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Corporate Presentation.

January 2024

Safe Harbor Statement

- Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements associated with the Company's RGLS8429 program, the expected timing for initiating clinical studies, potentially achieving therapeutic efficacy and clinical translation for ADPKD patients, the expected timing for reporting topline data, the timing and future occurrence of other preclinical and clinical activities and the expected length of our cash runway. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "intends," "will," "goal," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Regulus' current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, the approach we are taking to discover and develop drugs is novel and may never lead to marketable products, preliminary or initial results may not be indicative of future results, preclinical and clinical studies may not be successful, risks related to regulatory review and approval, risks related to our reliance on third-party collaborators and other third parties, risks related to intellectual property, risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and in the endeavor of building a business around such drugs, and the risk additional toxicology data may be negative and our need for additional capital. These and other risks are described in additional detail in Regulus' filings with the Securities and Exchange Commission, including under the "Risk Factors" heading of Regulus' most recently filed quarterly report on Form 10-Q. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Regulus undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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First-in-Class Antisense Therapeutics for Genetic Disease.

Leading antisense oligonucleotide company, co-founded by Ionis and Alnylam, to address genetic disease driven by dysregulated microRNA biology (anti-miRNA)

Executing in the clinic with anti-miR-17 oligonucleotide RGLS8429, the first potential disease-modifying approach for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Broad platform includes oligos optimized to deliver preferentially to the kidney

Early development programs targeting additional kidney and CNS diseases

Seasoned leadership team experienced in nephrology drug development

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Regulus Investment Highlights.

- **RGLS8429: Phase 1b MAD study ongoing**
  - Presented topline data in September 2023 from the first cohort of patients in the Phase 1b MAD study indicating increases in both PC1 and PC2 urine biomarkers after treatment
  - Topline data from second cohort anticipated Q1 2024
  - Completed enrollment in third and final randomized placebo-controlled weight-based cohort
    - Topline data anticipated mid-2024
  - Protocol amended to include a fourth cohort of patients who will receive open label fixed dose of RGLS8429
- **Phase 2 enabling safety tox study and CMC activities underway**
- **$30.8m in cash on the balance sheet as of September 30, 2023**
  - **Completed a $15M private placement in April 2023 with existing shareholders, extending runway into mid-2024**

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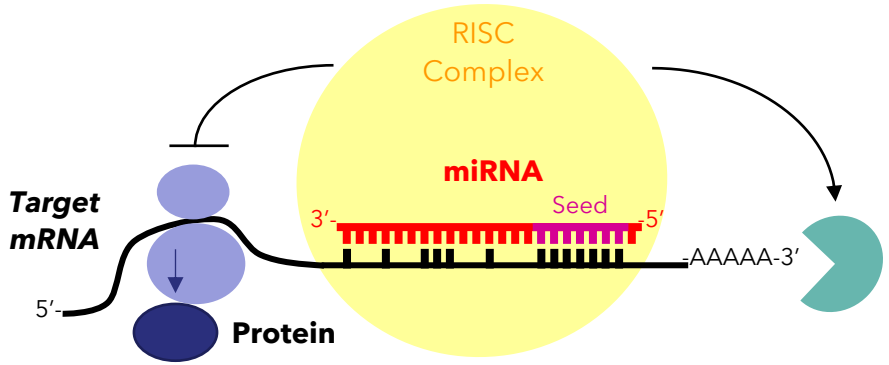
What are microRNAs?

POST-TRANSLATIONAL INHIBITORS OF GENE EXPRESSION

- MicroRNAs (miRNAs) are short (~20nt) non-coding RNAs that bind to complementary sequences located in the 3′ untranslated region (3′UTR) of target mRNA, controlling translation and eventual degradation of the target mRNA transcripts



- Aberrant expression of miRNAs has been shown to promote the progression of many human diseases, including proliferative, cardiovascular, metabolic, fibrotic, and neurodegenerative diseases
- Inhibition of specific pathogenic miRNA (by anti-miRs) have been shown to attenuate disease progression in both preclinical and clinical settings

