Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 11 ASIGNADO

Title: Development of new therapeutic strategies for inherited liver metabolic disorders. Gene therapy and genetic corrections

Department/ Laboratory. Laboratory 4.05, Gene Therapy and regulation of Gene expression program, FIMA. Center for Applied Medical Research (CIMA)

Director: Dra. Gloria González Aseguinolaza

Contact: ggasegui@unav.es

Summary

One of the main objectives of our laboratory is the development of gene therapy strategies for inherited liver metabolic disorders. Most of them are rare diseases that have not cure except for liver transplantation. We are currently working of three different diseases. The gene therapy vector we are using is based on the AdenoAssociated virus, which has an extraordinary safety profile and after injection in adult animals expresses the therapeutic gene for a long time.

A number of these diseases affect new-born, these diseases can be lethal or associated with the development of severe pathologies, like the urea cycle disorders.
The liver of new-borns is still an immature and growing organ, for this reason when the AAV vector is injected transgene expression disappear with time. The goal of this project will be the development of new AAV based vectors containing sequences that allows transferring the AAV genome from mother cells to daughter cells and in this way the expression is maintained. Those vectors will be tested in cell culture and animal models using reporter genes. Those that showed a better capacity to transduce the liver will be tested in a Wilson disease animal model
References References could be added (no more than three)

1: Kok CY, Cunningham SC, Carpenter KH, Dane AP, Siew SM, Logan GJ, Kuchel PW, Alexander IE. Adeno-associated virus-mediated rescue of neonatal lethality in argininosuccinate synthetase-deficient mice. Mol Ther. 2013 Oct;21(10):1823-31.

2: Wang L, Wang H, Bell P, McMenamin D, Wilson JM. Hepatic gene transfer in neonatal mice by adeno-associated virus serotype 8 vector. Hum Gene Ther. 2012 May;23(5):533-9.

3: Bortolussi G, Zentilin L, Baj G, Giraudi P, Bellarosa C, Giacca M, Tiribelli C, Muro AF. Rescue of bilirubin-induced neonatal lethality in a mouse model of Crigler-Najjar

syndrome type I by AAV9-mediated gene transfer. FASEB J. 2012 Mar;26(3):1052-63.

4: Chandler RJ, Chandrasekaran S, Carrillo-Carrasco N, Senac JS, Hofherr SE,Barry MA, Venditti CP. Adeno-associated virus serotype 8 gene transfer rescues a neonatal lethal murine model of propionic acidemia. Hum Gene Ther. 2011 Apr;22(4):477-81.

5: Flageul M, Aubert D, Pichard V, Nguyen TH, Nowrouzi A, Schmidt M, Ferry N. Transient expression of genes delivered to newborn rat liver using recombinant adeno-associated virus 2/8 vectors. J Gene Med. 2009 Aug;11(8):689-96.

POSSIBILITY OF PhD

YES*

* (PhD grant required)