Universität Basel

Research Project

Development of novel synthetic gene transfer vectors for metabolic liver therapy

Third-party funded project

Project title Development of novel synthetic gene transfer vectors for metabolic liver therapy
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Therapeutic vectors for gene delivery remain the currently most challenging factor for human gene therapy. The translation from in vitro to in vivo applications remains a major hurdle for most nucleic acid delivery systems since there is an inherent lack of both efficient and safe carrier systems. For liver targeting of postmitotic hepatocytes, adeno-associated virus (AAV) derived vectors are thought to have the greatest potential despite concerns about a future routine clinical use. The major hurdles of AAV vectors for long-term treatment of pediatric patients are the risk of chromosomal integration and development of hepatocellular carcinoma, immune responses to viral vectors, limited loading capacity, and the difficulty to treat neonates which likely would require subsequent further injections. Consequently, the development of non-viral gene delivery systems has gained much attention due to their versatility, safety, and ease of manufacturing. During the last decades, a wide range of nanoparticle based gene delivery systems were developed and remarkable results in the field of RNA therapeutics were achieved. However, the induced pharmacological effects obtained by these siRNA or mRNA delivery strategies are short-lived and thus weekly administrations of therapeutic formulations are necessary. The use of DNA-based therapeutics would offer a favorable option for the induction of long-term therapeutic effects without need for insertion into the genome. Here, we propose an alternative approach to overcome the challenges of viral vectors or RNA-based therapeutics by developing novel nanoparticles for delivery of non-integrating, so-called minicircle (MC) vectors lacking any viral or bacterial components for liver-directed gene therapy. The successful use of MC vectors to treat genetic (metabolic) liver defects is based on the experience of one application partner with naked DNA-vectors delivered in an experimental setting by hydrodynamic pressure to either target pericentral or periportal hepatocytes to treat two classical defects in mouse models for human diseases, phenylketonuria (PKU) and ornithine transcarbamylase (OTC) deficiency, respectively. Such MC vectors exhibited persistent expression combined with basically no DNA size limitation, which made it possible to use natural promoters/enhancers in combination with introns to mimic “physiological” expression. While MC vectors bear almost ideal properties with great potential for liver gene therapy, delivery of naked DNA solely by hydrodynamic pressure is not applicable in a clinical setting. In an interdisciplinary approach, we want to develop multifunctional polymeric nanoparticles encapsulating MC vectors for non-viral gene delivery specifically to the key pathogenic cell type, i.e. hepatocytes. In order to optimize gene delivery efficiency, a novel library of polymer-peptide hybrids will be created, formulations strategies will be optimized and resulting nanoparticles will be validated in vivo using various animal models, i.e. transgenic mice, xenotransplanted mice with human liver or pig models. The combination of this novel class of polymer-peptide hybrids with a reproducible and scalable nanoparticle formulation technique (i.e. microfluidics) is expected to greatly

impact further optimization of the synthetic gene delivery system for clinical applications. The overall aim of this translational project is the development of an alternative approach to AAV vectors with the potential of a breakthrough for liver gene therapy and thus a paradigm shift from potentially harmful viral vectors to safe, efficient and completely synthetic non-viral vectors.

Keywords metabolic liver disesase; ornithine transcarbamylase (OTC) deficiency; phenylketonuria (PKU); DNA based therapeutics; non-viral gene delivery; polymer based nanoparticles; liver gene therapy

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