Universität Basel

Research Project

Drug Targeting to Hepatocytes: Gene Delivery using Myrcludex B Coupled Lipid Nanoparticles

Third-party funded project

Project title Drug Targeting to Hepatocytes: Gene Delivery using Myrcludex B Coupled Lipid Nanoparticles
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Hepatic disorders affect millions of people around the globe and incidence rates are further increasing. Current therapies for diseases of hepatocytes are limited and in most cases only treat symptoms. Therefore, improved therapeutic technologies are needed. Nanomedicines for the delivery of therapeutic genes have the potential to overcome the lack of satisfactory and alternative treatment options. This grant application focuses on the design of functional nanomedicines for targeted nucleic acid delivery (i.e. plasmid DNA) to liver parenchymal cells. The proposed project consists of three work-packages, which can be summarized as follows:First, specific and highly selective targeting of hepatocytes will be achieved using a targeting ligand derived from hepatitis B virus (HBV). This HBV entry inhibitor “Myrcludex B” consists of a lipid-conjugated polypeptide (i.e. the PreS1 domain of the large surface glycoprotein of HBV) and is characterized by a strong tropism for hepatocytes. Optimized Myrcludex B-derived lipopeptides will be conjugated to the surface of pegylated liposomes to mediate hepatocyte specific drug delivery. Second, in order to optimize loading and retention of DNA expression plasmids within lipid nanoparticles, a novel library of double tailed, ionizable amino-lipids will be created and screened for efficient and safe transfection activity. The combination of this new class of amino-lipids with a novel nanoparticle formulation technique (i.e. microfluidics) offers the possibility to optimize the transfection efficiency of the lipid-based delivery system. Third, in the final part of the project, both technologies will be combined to achieve targeted gene delivery to human hepatocytes; both in vitro in human liver derived cell lines as well as in vivo in different mouse models expressing the mouse or human NTCP, i.e. the entry point for HBV and at the same time our highly selective target structure on hepatocytes. With our novel targeting strategy, we have the possibility to address an unmet medical need. Non-viral gene delivery may offer well tolerated therapeutic options for diseases of the liver such as Crigler-Najjar syndrome, where a single gene defect leads to severe clinical manifestations. The proposed project will be the first step towards a future therapeutic intervention for this and other orphan liver diseases.

Keywords liver; gene delivery; nanomaterials; drug targeting; disease; hepatocyte; liposomes
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