

Research Project Proposal
Academic year 2016-2017

Project Nº 6
Title: Innovative therapeutic approaches for rare diseases by in vivo CRISPR/Cas gene editing.
Department/ Laboratory Laboratory of stem cells and reprogramming, Cell Therapy Program, Center for Applied Medical Research (CIMA)
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<p>Summary</p> <p>Primary hyperoxaluria type 1 (PH1) is a rare, autosomal recessive metabolic disorder caused by mutations in the hepatic alanine-glyoxylate aminotransferase (AGT). Defective AGT results in excessive oxalate synthesis that induces urolithiasis, nephrocalcinosis, chronic renal failure, and ultimately to end-stage renal disease and multisystemic deposition of oxalate salts. Combined liver-kidney transplantation is the only curative treatment approach, but associated with significant morbidity and mortality, as well as medical standards, which are simply not available to most patients suffering from PH1 worldwide. Thus, there is an urgent need for new therapies besides transplantation. Our general aim is to transform the critical mass of molecular knowledge into the generation of disease models for PH1 by cell reprogramming that allow the development of (synergistic) novel therapeutic approaches. For this research project proposal, we specifically aim to develop in vitro PH1 disease models by the generation of human induced pluripotent stem cells (hiPSCs) from PH1 patients as well as liver-specific AAV vectors for in vivo CRISPR/Cas gene editing strategies to treat PH1.</p> <p>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.</p> <p>References</p> <ol style="list-style-type: none"> 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. <i>Stem Cell Research</i> 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).

POSSIBILITY OF PhD YES*

* (PhD grant required)