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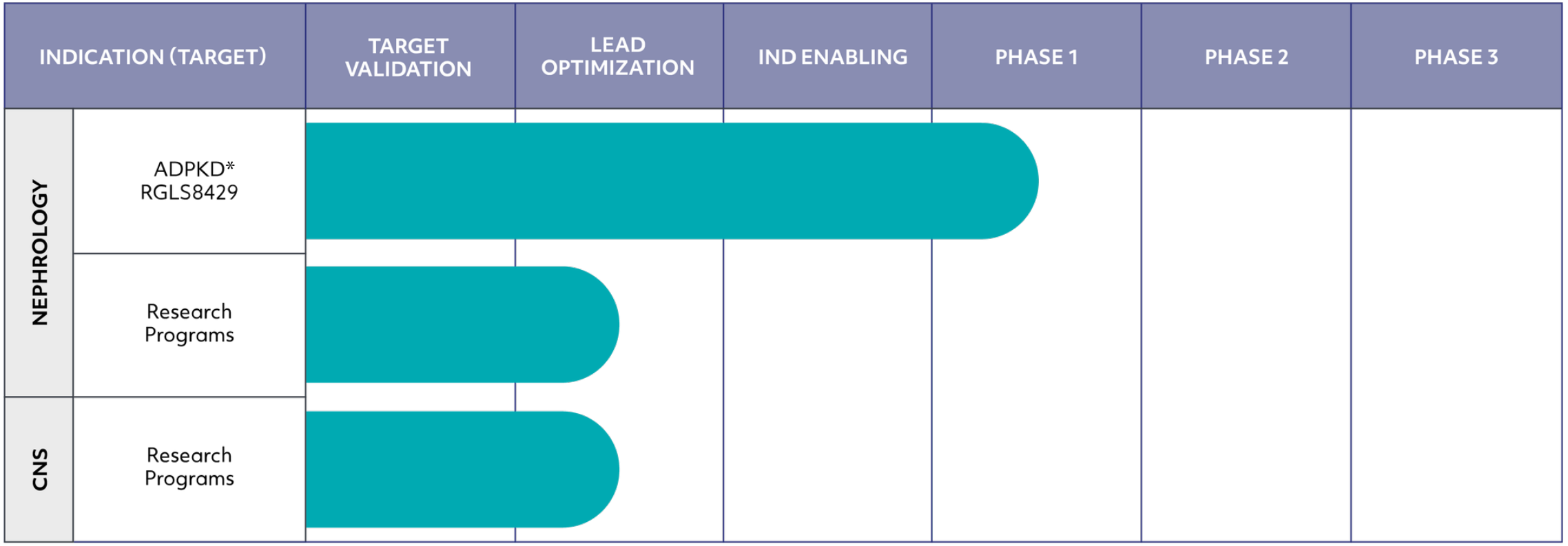
Innovative Pipeline: Primary Focus on Kidney Diseases.



*Autosomal Dominant Polycystic Kidney Disease

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Autosomal Dominant Polycystic Kidney Disease (ADPKD).

ORPHAN DISEASE & HIGH UNMET MEDICAL NEED

The Unmet Medical Need

- 50% of patients develop ESRD by age 60 and require dialysis or transplantation
- Kidney failure average age:
  - 55 years for *PKD1* patients
  - 74 years for *PKD2* patients
- Only FDA approved therapy (tolvaptan) has boxed warning for potentially fatal liver toxicity and significant tolerability concerns related to free water excretion
  - Despite limitations, 2022 sales were $1.12B in US

PATIENT POPULATION.

~80%
patients with ***PKD1*** mutation

160K
diagnosed individuals in U.S.

HEALTH BURDEN.

50%
patients develop ESRD by age 60

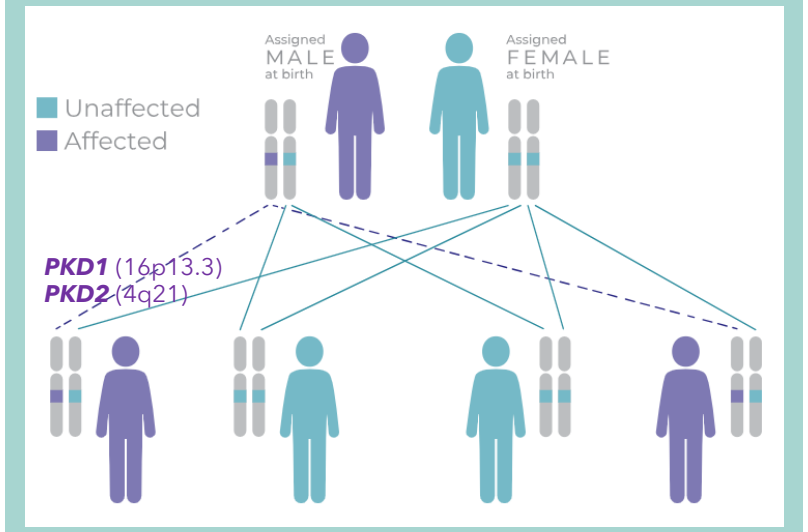
$3.8B+
estimated annual cost of renal replacement therapy in U.S.[1]

