The liver is a critical organ for many metabolic pathways and thus a vast source for monogenic inborn errors of metabolism. A promising treatment option is liver-directed gene therapy which is still in its infancy regarding human application. Model systems to evaluate novel medications are essential and critical for devolving novel gene therapeutic medicines. As an example, phenylketonuria (PKU) which is considered to be a paradigm for a monogenic metabolic disorder turns out to be an excellent test system for experimental gene therapy of a Mendelian autosomal recessive defect of the liver due to an outstanding mouse model and the easy to analyze and well-defined therapeutic endpoint. Lifelong treatment by targeting the mouse liver (or skeletal muscle) was achieved using different approaches, including (i) recombinant adeno-associated viral (rAAV) or non-viral (non-plasmid-based) naked DNA vector-based gene addition, (ii) genome editing using base editors delivered by rAAV vectors or as LNP-mRNA, and (iii) by delivering rAAVs for promoter-less insertion of the PAH-cDNA into the Pah locus (ref. 1). AAV-based vectors are currently at the forefront for clinic or pre-clinical application for in vivo liver targeting (ref. 2) as they are considered to persist episomally and do not integrate into the patient genome. Furthermore, this vector elicits low immunogenicity upon application for subjects that are not seropositive. However, mounting evidence supports the notion that AAV vectors can be genotoxic (ref. 3). In my presentation, I will summarize the gene therapeutic attempts of correcting mouse models for metabolic liver diseases (for PKU and the ureagenesis defect OTC) and discuss the future implications and alternative strategies we pursue with emphasis on non-viral-based DNA vectors (ref. 4) as a therapeutic tool to hopefully develop safer clinical applications.

References:
3. AAV joins the rank of genotoxic vectors (doi.org/10.1016/j.ymthe.2021.01.007)