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Platelets are a safe way to deliver factor VIII. After 13 years of preclinical research it is now time for a clinical trial.

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The declarative title is a fair summary of research described in this paper (*Targeting Factor VIII expression to platelets for hemophilia A gene therapy does not induce an apparent thrombotic risk in mice*)¹⁰, is a fair summary of research described in this paper, which is itself the 14th in a series from the group of researchers led by Montgomery who, since 2003 have progressively advanced the idea of storing factor VIII in platelets to treat hemophilia A. Why, one might ask, would one do such a thing when evolution has selected endothelial cells as both the site for synthesis and release of factor VIII complexed with Von Willebrand factor to provide the cofactor when and where needed?^{1,2} The answer lies in the unfortunate fact that a high proportion of patients with hemophilia develop resistance to factor VIII due to alloimmunity to the protein, which is foreign to their immune system, leading to production of inhibitory antibodies to the cofactor. But Factor VIII released from platelets seems to evade such antibodies³.

Many and diverse are the attempts that have been made to treat the dire consequences of inhibitory antibodies to factor VIII which so often complicate standard replacement therapy. The best of these treatments are only partly effective. Literally thousands of clinical and basic research publications have addressed this topic over the past 60 years (3387 since 1955 – PubMed search terms Factor VIII AND inhibitor) and there is no sign of the flow abating - in fact the past 10 years have seen an upsurge of research on novel treatments for antibodies to factor VIII, including an antibody that itself mimics the action of factor VIII (ACE9/10)⁴, inhibitory mRNA to reduce anti-thrombin levels⁵ and a modified factor Xa that is zymogen like⁶. The first two of these treatments already show promise in the clinic. So one may ask 'has the technically demanding approach of genetic modification to express factor VIII in platelets pursued by Montgomery (and also in parallel by others) been rendered redundant even before clinical trials begin'?

There are several reasons why I believe this approach should be tried in the clinic. Firstly it is clearly highly effective in a relevant mouse model of hemophilia A using genetically manipulated human cord blood cells⁷. Secondly it seems to completely normalize haemostasis, unlike other methods of bypassing inhibitory antibodies. Thirdly it is long lasting with no requirement to continue topping up the treatment. Fourthly it may also induce tolerance in already immunized subjects⁸. And fifthly this paper shows that it has now passed an important theoretical safety risk with no evidence of thrombotic tendency even when over expressed in a thrombosis prone mouse model.

It must now be time after 13 years of exhaustive preparation in preclinical studies of platelets containing factor VIII to initiate a clinical trial in Hemophilia A patients with inhibitors. The protocol would require hemopoetic stem cells to be collected from peripheral blood, then

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modified by lentivirus mediated transfer of a modified factor VIII gene under control of the alpha IIB promoter and reinfused with suitable conditioning to allow partial engraftment of clones producing platelets containing factor VIII. The risks of such a trial are chiefly the possibility of insertional mutagenesis causing clonal expansion and leukemia. This has only previously been seen in comparable treatment for severe combined immune deficiency where unique features of the transgene confer a replication advantage on cells with a rare insertion leading to a type of T cell leukemia⁹. This would not be the case for the factor VIII transgene under control of alpha IIB promoter. Another risk would be that of conditioning causing temporary immune suppression, neutropenia and thrombocytopenia. As the conditioning need only be mild these risks are tolerable. Should there be success in patients with inhibitors then other patient groups and conditions could be suitable for such treatment. Amongst these would be hemophilia A without inhibitor and severe Von Willebrand Disease. Using other transgenes, the major platelet receptor disorders would also become accessible to such treatment.

Now that we are clearly entering an era of wider trial of gene transfer in many disorders, both inherited and acquired the time is ripe for a clinical trial of factor VIII ectopically expressed in autologous platelets of patients with hemophilia A complicated by inhibitory antibody.

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