1. Cloutier et al. (2020) BMC Health Serv. Res. 20:126

ADPKD Genetic Mutation Drives Clinical Pathology.

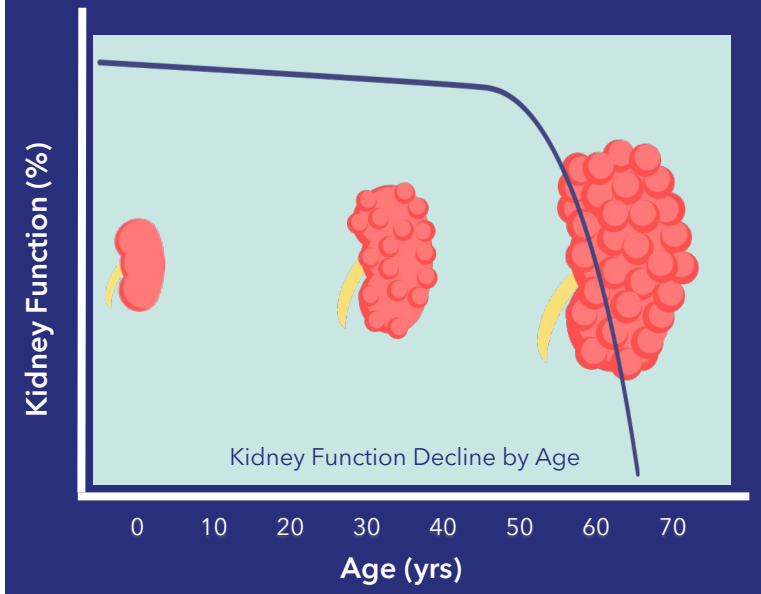
PROLIFERATIVE, CYSTIC DISEASE LEADS TO ENLARGED KIDNEYS WITH PROGRESSIVE FAILURE

- Mutation of either ***PKD1*** or ***PKD2*** genes, which reduce levels of their encoded proteins polycystin-1 (PC1) or polycystin-2 (PC2), causes formation and proliferation of multiple fluid-filled cysts in the kidneys leading to loss of kidney function over time



Adapted from PKD Foundation website

- Cystic expansion drives kidney growth throughout life, while decline in kidney function generally occurs late in adulthood.



- Polycystic kidneys taken from an ADPKD patient during nephrectomy:

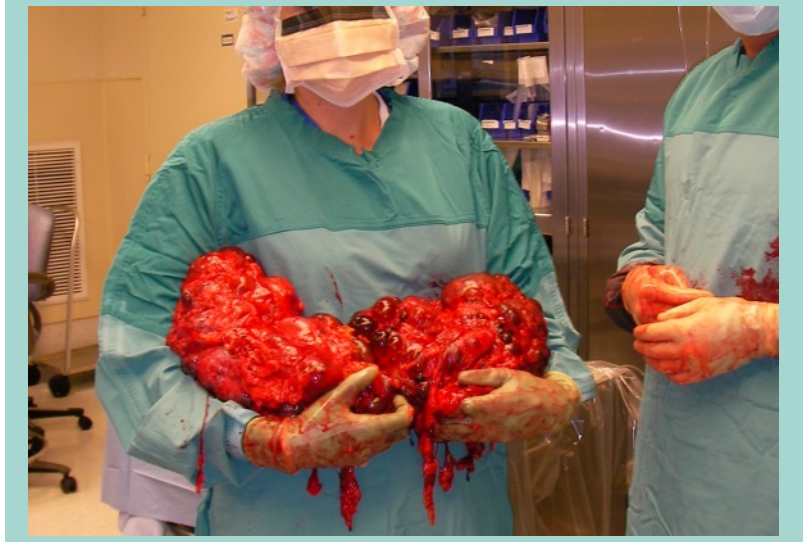


Photo courtesy of Dr. Vishal Patel

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Increased miR-17 Expression Drives Cystic Proliferation In ADPKD.

