GENE THERAPY APPROACHES FOR HEMOPHILIA

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1- INTRODUCTION

Hemophilia is a hereditary coagulation disorder caused by **lack of a coagulation factor**. Patients have frequent bleeding that sometimes can cause death. The main forms of this disease are **hemophilia A** (deficiency of FVIII factor) and **hemophilia B** (deficiency of FIX factor). Both of them have an **X-linked inheritance**.

The current treatment involves frequent intravenous injections of the clotting factor. But this approach has limitations (price, accessibility and development of inhibitors), so it's important to develop a new treatment. This work presents **gene therapy** as an option to treat hemophilia.

2- OBJECTIVES

- To understand the clinical and genetic characteristics of hemophilia as a disease, as well as current treatments available.
- To consolidate the concept of gene therapy and its technical characteristics.
- To determine the evolution of the field of gene therapy for hemophilia in the last years: from the early clinical trials to the present.
- To establish whether gene therapy is an appropriate and beneficial treatment for hemophilia: determine the clinical hardships of the gene therapy.

3- METHODOLOGY

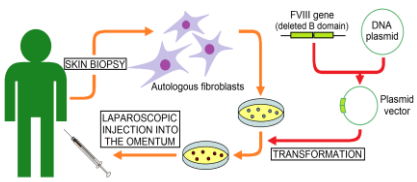
As a basis for the development of this work, **many information sources** such as reviews, scientific papers, theses, books and official websites were consulted. All the information was verified and filtered to obtain a well structured study. Only those topics of greatest interest were selected. With all the gathered information, a written report and a poster were made.

4- CHARACTARISTICS OF THE VECTORS

	DNA plasmid	Retroviral	Lentiviral	Adenoviral	AAV
Maximum size of the insert (kb)	Unlimited	7	7	36	4,5
Chromosome integration	No	Yes	Yes	No	No
Quiescent cells transduction	Yes	No	Yes	Yes	Yes
Immunogenicity	None	Unlikely	Unlikely	Possible	Possible
Safety concerns	None	Possibility of insertional mutagenesis	Possibility of insertional mutagenesis	Toxicity	Toxicity

5- GENE THERAPY: CLINICAL AND PRECLINICAL TRIALS

Ex vivo approach: transduction of fibroblasts with plasmid vectors (2001)



Phase I Clinical trial
Hemophilia A

Results:

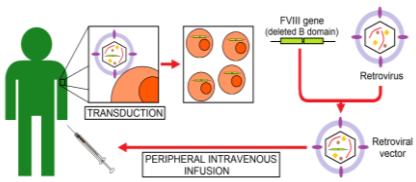
-Safe and well tolerated.
-Modest expression.
-Transient effect.

In vivo approach: cell transduction with γ-retroviral vectors (2003)

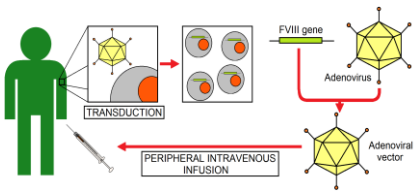
Phase I Clinical trial
Hemophilia A

Results:

-Safe and well tolerated.
-Low expression.
-Transient effect.
-Higher doses are needed.



In vivo approach: cell transduction with HD-adenoviral vectors (2005)



Phase I Clinical trial
Hemophilia A

Results:

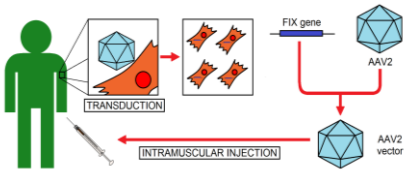
-Severe hepatotoxicity.
-Discontinued.

In vivo approach: transduction of the skeletal muscle with AAV2 (2003)

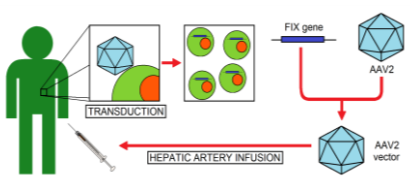
Phase I/II Clinical trial
Hemophilia B

Results:

-Safe and well tolerated.
-Modest expression.
-Long term local effect.
-Multiple injections.



In vivo approach: transduction of the liver with AAV2 (2006)



Phase I/II Clinical trial
Hemophilia B

Results:

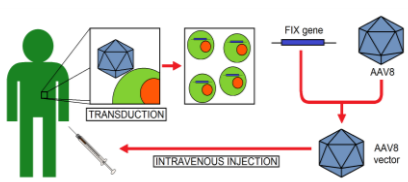
-Transient hepatotoxicity.
-Modest expression.
-Transient effect.
-Immune destruction of transduced hepatocytes.

In vivo approach: transduction of the liver AAV8 (2011)

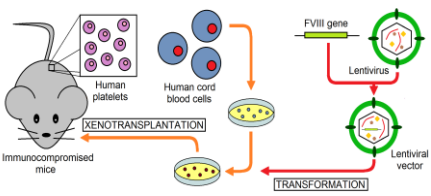
Phase I/II Clinical trial
Hemophilia B

Results:

-Hepatotoxicity: resolved with corticosteroids.
-Modest expression.
-Long term effect.



Ex vivo approach: transduction of HSCs with lentiviral vectors (2014)



Preclinical trial
Hemophilia A

Results:

-Phenotype correction.
-Modest expression.
-Promising approach.

6- RELEVANT FACTS

✓ Currently the most promising approaches are the **lentiviral** and **AAV vectors**, based on the level of expression and immunogenicity. From now on the aim is to improve these vectors to obtain greater expression using lower doses to **reduce the immune response**.

✓ The **liver** is a promising target tissue due to its ability to induce immune tolerance, its high secretory capacity and its aptitude to create the endogenous post-translational modifications.

✓ One of the bottlenecks of gene therapy is the **vector production**.

✓ Gene therapy is a relatively new field so we have yet to see the **long term effects**.

7- DISCUSSION AND CONCLUSIONS

-The work presented in this poster is a general view about the **evolution of gene therapy strategies to treat hemophilia**. There exist multiple preclinical and clinical trials for this disease, but this work is centered in the most relevant ones.

-In conclusion, in this work **all the objectives were met**. A general knowledge about clinical and genetic characteristics, and treatments of hemophilia was reached. With the information sources consulted it was possible to determine the evolution of the trials used since the beginning to the present, and the feasibility and appropriateness of gene therapy as a treatment for hemophilia.

8- REFERENCES

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