Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 20
Title: Development of a gene therapy treatment for Gene Therapy for a rare disease Progressive familial intrahepatic cholestasis (PFIC)
Department/ Laboratory Laboratory of gene therapy for rare diseases. Gene Therapy and Regulation of gene expression. CIMA
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Summary Progressive familial intrahepatic cholestasis (PFICs) refers to a heterogeneous group of rare autosomal-recessive diseases of childhood that is caused by a defect in bile acid transport because of genetic mutation. In this group of pathologies, cholestasis of hepatocellular origin often presents in the neonatal period of first year of life and leads to death from liver failure at ages usually ranging from infancy to adolescence. The exact prevalence remains unknown, but the estimated incidence varies between 1/50,000 and 1/100,000 births. PFIC2 progressive familial intrahepatic cholestasis type 2 results from mutations affecting the gene ABCB11 encoding the bile salt export pump (BSEP) It is estimated that PFIC represenst 10-15% of causes of cholestasis and 10-15% of liver transplantation indications in children;2 among the three types of PFICs, PFIC2 is the most frequent representing half of the PFIC cases, these data clearly indicate that PFIC2 could be an important disease-target of new therapy approaches. As above mentioned, defects in the Bile Salt Export Pump (BSEP) also known as the sister of P-glycoprotein (Spgp) are correlated with PFIC2 pathology. BSEP is a member of the ATP-binding cassette (ABC) family of proteins, is localized exclusively in the hepatocyte canalicular membrane and is critical to the formation of bile salt dependent bile flow and the normal enterohepatic circulation of bile salts from the distal intestine back to the liver. most patients with progressive cholestasis eventually need invasive surgical intervention such as partial biliary diversion (in which bile is diverted from the gallbladder through a loop of jejunum connecting the dome of the gallbladder to the abdominal skin, interrupting the enterohepatic circulation of bile salts), ileal bypass (ileum is bypassed through an ileocolonic anastomatosis) or finally liver transplantation.

Considering that the only functional treatments are represented by invasive chirurgical techniques, in this project we want to propose a non-invasive procedure able to deliver normal BSEP gene in liver hepatocytes though a gene therapy approach.

1. Jacquemin E. Progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2012;36 Suppl 1:S26-35.

2. Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis. 2009;4:1-1172-4-1.

3. Wang R, Salem M, Yousef IM, et al. Targeted inactivation of sister of P-glycoprotein gene (spgp) in mice results in nonprogressive but persistent intrahepatic cholestasis. Proc Natl Acad Sci U S A. 2001;98(4):2011-2016.

POSSIBILITY OF PhD

YES*

* (PhD grant required)