BLOCKING miR-17 ACTIVITY REDUCES KEY PROLIFERATIVE SIGNAL PATHWAYS

Mutations in *PKD1* or *PKD2* genes

Increased *c-Myc* expression

Increased miR-17 expression

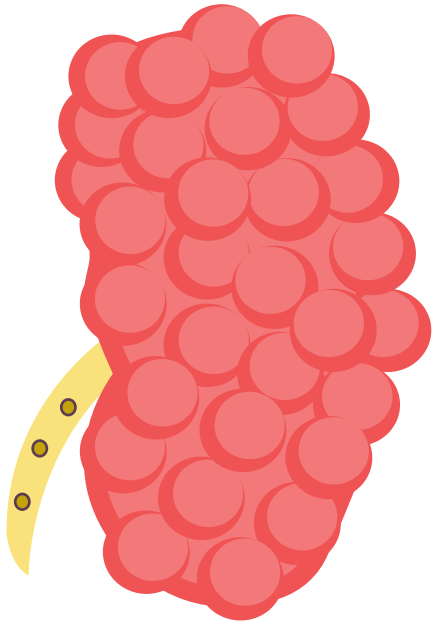
Represses miR-17 targets

Other miR-17 target genes

PKD1 PKD2

Dysregulated gene networks

Low PC1 and PC2



Mutations in *PKD1* or *PKD2* genes

Increased *c-Myc* expression

Increased miR-17 expression

Treatment with Anti-miR-17

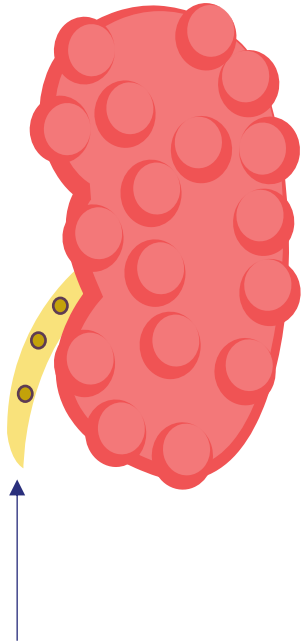
De-represses miR-17 targets

Other miR-17 target genes

PKD1 PKD2

Improved gene networks

Increase PC1 and PC2



Increase in PC1 and PC2 measured in urinary exosome

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Lee (2019) Nat Commun

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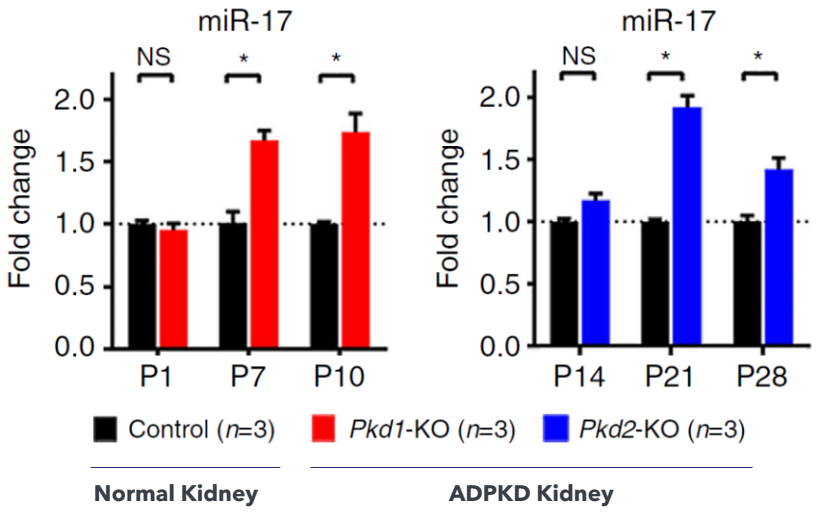
Anti-miR-17 as a Therapeutic Strategy in ADPKD.

miR-17 is Upregulated in ADPKD.

