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Gene therapy for liver inherited diseases

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Host. Niels Reichardt

Wednesday, 29th May
12.00 p.m.

CIC biomaGUNE - Seminar Room

In vertebrates, the liver is the central metabolic organ of the body, which carries out an estimated 500 functions that range from general detoxification to protein synthesis, bile production, metabolism of fats, carbohydrates, proteins, bilirubin, vitamin and mineral storage and it even has an immune function. Hepatocytes are considered the professional liver cells, which carry out all these functions. With such a variety of tasks to perform, it is not surprising that more than 400 rare monogenic disorders of hepatic origin have been described. For many of these, liver transplantation remains the only curative strategy, however, this is limited by organ availability and requires lifelong immune suppression. The fact that liver transplantation is curative led to the assumption that the restoration of the expression of the defective gene would result in the resolution of the disease. Thus, liver-directed gene therapy and gene editing strategies have emerged as promising alternatives to transplantation in inherited monogenic liver disorders. To date, the most efficient vectors for delivering genetic material to the nucleus of liver cells and leading to long term expression of the therapeutic transgene are based on adeno-associated viral vectors (AAVs).
Herein, we will present our more recent progresses on the development of AAV-mediated gene addition and AAV-CRISPR-Cas9 gene editing approaches for the treatment of Wilson's disease and Primary hyperoxaluria type I, respectively.

- *Murillo O, et al. Long-term metabolic correction of Wilson's disease in a murine model by gene therapy. J Hepatol. 2016 Feb;64(2):419-426.*
- *Uerlings R, et al. Brain copper storage after genetic long-term correction in a mouse model of Wilson disease. Neurol Genet. 2018 May 18;4(3):e243.*
- *Moreno D et al.. Visualization of the therapeutic efficacy of a gene correction approach in Wilson's disease by laser-ablation inductively coupled mass spectrometry. J Hepatol. 2018 May;68(5):1088-1090.*
- *Zabaleta N, et al. CRISPR/Cas9-mediated glycolate oxidase disruption is an efficacious and safe treatment for primary hyperoxaluria type I. Nat Commun. 2018 Dec 21;9(1):5454.*
- *Murillo O, et al. Liver Expression of a MiniATP7B Gene Results in Long-Term Restoration of Copper Homeostasis in a Wilson Disease Model in Mice. Hepatology. 2019 Jul;70(1):108-126.*
- *Murillo O, et al. High value of 64Cu as a tool to evaluate the restoration of physiological copper excretion after gene therapy in Wilson's disease. Mol Ther Methods Clin Dev. 2022 Jun 9;26:98-106.*
- *Zabaleta N, Unzu C, Weber ND, Gonzalez-Aseguinolaza G. Gene therapy for liver diseases - progress and challenges. Nat Rev Gastroenterol Hepatol. 2023 May;20(5):288-305.*
- *Torella L, et al. Efficient and safe therapeutic use of paired Cas9-nickases for primary hyperoxaluria type 1. EMBO Mol Med. 2024 Jan;16(1):112-131.*