Discovery and Preclinical Characterization of RGLS4326 for the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Abstract

Background
Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in the PKD1 or PKD2 genes, is among the most common human monogenic disorders and a leading genetic cause of end-stage renal disease (ESRD). MicroRNAs (miRs) are non-coding RNAs that play central roles in cell differentiation, proliferation and survival by binding to complementary target miRNAs, resulting in repression of translation and eventual degradation of the targeted miRNAs. We have previously demonstrated that miR-17 play important roles in ADPKD, and that miR-17 is a promising drug target for the treatment of the disease.

Methods:
RGLS4326 was discovered through screening a chemically-diverse library of >100 oligonucleotides for their ability to inhibit miR-17 in a miR-17 luciferase sensor assay. RGLS4326 was extensively profiled in multiple safety assays, including biochemical, ex vivo tissues slices and in vivo studies. Preclinical efficacy of RGLS4326 was studied in both PKDKO and Pgy mouse models of PKD.

Results:
In preclinical studies, RGLS4326 potently inhibited miR-17 activity, displaced miR-17 from the transcriptionally active high molecular weight polymers, and de-repressed multiple miR-17 target genes in different mouse kidney cell lines. RGLS4326 shows favorable pharmacokinetic profiles in both normal and PKD mouse models, where preferential distribution to kidney compared to other tissues was evident. Most importantly, we have demonstrated that RGLS4326 confers efficacy in two mouse models of PKD following subcutaneous administrations.

Conclusion:
Our preclinical data support the clinical development of RGLS4326 for the treatment of ADPKD.

What are microRNAs?
• MicroRNAs are highly conserved, short non-coding RNAs (20-22 nucleotides) with unique seed sequence of ~8 nucleotides that bind to complementary target sequences located primary in the 3’ untranslated region of targeted mRNAs.
• A single microRNA can bind to and repress translation of different mRNAs, eventually resulting in the degradation of the transcripts.
• Aberrant microRNA activity, such as miR-17, has been shown to be important in multiple human diseases, including ADPKD.
• Anti-miRs are designed to inhibit microRNA function and de-repress their downstream target mRNAs and encoded proteins.

RGLS4326 de-represses miR-17 downstream target genes, including Pkd1 and Pkd2

RGLS4326 inhibits miR-17 family of microRNAs in luciferase assays in vitro

Functions of miR-17 in kidney
• Specific knockdown in mouse nephron progenitors impaired nephrogenesis and renal function.
• Overexpression in renal tubules promoted kidney cyst growth.
• Knockdown of miR-17-92 in multiple mouse models of ADPKD, including the PKD1-KO, Pkd1Frc/Frc, Pkd2Glc/Glc, Kidza-KO and Pkd2-KO models, showed reduction of cyst growth.
• Knockdown of miR-17-92 in renal tubules did not display any appreciable defects in kidney morphology and histology in normal mice.

RGLS4326 shows favorable pharmacokinetic and pharmacodynamic profiles

RGLS4326 reduces rate of bwTKV increase by MRI in the PcyDBA mouse model of PKD

Characteristics of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is a monogenic disorder caused by mutations in either PKD1 (85%) or PKD2 genes (15%), which encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively.

Mutations disrupt normal functions of PC1 and PC2 in renal tubular epithelium, causing growth of multiple kidney cysts that displace and destroy normal kidney tissues, ultimately leading to fibrosis, derangement in renal architecture and kidney failure.