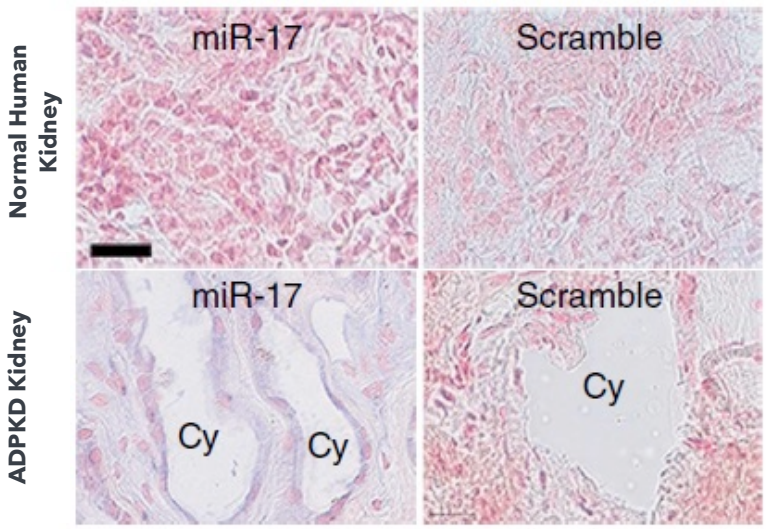
OVEREXPRESSION OF miR-17 PROMOTES DISEASE PROGRESSION

- miR-17 is upregulated in mouse kidney cysts and human ADPKD cysts cells[1,2]
- Overexpression of miR-17 in renal tubules in normal mice promoted kidney cyst growth[1]

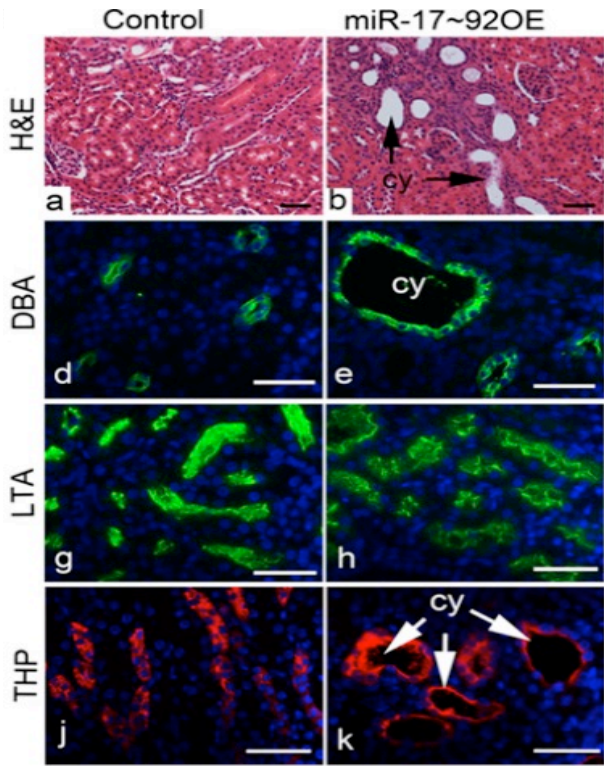
Mouse Kidney Samples
qPCR analysis



Human Kidney Samples
In-situ hybridization



Mouse Kidney



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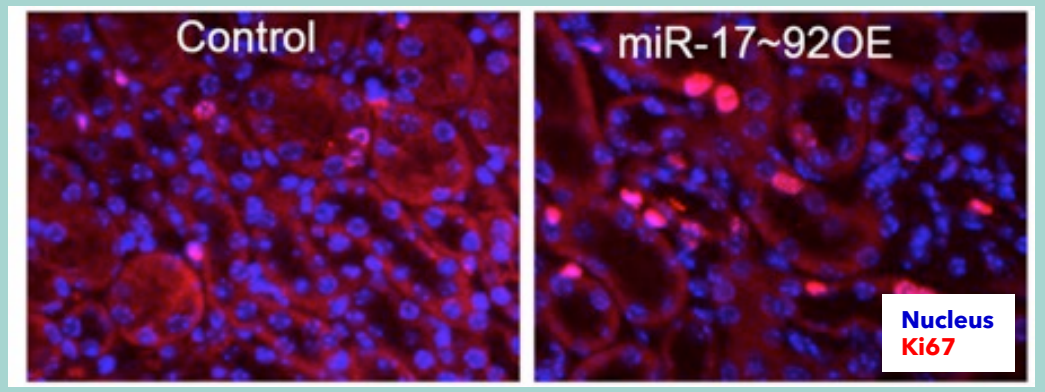
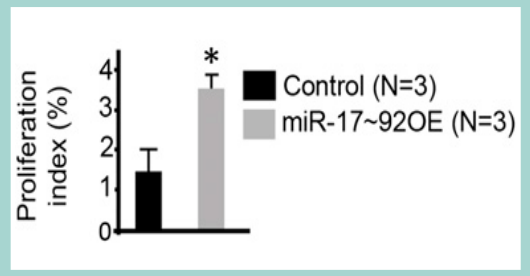
1, Patel (2013) PNAS; 2, Hajarnis (2017) Nat Commun.

