NIHR Great Ormond Street Biomedical Research Centre

Doctoral Training Support Fund 2022

Student Name: Andrei Claudiu Cozmescu Research & Teaching Department: Genetics and Genomic Medicine

Primary Supervisor Name: Paul Gissen Research & Teaching Department: Genetics and Genomic Medicine

Secondary Supervisor Name: John Counsell Research & Teaching Department: Genetics and Genomic Medicine

Lentiviral gene therapy for cholestatic liver disorders

Neonatal cholestasis is characterised by impaired bile secretion and has an incidence of about 1 in 2500 live births. Up to 50% of the neonatal cholestasis causing disorders have known mutations in genes involved in bile metabolism and secretion. Progressive familial intrahepatic cholestasis types 2 and 3 (PFIC-2 and 3) are such disorders and have no curative treatment. PFIC-2 is caused by faulty genetic instructions for the production of a protein called the bile salt export pump. This protein is responsible for secretion of bile salts from the liver cells (hepatocytes) into the bile and when it is dysfunctional the bile salts are not secreted and the liver is damaged.

To permanently correct the phenotypes of inherited cholestatic diseases, our group engineers viral vectors as microscopic vehicles to carry the flawless genetic information back in the affected cells. Developing a treatment for PFIC disorders using the standard approach was hindered by several challenges. However, we have changed the structure of the standard vectors and this resolved the issues for the PFIC-3 disease. This grant would allow us to test if the new vector can also resolve these challenges for PFIC-2. If successful this project might improve the PFIC-2 patients' outcomes.