Research Project Proposal
Academic year 2018-2019

Project Nº 43

Project title:
Preclinical development of systemic delivery of PBGD messenger RNA as an etiological treatment for acute intermittent porphyria.

Department/ Laboratory
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Summary *:*

Acute intermittent porphyria (AIP) results from haploinsufficiency of porphobilinogen deaminase (PBGD), the third enzyme in the heme biosynthesis pathway. AIP patients have neurovisceral attacks associated with increased hepatic heme demand. Systemic delivery of lipid nanoparticles containing PBGD-mRNA represents a promising aetiological treatment for PAI. The Proof-of-Concept, performed in AIP mice, confirms the efficacy of PBGD-mRNA for the treatment and prevention of porphyria crisis. PBGD-mRNA therapy acts in few hours and maintains the same efficacy after repeat administration in AIP mice. The aim of this work is to confirm the therapeutic efficacy and safety after single and multi-dose of the PBGD-mRNA in large animals. A new pharmacological-induced acute porphyria model was developed in rabbits. High ALA and PBG accumulations will be induced in female New Zealand rabbits challenged with allyl-isopropylacetamide (AIA, 350 mg/kg, sc in the morning) and rifampicin (200 mg/kg, ip in the afternoon) for 5 days in a row. Biochemical efficacy of PBGD mRNA (0.5 mg/kg, i.v.) will be assayed by measurements of heme precursors in urine, blood and cerebrospinal fluid during the acute attack. As a clinical parameter, motor-evoked potentials will be recorded in the tibial nerve branches of rabbits 6 h after the fifth dose of AIA. The tolerability/safety of the procedure after a single or multi-dose of hPBGD mRNA (0.5 mg/kg, i.v.) will be assessed in female non-human primates. Hematology parameters, serum ADA, serum cytokine and serum coagulation and biochemical parameters were measured at baseline and 2, 6 and 24h after mRNA administration. Zonal distribution patterning in the liver of non-human-primate of exogenous PBGD will also be studied.

yes	
no	**X**

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?