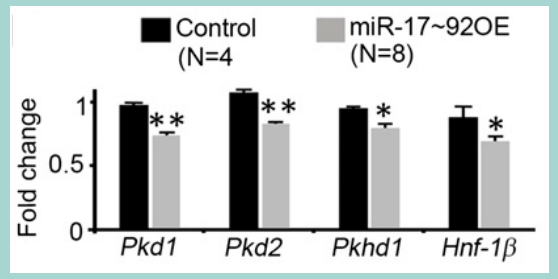
miR-17 Promotes Proliferation and Represses Many Pathogenic Genes of PKD.

KNOCKDOWN OF miR-17 IMPROVES MANY PKD PATHOGENIC GENE-NETWORKS

- Overexpression of miR-17 promotes proliferation and repressed PKD-pathogenic genes, including *Pkd1* and *Pkd2*

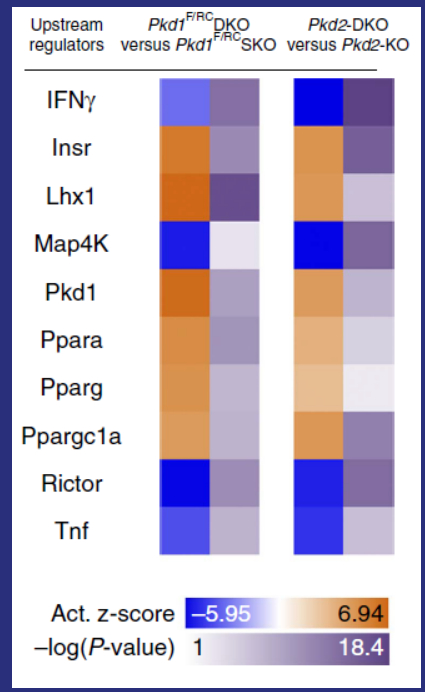






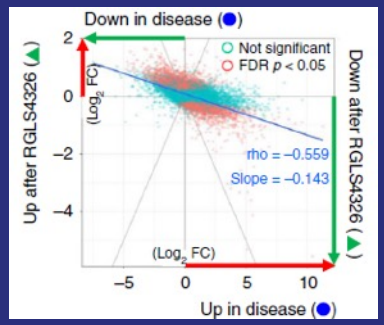
Patel 2013, PNAS.

- Genetic-knockdown or pharmacologic inhibition of miR-17 improves many PKD-pathogenic pathways, including activation of *Pkd1* gene-network in mouse models of ADPKD

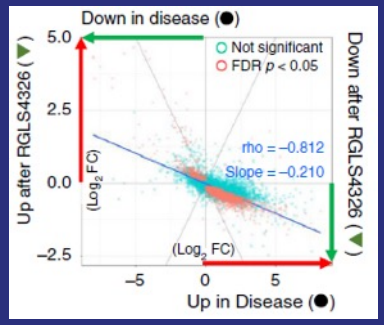


Hajarnis 2017, Nat Commun.

Pkd2-KO



Pcy/CD1

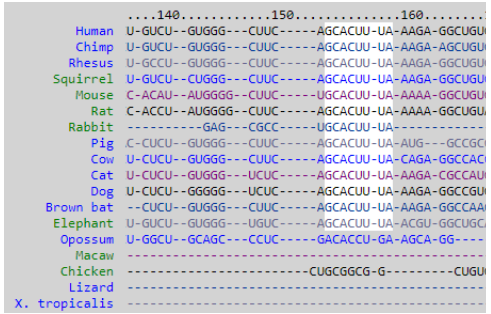


Lee 2019, Nat Commun.

