

## Theme Issue Editorial

# Current use of biologicals in thrombosis and haemostasis

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Biological medicines have been used to treat or prevent disease for over a hundred years beginning with the development of effective vaccines, followed over time by the isolation of bovine and porcine insulins (1), porcine and bovine heparins (2), large scale production of fractionated plasma products (3), to the era of the manufacture of recombinant human proteins (4). Randomized control trials demonstrating the effectiveness of heparin and low-molecular-weight heparins for preventing post-operative deep vein thrombosis, initiating the treatment of venous thrombosis, preventing or treating arterial thrombosis had become widespread by the late 1970s and 1980s (5–8). The 1970s and later periods also ushered in the prophylactic and therapeutic uses of manufactured plasma fractionation products approved for the effective management of haemophilia A (plasma-derived factor VIII concentrates of increasing purity) (9) and haemophilia B (prothrombin complex concentrates leading to the isolation of factor IX free of prothrombin, factor VII, or factor X) (10), and a variety of topical haemostatic agents containing human or bovine thrombin for accelerating haemostasis after some surgeries (11).

Although the wide availability and clinical use of biological medicines have brought enormous benefits, severe adverse events can occur, as with any medicine. The most serious of these include bleeding and thrombocytopenia (heparin), development of product neutralizing antibodies (plasma-derived and recombinant human factor VIII, factor IX, factor XI and other recombinant therapeutic proteins) that can render the products therapeutically ineffective (12–14), and the potential, however low, for pathogen transmission (by plasma products) (15, 16). A potentially deadly and unanticipated consequence of the widespread use of human plasma-derived clotting factor concentrates was their ability to infect patients with previously unknown human viruses, specifically human immunodeficiency virus (HIV) and hepatitis C in the early 1980s (15). The successful application of recombinant DNA technology to manufacture insu-

lin (1) and human growth hormone (17) that had been approved for clinical use by the 1980s no doubt provided a strong stimulus for the successful development of recombinant human factor IX and factor VIII for clinical use (18). Around the same time more rigorous testing methods for plasmas destined for fractionation and new methods for pathogen reduction were implemented to reduce risk of virus transmission by plasma products (15, 16). Even more sensitive methods for detecting extremely low numbers of infectious agents in plasmas that are based on detecting DNA or RNA of infectious viruses of concern have since been introduced, and both plasma-derived and recombinant clotting factors and haemostatic agents are now subjected to additional pathogen reduction steps prior to their release for clinical use (15, 16). The success of these pathogen reduction strategies is evident from the observation that no pathogen transmission by a manufactured plasma-derived or recombinant therapeutic protein has been observed in North America since 1995 (15).

The Theme Issue in this edition of *Thrombosis and Haemostasis* brings together investigators who are well versed in several aspects of the manufacture, characterization, standardization and specific clinical use of biological medicines to prevent or treat inherited or acquired disorders of haemostasis. As well as chapters on heparin (19), hirudin and its derivative bivalirudin (20, 21), plasma products (22), and recombinant clotting factors (23), we have included a chapter on recombinant haematopoietic growth factors. Although the latter are not usually considered as primary medicines for disorders of haemostasis, the salutary experiences with thrombopoietin illustrate some of the problems that can occur with this type of biological medicine, and we thought a general review might be of interest. The final chapter deals with a relatively common and occasionally serious side-effect of all therapeutic proteins (24), whether plasma-derived or recombinant, namely the induction of specific anti-therapeutic protein antibodies that may inactivate the therapeutic proteins.

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The information provided in the seven articles in this Theme Issue demonstrates biological medicines to be highly beneficial in treating many types of patients with congenital or acquired haemostatic abnormalities. One of the significant drawbacks associated with their use is the development of product neutralizing antibodies in a number of patients, depending on the product, and as noted previously. Nonetheless the benefits associated

with clinical uses of these biological medicines far outweigh the risks of adverse events attributable to their use. Given the proven efficacy and safety profiles of these drugs, their availability and current cost considerations, biological medicines isolated from animal tissues, human plasma or made by recombinant DNA technology will be required for some time to come.

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