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Adeno-Associated Virus Vector Gene Therapy Ameliorates Nephrosis in a Podocin-deficient Mouse Model of Nephrotic Syndrome

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Background: Gene therapy targeting the kidney has proven challenging thus far. Adeno-Associated Virus (AAV) has been used successfully for gene therapy targeting other organs including liver, eyes and nervous system, with particular success demonstrated in targeting monogenic diseases. Here we aimed to advance gene therapy in the kidney by targeting a monogenic disease of the kidney. The commonest cause of genetic nephrotic syndrome in children is a mutation in NPHS2 encoding podocin. Here, we use AAV-mediated gene therapy on a conditional podocin knock-out mouse model that recapitulates the disease seen in humans.

Methods: We used AAV serotype 9 expressing mouse podocin with a podocyte-specific promoter (either a mouse or human nephrin promoter) as a vector for gene replacement. This was delivered via tail vein injection to the conditional podocin knock-out mouse model. AAV serotypes LK03 and 9 were used to transduce immortalised human kidney cell lines to test for transduction efficiency and podocyte specificity. AAV LK03 expressing human podocin with a minimal nephrin promoter was used to transduce immortalised human podocytes with the R138Q podocin mutation.

Results: AAV serotype 9 gene transfer resulted in successful transduction of podocytes with resultant rescue of podocin expression in the conditional podocin knock-out mouse model. Mice injected with AAV expressing podocin showed a significant decrease in urinary albumin creatinine ratio (Figure 1a) and prolonged survival (Figure 1b). Transduction of the R138Q podocin mutant human podocyte cell line with AAV LK03 expressing podocin showed efficient transduction and functional rescue in vitro.

Conclusion: To our knowledge, this is the first study demonstrating successful gene transfer using AAV in a monogenic kidney disease in a mouse model.