RGLS4326 inhibits miR-17 and reduces ADPKD progression in preclinical models

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a complex monogenetic disease caused by mutations in *PKD1* and *PKD2*. The disease is characterized by proliferation of fluid-filled renal cysts that eventually leads to renal failure. MicroRNAs (miRNA) are short noncoding RNAs that negatively regulate gene expression by binding to complementary sequences of miRNA target genes. Previously we have demonstrated that miR17 families of miRNAs are upregulated in human and mouse ADPKD models and contributed to disease progression. We previously demonstrated that genetic deletion of miR17~92 cluster attenuates disease progression. In this study, we examined the pharmacological effect of RGLS4326, an anti-miR17 chemically-modified oligonucleotide, in renal murine and primary human ADPKD cells in vitro and in a mouse efficacy model of ADPKD in vivo.

METHODS

De-repression of miR17 target genes (PD signature score) and displacement of miR17 from polysomes (Polysome shift assay) were measured in renal cells after transfection with RGLS4326, oligo control or PBS. Human primary ADPKD cells transfected for 24 hrs were embedded in Matrigel for 8 days and cyst index calculated. For efficacy studies, *Pkd2*KO mice were subcutaneously dose at p10, 11, 12 and p19 with 20 mg/kg of RGLS4326, oligo control or PBS. Kidney weight to body weight (KW/BW) was used as efficacy endpoint at p28. pHH3 staining was used to assess renal cyst proliferation.

RESULTS

This study demonstrated that inhibition of miR17 in renal cells by RGLS4326 treatment resulted in de- repression of miR17 target genes and displacement of miR-17 from the HMW polysome complexes in a dose-dependent manner. RGLS4326 treatment reduced proliferation and growth of primary ADPKD cyst. Furthermore, distribution of RGLS4326 to renal cysts was demonstrated by immunofluorescence staining following subcutaneous administrations in *Pkd2*KO mice. Importantly, RGLS4326 significantly suppressed the formation of renal cysts and slowed disease progression.

CONCLUSIONS

Our data indicated that inhibition of miR17 by RGLS4326 treatment prevented cyst formation and growth in preclinical models of ADPKD in vivo and in vitro. RGLS4326 is currently in clinical development for the treatment of ADPKD.