Gene Therapy in Haemophilia B: Efficacy and Optimization

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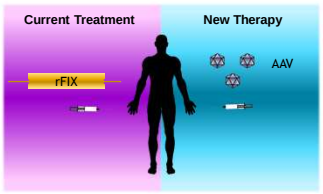
Introduction

Haemophilia B is a monogenic hereditary X-linked bleeding disorder that results from a defect in the gene encoding coagulation factor IX which frequency in males of 1/25,000. People with severe haemophilia have <1% of the normal clotting factor in their blood and levels considered therapeutic are slightly above the 1% threshold and can convert severe haemophilia into a moderate form.

Current treatment involves frequent intravenous injection of clotting factor concentrates two or three times a week. This treatment is prophylactic rather than curative, moreover, in some cases there is a complication with the formation of antibodies 'inhibitors' which block the recombinant protein.

Gene therapy would be a very attractive treatment to cure the disease allowing endogenous production of FIX. For these reasons, researchers are developing new and improved cassettes and vectors designs, doses optimization and they are finding new alternatives with non-viral vectors.

The **objective** of this study is to investigate the approaches which allow more efficient vector design and cassettes to optimize haemophilia gene therapy.



Approaches

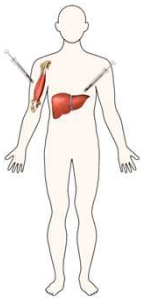
Alternatives Strategies

Tranposon-transposase System: it allows the transgene *FIX* insertion in the murine genome with a liver-specific promoter and results in a stable and long-term expression

Zinc Finger Nucleases: it induces double-strand breaks to insert the cassette in the murine genome and results in a long-term expression

Alternative Serotypes

The safest and most efficient serotypes are AAV2/7, AAV2/8 and AAV2/9 because of they do not develop inhibitors and it maintain transgene expression



Cassette Design

The aim to improve the cassette design is to achieve a long-term expression and decrease the immune response. It could be achieved by specific-promoter, hyperfunctional mutation, codon usage optimization, silent sequences among others

Tolerance Induction

The patients could develop capsid-specific T-cell response and/or inhibitors antibodies against the transgene. In order to avoid these, it can immunosuppress the patients and/or introduce tregitopes in the cassette.

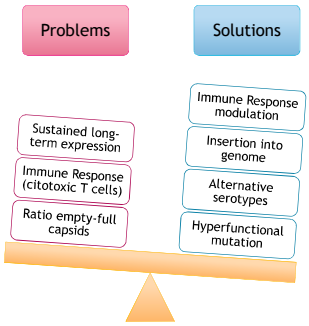
Target tissues

Liver	Muscle
Non-invasive administration	Non-invasive administration
Normally produces and secretes FIX into the blood system	Capacity of produce FIX and secretes it into the bloodstream
Long-term and therapeutic level expression of the transgene	Alternative target in cases of liver disease
Immune Tolerance can be induced to the transgene	
T-cell cytotoxic response	Inhibitor antibodies
Liver diseases	Long-term expression but in sub-therapeutic levels

If it is possible, it will be used liver as a target tissue

Future Directions

A clinical trial has been reported which achieves the cure of haemophilia B , but in some restricted patients.



Gene therapy will become the definitive treatment to cure haemophilia B

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