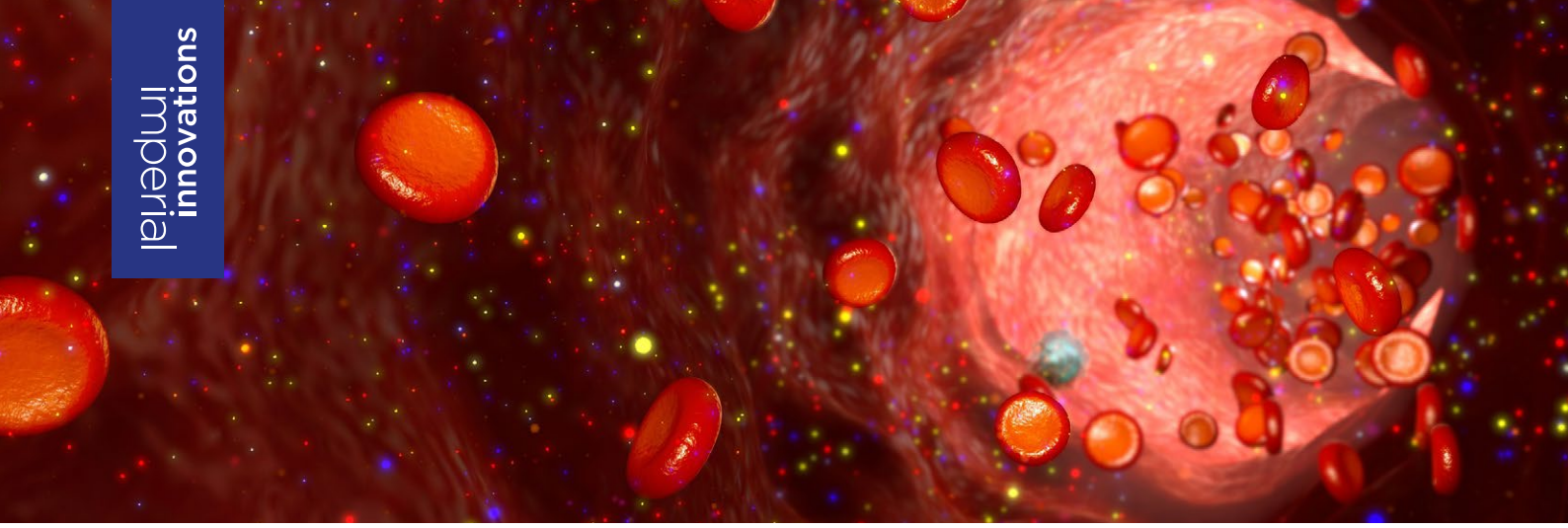

Novel protein fragment of von Willebrand's factor for treating VWD and haemophilia A

Summary

The present invention relates to novel truncated fragments of von Willebrand factor (VWF) engineered by a team at Imperial College London. The use of such fragments and nucleic acids encoding such fragments can be used in the treatment of von Willebrand disease (VWD) and haemophilia.

Background

Von Willebrand Factor (VWF) is a large multimeric plasma glycoprotein that performs two essential roles in haemostasis. Firstly, VWF mediates platelet adhesion to sites of vessel injury under high shear stress and secondly, VWF is the carrier molecule of coagulation factor VIII (FVIII), prolonging its otherwise short half-life.

Deficiency of VWF results in the bleeding disorder von Willebrand disease (VWD), which is the most common inherited bleeding disorder, affecting ~3-4 individuals in every 100,000 representing 1.3% of the population. Treatment of VWD is usually performed with either desmopressin to promote release of VWF or with replacement therapy involving the administration of VWF concentrates, at a cost to the NHS of approximately £10 million per year in drug alone.

Haemophilia is a mostly inherited bleeding disorder, which affects a patient's ability to form blood clots. Haemophilia A is caused by a lack of factor VIII. The use of recombinant factor VIII for the treatment of Haemophilia A has previously required the co-delivery of full length VWF in order to stabilise the delivered FVIII. However, the short half-life of FVIII is an issue impacting frequency of injection, dose trough levels, continuous protection from bleeding, convenience and cost. There is also a risk of complications including excessive clotting.

Several recent attempts to circumvent the use of co-delivery of VWF using modified FVIII molecules have been reported recently but the results are universally disappointing. This is in stark contrast to similar modification of the FIX molecule which produced dramatic prolongation and look set to revolutionise treatment of haemophilia B.

Quick Info

Benefits

- Shorter polypeptide fragment for use in treating VWD and haemophilia A
- Treatment may take form of recombinant protein therapy or gene therapy
- Reduced risk of complications compared to existing treatments
- Potential for reduced cost and increased consistency in protection over existing treatments
- Complementary to existing efforts in Factor VIII gene therapy

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Technology

The present invention provides a gene therapy or recombinant protein approach for the treatment of VWD or haemophilia. A team at Imperial College London have produced a novel truncated VWF variant in which several domains are deleted, yet sharing the function of the full-length protein. In particular it demonstrates normal multimer formation, is able to interact with collagen under static conditions and the ability of the variant to capture platelets under shear stress is not altered. The variant can therefore be used in place of the full-length protein in the treatment of VWD or haemophilia.

The removal of this region, which comprises 845 amino acids, reduces the size of VWF to 1968 amino acids. It has been determined that this is the minimal VWF molecule possible without reducing functionality. The inventors have also determined the nucleotide sequence encoding the above polypeptide. A nucleic acid construct may therefore conceivably be inserted into a vector, such as a virus, for use in gene therapy of VWD or haemophilia A.

There is scope to modify FVIII or indeed the VWF fragment using PEG, FC or albumin fusion to achieve improved FVIII half-life and effect.

Applications

The present invention finds use in the treatment of any one or more of the various subtypes of VWD (Type 1, Type 2A, Type 2B, Type 2M, Type 2N, VWD Vicenza and Type 3) in restoring VWF plasma levels. This may be achieved through a gene therapy or recombinant protein treatment approach.

Since VWD is the carrier for factor VIII and prolongs its half-life, the present invention therefore also finds use in the treatment of haemophilia A. The removal of the C-terminal domain in the present invention avoids the risk of excessive clotting and therefore provides an improved treatment for haemophilia, particularly haemophilia A.

A great deal of preclinical and early phase trials are underway to investigate the effect of gene therapy for FVIII, therefore development of a complementary gene therapy expression system for VWF would support these attempts.

Value proposition

The global bleeding disorders treatment market was valued at USD 10.33 Billion in 2016 and expected to grow at a CAGR of 7.9% to 2021, to reach an estimated value of USD 15.09 Billion by 2021 (Markets & Markets).

Team

Dr Tom McKinnon is a British Heart Foundation Intermediate research fellow in the Thrombosis and Haemostasis research group in the Centre for Haematology of the Imperial College Department of Medicine.

Intellectual Property

This technology is subject of a patent application (GB1707139.0).

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