Discovery of anti-miR-17 oligonucleotide RGLS4326 for the treatment of autosomal dominant polycystic kidney disease

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Abstract
Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in either PKD1 or PKD2 genes, is one of the most common human monogenic disorders and the leading genetic cause of end-stage renal disease. Unfortunately, treatment options for ADPKD are limited. Here we report the discovery and characterization of RGLS4326, a small interfering oligonucleotide of miRNA-17 (miR-17) as a potential treatment for ADPKD. RGLS4326 was discovered by screening a chemically-diverse and rationally-designed library of anti-miR-17 oligonucleotides for optimal pharmacological properties in preclinical models. RGLS4326 preferentially inhibits miRNA-17 (miR-17) activity by increasing the level of its target mRNA, and thus reducing the level of protein expression. RGLS4326 is efficacious in multiple ADPKD models and multiple PKD mouse models after subcutaneous administration. The preclinical characteristics of RGLS4326 support its clinical development as a disease-modifying treatment for ADPKD.

ADPKD and miR-17 family of microRNAs
Mutations in PKD1 and PKD2 genes disrupt normal functions of their encoded proteins polycystin-1 (PC1) and polycystin-2 (PC2) in renal tubular epithelium, cause growth of multiple kidney cysts that displace and destroy normal kidney tissue, and ultimately lead to fibrosis, enlargement in renal architecture and kidney failure.

Discovery of RGLS4326, a chemically-modified oligonucleotide inhibitor of miR-17

- RGLS4326 inhibits miR-17 and de-represses direct miR-17 targets
- RGLS4326 confers efficacy in Pcy/Cd1 mouse model of PKD

RGLS4326 improves expression of dysregulated gene networks in PKD models

- RGLS4326 confers efficacy in Pcy/Cd1 mouse model of PKD

Conclusion
RGLS4326 is a first-in-class anti-miR-17 oligonucleotide with promising potential as a disease-modifying treatment for ADPKD. In preclinical studies, RGLS4326 has favorable potency, safety, stability, and pharmacokinetic/pharmacodynamic characteristics, including preferential distribution to kidney. RGLS4326 attenuates cyst growth in human ADPKD models in vitro and is efficacious in multiple PKD mouse models in vivo. Our data support the clinical development of RGLS4326 for the treatment of ADPKD.

- RGLS4326 improves expression of dysregulated gene networks in PKD models

- RGLS4326 confers efficacy in Pcy/Cd1 mouse model of PKD