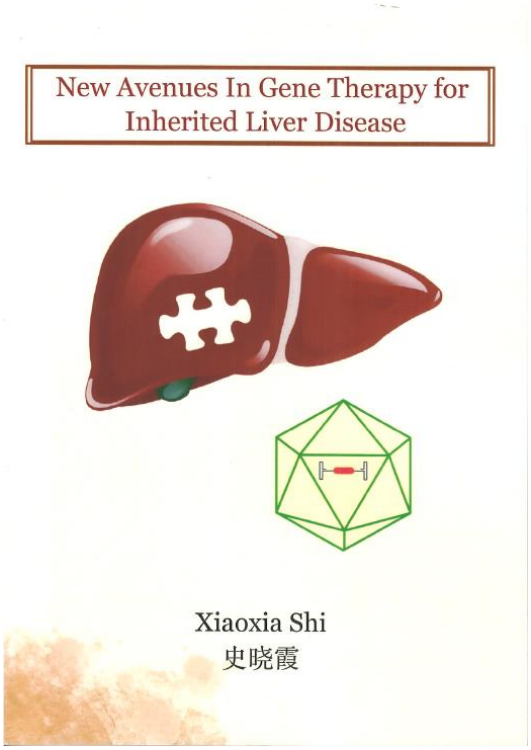

Samenvatting proefschrift X. Shi

'New Avenues in Gene Therapy for Inherited Liver Disease'

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Treatment options for inherited severe liver disorders, such as unconjugated hyperbilirubinemia (Crigler-Najjar syndrome) and progressive familial intrahepatic cholestasis (PFIC), are limited. For most affected patients the only curative option is a liver transplant, a highly invasive procedure. AAV mediated liver directed gene therapy as a preferable option is currently tested in adult Crigler-Najjar patients. However, pre-existing immunity towards AAV renders 30% of adult patients not eligible for this approach. Treatment early after birth, when pre-existing immunity is low, will overcome this problem and will also prevent irreversible bilirubin induced brain damage during childhood and adolescence. However, the loss of AAV vectors due to hepatocyte proliferation compromises its long term efficacy in children, while neutralizing antibodies (NAbs) induced by vector administration blocks effective re-treatment. This study demonstrated that immune suppression at the time of vector administration can prevent NAb thereby allowing effective re-treatment. AAV gene therapy also appeared effective in a model for PFIC type 3. In adult mice, the hepatocyte damage was completely prevented and proliferation, that would have compromised long term efficacy, was stopped. Application of an alternative vectors, recombinant SV40, reported to provide effective correction in liver without inducing NAbs, was investigated but shown to be ineffective and to induce NAbs. Since gene therapy is not available for all Crigler-Najjar patients, preventing accumulation by inhibiting bilirubin production catalyzed by biliverdin reductase (BVRa) seems an alternative. A Crigler-Najjar mouse model, neonatal lethal, was rescued upon deleting on Bvra, which warrants the development Bvra inhibitors as alternative treatment.

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