

Abstract

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common potentially lethal genetic disease, affecting 500,000 people in the United States alone and accounting for 5% of end-stage renal disease. ADPKD is characterized by excessive cystic growth in the kidney and consequent obliteration of normal kidney architecture and function. There are currently no approved therapies for ADPKD other than supportive care. Mutations in the *PKD1* and *PKD2* genes, which encode the integral membrane proteins polycystin-1 and polycystin-2, lead to ADPKD. The pathophysiologic mechanism of ADPKD is loss of heterozygosity. An outstanding mouse model of ADPKD exists and is currently being used in our laboratory. This model, the double heterozygote $Pkd2^{WS25/WS183}$, contains one true null allele (*WS183*), and one allele that undergoes intragenic recombination (*WS25*), resulting in accelerated loss of heterozygosity. In recent years there have been significant advances in the generation of vectors for gene delivery, and the adeno associated virus (AAV), has many characteristics of an ideal gene therapy vector. We have strong preliminary data showing luciferase and EGFP reporter expression in kidney tubular epithelial cells, the cells of origin of renal cysts, using AAV and a retrograde injection approach. We also have in hand wild-type mouse and human *PKD2* cDNA. Here we propose using gene therapy to cure or ameliorate cystogenesis in the "gold standard" mouse model of ADPKD that faithfully recapitulates human disease. Once proof of concept is obtained, we will, in future studies, optimize the treatment and generate pre-clinical safety and toxicity data, prerequisite to initiating a clinical trial in human ADPKD.