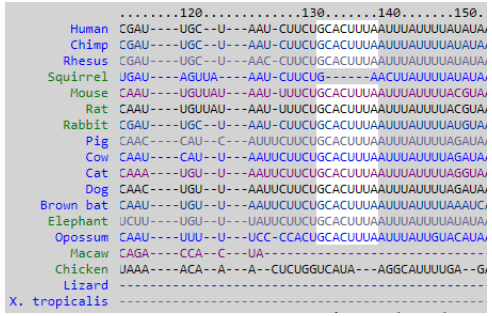
miR-17 Directly Binds to 3'UTRs of *Pkd1* and *Pkd2*.

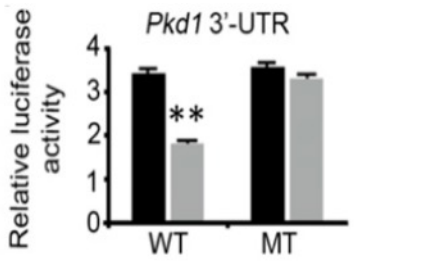
- 3'UTRs of *Pkd1* and *Pkd2* contain conserved miR-17 binding sequences across species[1]
- miR-17 mimic represses *Pkd1* and *Pkd2* in mouse collecting duct (IMCD3) cells[2]
- Deletion of miR-17 binding site at 3'UTR of *Pkd1* and *Pkd2* improves stability of their mRNAs, increases levels of PC1 and PC2, and reduces disease in *Pkd1*$^{F/RC}$ mice[3]

