulants can be treated just like bleeding caused by warfarin. There are rare cases in which an antidote can be an additional useful treatment option.

The agent is a humanised antibody fragment. Does this smaller molecule have any advantages? Why don't you use whole antibodies? How does Praxbind work?

The advantage of an antibody fragment is that it has a much shorter half-life than a monoclonal antibody, which has a half-life of several days, sometimes even weeks. Once an antidote has been injected into the body, the initial half-life is about 45 minutes. After five hours, more than 95 percent of the antidote has as good as disappeared. It works very quickly and is ideal for emergencies. Immediately after injection, it unfolds its effect. It has a very high affinity for dabigatran, which it binds within minutes, almost simultaneously. The binding is almost irreversible. Once dabigatran is bound, it is excreted as complex, and is no longer present in the body after a few hours.

So the antidote doesn't interfere directly with the coagulation process, but only checkmates dabigatran. Have I understood this correctly?

Yes. It is an antibody that is directed against a tiny chemically synthesised molecule. The risk of off-target binding is relatively low as the antidote is highly specific. We have never observed anything but dabigatran binding.



The antidote, which is a hundred times larger than dabigatran, checkmates the latter as it binds highly specifically.

Let us go back to the conference in 2008. What happened afterwards?

If you are involved in research you need creativity and freedom, and that is what we have here. I knew the chemist who synthesised dabigatran and I spoke with our antibody experts about the poster that had attracted my attention. We brainstormed for a while and thought about an approach that could work. At the same time, we knew that we had to present our senior management with proof-of-concept. We produced antibody prototypes and, after six months or so, we were able to show that our approach worked. We presented this approach to senior management and were given full support.

Was it coincidence that Praxbind binds so fast or did you do anything to make this come about?

The answer to both questions is yes. We screened as many antibodies as we could until we found the candidates that bound effectively. These were murine antibody fragments. We handed these fragments over to our specialists in Ridgefield (ed. note: one of Boehringer Ingelheim's three R&D locations) to engineer and humanise them. The specialists tested the candidates and made sure that they retained their binding affinity despite humanisation. They also exchanged some amino acids in order to minimise the risk of immunogenicity. We were quite happy with the very first molecule we produced. This molecule bound with 40 picomolar affinity. When it came back from Ridgefield it bound with 2 picomolar affinity.

Would it have been possible to inhibit thrombin?

Yes, that was discussed at the outset as well: carefully modified thrombin that does not interfere with the coagulation cascade, which might cause thrombosis and also bind dabigatran. The problem is that thrombin binds to many sites in the body, not just to those that might cause a

thrombus. It would therefore have taken several years to find a modified neutral thrombin.

Boehringer Ingelheim will not have to sell so much Praxmind, right?

Yes and no. Every hospital should have Praxmind available. The infusion solution can be stored at four degrees Celsius for around two years or so. This is a relatively long time. We hope that it will stay in the refrigerator for many years and not have to be used.

This biological agent was basically developed in Biberach?

As far as the molecule is concerned, yes. Biopharmaceutical production also takes place in Biberach, as does the fill and finish process. Of course, we also have experts dealing with the valid regulations, and their offices are in Boehringer Ingelheim's headquarters. The principal trial investigator's office is in Ridgefield, but clinical pharmacology is located in Biberach. As you can see, the antidote was developed in cooperation with Boehringer R&D sites around the world, but the major tasks were carried out in Biberach.

Article

25-Jan-2016
wp
BioRegionUlm

Further information

- Boehringer Ingelheim

The article is part of the following dossiers

Biopharmaceuticals continue their triumphant success

pharma | antibody | blood | active pharmaceutical ingredient | drug application