 DOI: 10.1111/jth.13567

EDITORIAL

Out of the box

F. R. ROSENDAAL*† and P. H. REITSMA†‡
**Department of Clinical Epidemiology; †Einthoven Laboratory for Experimental Vascular Medicine; and ‡Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands*

To cite this article: Rosendaal FR, Reitsma PH. Out of the box. *J Thromb Haemost* 2016; **14**: 2323.

'The value of an idea lies in the using of it.'
(Thomas Edison, 1847–1931)

Treatment of severe hemophilia A requires several intravenous infusions of factor VIII concentrate per week, which has brought enormous health benefits, but is a particular burden for young children and their parents. A substantial proportion of patients develop inhibitory antibodies against infused coagulation factor VIII, which frustrates treatment. Therefore, there is a need for long-acting agents that can be administered less frequently by an alternative route, and for agents that can bypass or mimic coagulation factor VIIIa activity.

In this last editorial of the year, we would like to highlight a breakthrough in our field in 2016, published by Shima *et al*. (*New England Journal of Medicine*). Their article described the first clinical trial that evaluated a factor VIII mimetic that seems to have combined most wishes in a single package. The engineering of the mimetic was not so much based on a thorough understanding of coagulation factor VIII, but used an approach that built on the potential of so-called bispecific antibodies.

A bispecific antibody is an artificial protein created by bringing together fragments from two different monoclonal antibodies so that it can bind to two different antigens. The factor VIII mimetic used in the trial was engineered in such a way that it brings coagulation factor IXa and factor X into close proximity, thereby activating factor X to factor Xa, i.e. what normally happens when factor VIII is present.

The mimetic was created as follows. First, a set of monoclonal antibodies specific for factor IXa and factor X were generated in rodents. Next, cells were transfected with four plasmids encoding heavy and light chains of antibodies specific for factor IXa and factor X. The supernatants of these cultures were assayed for promotion of factor Xa generation. From approximately 40 000 combinations, a lead chimeric bispecific antibody was selected, which was further optimized by using one light chain for both arms, and 'humanized'. Transfections of cells with plasmids encoding the common light chain and the two heavy chains generated the final agent, called hBS23 at that time, and now called ACE910.

The developers checked whether hBS23 was capable of normalizing clot formation in factor VIII-deficient plasma. Indeed, the activated partial thromboplastin time was normalized after the addition of hBS23, in both the absence and presence of factor VIII inhibitors. Similar results were obtained with assays based on measuring the endogenous thrombin potential. When taken together, the results suggested that hBS23 has enough factor VIII-like activity for use in patients with hemophilia A. Importantly, antibodies against factor VIII would not affect the working of the antibody; that is, the drug would also work in patients with inhibitors.

Pharmacokinetics in the monkeys showed that intravenously injected hBS23 was cleared in a biphasic manner with a long half-life of approximately 14 days, which is typical for injected immunoglobulins, giving a bioavailability of subcutaneously administered hBS23 of 84%. A simulation indicated that that once-weekly subcutaneous injections of hBS23 would suffice for adequate prophylaxis.

The highly promising preclinical work prompted the first clinical trial, the results of which were heralded as a major breakthrough. This was illustrated by the Food and Drug Administration granting the drug a 'breakthrough designation' in September. However, there are no drugs without side-effects. On 2 November, information from Reuters indicated that, in the phase 3 trial with ACE910, serious complications occurred in four patients, consisting of venous thrombosis and microangiopathy. It is currently unknown what this means for the prospects of the drug, and it should be remembered that gene therapy trials were temporarily suspended because of liver toxicity in some patients, which was subsequently overcome. Hence, it is not possible to predict whether, eventually, the technological breakthrough of the bispecific antibody will offer the much needed major improvement in the treatment of hemophilia that it seemed to promise, or will it find itself as yet another addition to the boulevard of broken dreams.