Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2017-2018

Project Nº 9

Title: Potential of in vivo gene editing by CRISPR/Cas for the treatment and modelling of rare diseases.

Department/ Laboratory:
Laboratory of stem cells and reprogramming, Lab 1.01, Cell Therapy Program, , Center for Applied Medical Research (CIMA).

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Summary:

Primary hyperoxaluria type I (PH1) is a rare metabolic disorder of the glyoxylate metabolism, caused by mutations in the hepatic enzyme AGT that results in excessive oxalate synthesis. The general purpose of this project is to evaluate the potential of CRISPR/Cas mediated gene editing technologies for the development of **innovative therapeutic strategies** to treat PH1, and the generation of **relevant cellular models** to cover the deficiencies observed in current models. The specific objectives are: **1) To generate in vitro PH1 models by gene editing.** We propose to use quasi-primary liver cells (upcyte® hepatocytes) to introduce representative mutations of the different phenotypes observed in PH1 by CRISPR/Cas mediated gene editing. These cells could represent a useful tool to evaluate small molecules as new therapeutics against PH1. **2) To demonstrate the efficacy of the in vivo gene editing as PH1 treatment in an animal model.** We propose two different approaches: The first, based on the inhibition by CRISPR/Cas of the principal sources of glyoxylate to reduce oxalate production (substrate reduction). The second, based on the recovery of the AGT enzymatic activity by in vivo gene editing (enzyme replacement). **3) To evaluate the efficacy of the transplantation of edited upcyte® hepatocyte in a PH1 animal model.** We propose the generation of a PH1 model in an immuno-deficient background by in vivo gene editing to evaluate the efficacy of cell therapy strategies using edited human cells. This project could represent an improvement in the treatment of this disease, where current treatments are limited.

The candidate will be directly involved in the generation and characterization of hiPSCs as well as in the development of AAV vectors for in vivo gene editing. Thus, she/he will gain knowledge and expertise in cellular and molecular biology, stem cell culture and CRISPR/Cas gene editing technologies.

References:

1. Zapata-Linares, N. et al. Generation and characterization of human iPSC lines derived from a Primary Hyperoxaluria Type I patient with p.I244T mutation. Stem Cell Research 16, 116–119 (2016).

2. Hsu, P. D., Lander, E. S. & Zhang, F. Development and applications of CRISPR-Cas9 for genome engineering. Cell 157, 1262–1278 (2014).