Introduction

- Leukocyte Adhesion Deficiency Type I (LAD-I) is a primary immunodeficiency caused by mutations in the ITGB2 gene, encoding the CD18 subunit of β2 integrins. The defective expression of β2 on the leukocytes’ surface limits their adhesion to the endothelium and their extravasation to infection sites.
- A lentiviral vector was designed to enable expression of CD18 in mature granulocytes. In this construct, the gene ITGB2 was driven by a chimeric promoter consisting of the fusion of the 5'-flanking regions of the FES and CTSG genes (Chim.hCD18 LV); these genes encode for proteins predominantly expressed in mature myeloid lineages.

Objective

Complete the pre-clinical evaluation of the Chim.hCD18 LV and define the transduction conditions for a gene therapy clinical trial of LAD-I patients

Results

Bio distribution studies with Chim.hCD18 LV

Bio distribution studies were carried out in lethally irradiated B6D2F1 male and female mice. Bone marrow Lin- cells were transduced for 24h with the Chim.hCD18 LV at an MOI of 100 TU/cell. In all cases 3.3 x 10^5 transduced cells were transplanted. At one month post transplantation animals were sacrificed and different organs were obtained for analysis.

Optimization of the transduction protocol of CD34+ cells with the Chim.hCD18 LV

Transduction conditions were optimized in HD CD34+ cells. To increase the transduction efficiency transduction enhancers (TEs) were tested.

In vivo analyses of CD34+ cells transduced with Chim.hCD18 LV and TEs

All pre-clinical evaluations have confirmed the safety and efficacy of the Chim.hCD18 LV gene therapy approach. Transduction Enhancers improved transduction of CFUs and also NSG mice long term repopulating cells. Future studies will consist on the validation of the proposed transduction protocol and the initiation of a clinical trial in LAD-I patients.

Conclusions