Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
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Project Nº 3 ASIGNADO

Title: Improvement of gene therapy vectors for neonatal treatment of metabolic rare diseases

Department/ Laboratory Lab 4.04. Gene Therapy and Regulation of Gene Expression. Center for Applied Medical Research (CIMA)

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Summary

Most metabolic rare diseases manifest in young children and in many cases the first symptoms and consequences are observed in neonates. These diseases are characterized by an accumulation of toxic metabolic intermediate products that interfere with normal development, especially neurological development and function. In addition it is very difficult to restore normal neurological function once these defects have been established. Therefore the best intervention time point is as soon as possible, including neonatal treatment. Unfortunately most of these diseases present no cure and developed treatments just slow disease progression.

Several clinical and preclinical studies have shown gene therapy based on the AAV viral vector is a real treatment option for liver monogenic metabolic diseases. However there is a limitation for an effective neonatal treatment: when gene therapy vectors transduce immature livers there is a progressive elimination of the vector molecules limiting treatment efficacy. Vector are eliminated as they are diluted when the liver grows and by other active mechanisms.

We want to improve gene therapy vector stability when it is inoculated in neonatal liver modifying AAV viral genome with DNA sequences that will provide replication potential when cellular DNA is replicated, including maintenance in daughter cells. S/MARs are DNA sequences that provide replication and segregation potential to the DNA molecules where they are integrated. However this is not very efficient. We are going to evaluate them in the context of the AAV genome when it is inoculated in neonatal mice livers. We will compare long term expression and stability of AAV vector with and without S/MAR sequences when they are inoculated intravenously to neonate mice.