



Samenvatting proefschrift Paula de Sousa Montenegro Miranda

'Gene Therapy with Adeno-Associated Viral Vectors for Inherited Hyperbilirubinemia: Towards a Clinical Trial for Crigler-Najjar Syndrome'

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Crigler-Najjar (CN) syndrome is a recessive inherited metabolic liver disorder caused by deficiency of uridine diphosphoglucuronosyl transferase 1A1. This hepatic enzyme catalyzes the glucuronidation of bilirubin, an essential step in the excretion into bile of this neurotoxic compound. As a result, CN patients suffer from severe unconjugated hyperbilirubinemia and are at risk of bilirubin encephalopathy. The only curative treatment for these patients is a liver transplantation. In view of the shortage of donors and the adverse effects of lifelong immune suppression an effective liver directed gene therapy seems preferable. The study presented in this thesis describes the development of a safe and effective adeno-associated viral (AAV) vector for liver-directed gene therapy. In the relevant animal model for CN, the Gunn rat we show that gender influences ssAAV-mediated liver transduction. We were able to overcome the poor liver transduction in females by developing a novel double-stranded or self-complementary (scAAV) vector, an important step since CN syndrome is an autosomal disorder. In addition we show that MMF can be used to reduce the immune responses towards this novel vector. Next we evaluated scAAV vector persistence and possible host integration, revealing that integration of these vectors increases in time. Subsequently we tested the liver transduction efficiency of several AAV serotypes showing that serotype 8 is the best candidate and that AAV5 doesn't efficiently transduce rat liver. Since the adjuvant phototherapy applied in CN patients interferes with the pre-clinical monitoring of the pathophysiology we evaluated the use of exogenous compounds as serum markers for hepatic UGT1A1 activity restored upon gene therapy, and show that the cholesterol lowering drug ezetimibe seems suitable. All pre-clinical work described in this thesis has paved the road towards a phase I/2 clinical trial for CN syndrome. ◀

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