RGLS4326 confers efficacy and modulates aberrant signaling and metabolic pathways in PKD mouse models

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Abstract
Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in either PKD1 or PKD2 genes, where expansion of fluid-filled cysts and renal fibrosis often leads to end-stage renal disease. MicroRNAs are short non-coding RNAs that modulate several biological processes. We have previously shown that aberrant expression of miR-17 family of microRNAs is involved in human ADPKD pathogenesis. RGLS4326 is a chemically-modified digonucleotide designed to stericly inhibit miR-17-2 cluster and has been shown to reduce cyst growth in vivo and in vitro. The goal of this study was to determine the signaling pathways modulated by RGLS4326 treatment in PKD mouse models.

Methods:
RGLS4326 treatment was performed in the Pkd2KO and Pcy-CD1 mice models of PKD. We performed RNA sequencing and metabolite profiling using kidney samples from both mouse models following RGLS4326 treatment. Ingenuity Pathway Analysis was used to provide novel insights into signaling pathways modulated by RGLS4326 treatment.

Results:
Through RNA sequencing, we identified >1000 differentially expressed genes in the PKD kidney samples compared to their age- and strain-matched normal controls. Comparative pathway analysis identified several dysregulated signaling pathways in the two PKD mouse models, including the PI3k, Wnt/β-catenin, and PCP signaling, that were in turn modulated following RGLS4326 treatment. Next, we performed kidney global metabolite profiling comparing Pkd2KO and normal kidneys, and identified several biochemical alterations in the Pkd2KO model, including substantial changes in lipid metabolism. In particular, decrease in β-cholesterol oxidation pathway was observed in the Pkd2KO kidneys, which corroborates with previously observed β-cholesterol dysregulation in PKD mouse models.

Conclusion: Our results indicate that RGLS4326 confers efficacy and modulates aberrant PKD signaling and metabolic pathways. These results support the clinical development of RGLS4326 for the treatment of ADPKD.