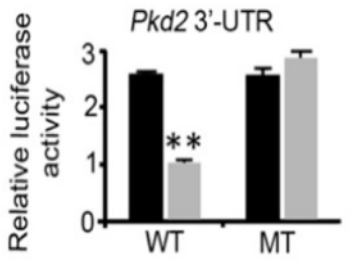
Pkd1
3'UTR conserved miR-17 motif

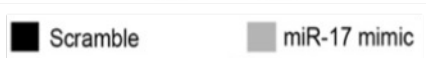


Pkd2
3'UTR conserved miR-17 motif



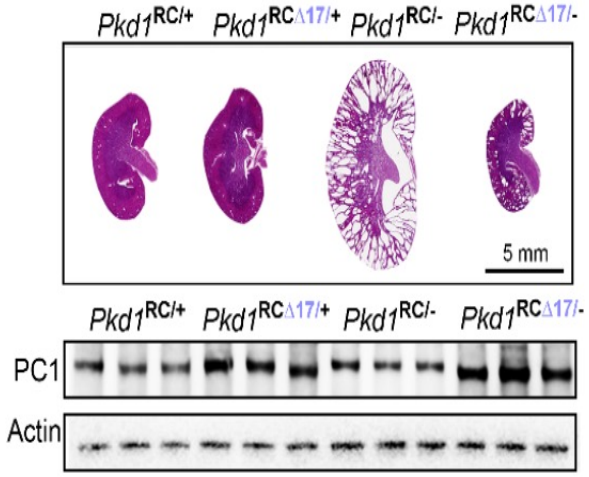




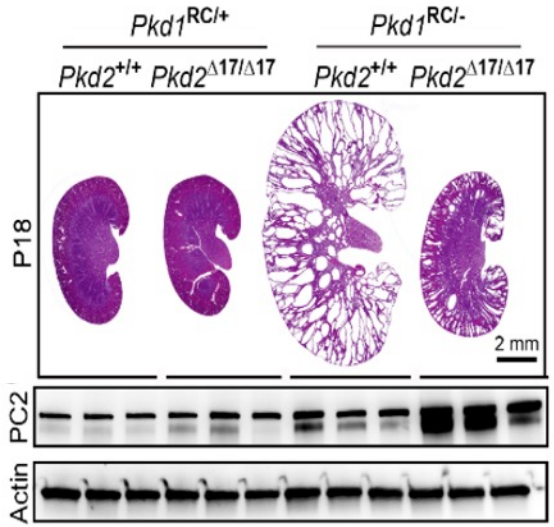


WT: wildtype 3'UTR; MT: mutated 3'UTR

Pkd1 3'UTR Δ17
miR-17 motif deletion
in *Pkd1*$^{F/RC}$ mice



Pkd2 3'UTR Δ17
miR-17 motif deletion
in *Pkd1*$^{F/RC}$ mice

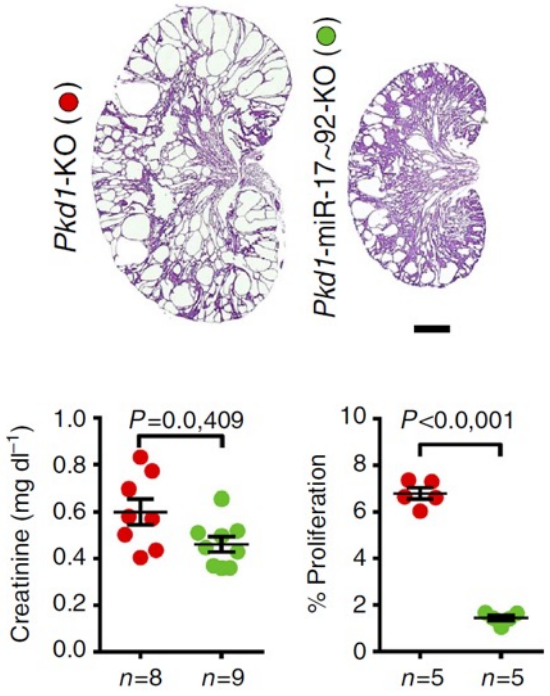


1, TargetScan; 2, Patel (2013) PNAS; 3, Lakhia (2022) Nat Commun.

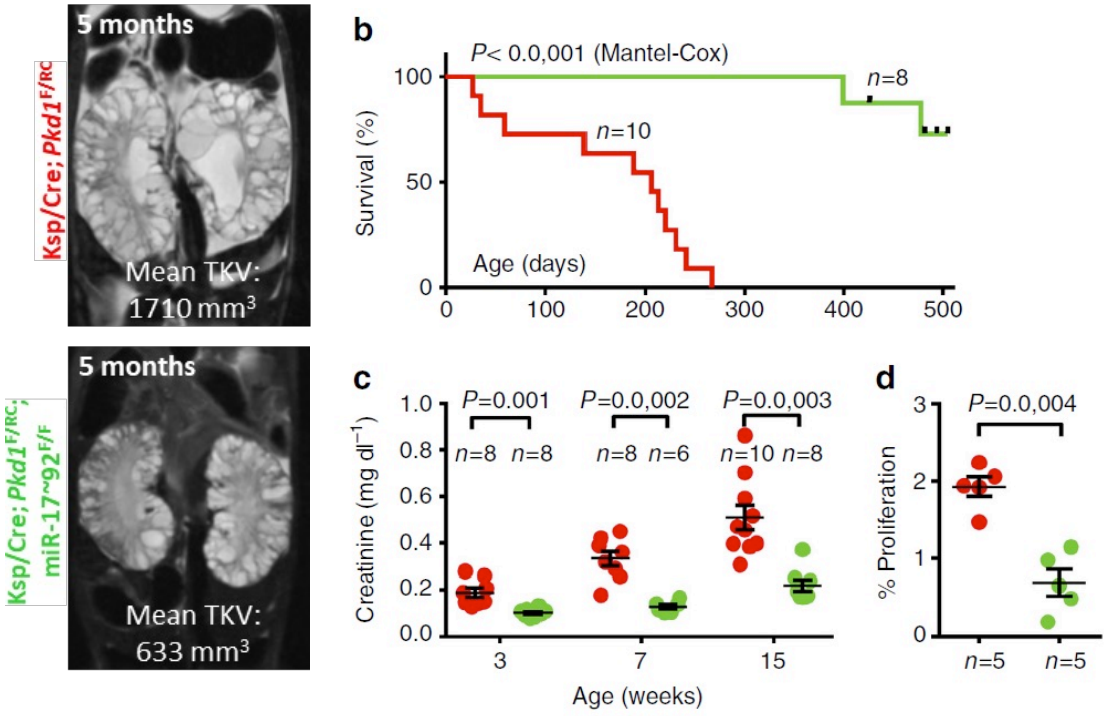
Knockdown of miR-17 Attenuates Disease Progression.

- Kidney-specific knockdown of miR-17 attenuated kidney cyst growth in multiple ADPKD mouse models, including *Pkd1*^{null}, *Pkd1*^{hypomorphic} ,and *Pkd2*^{null} mice[1-4]

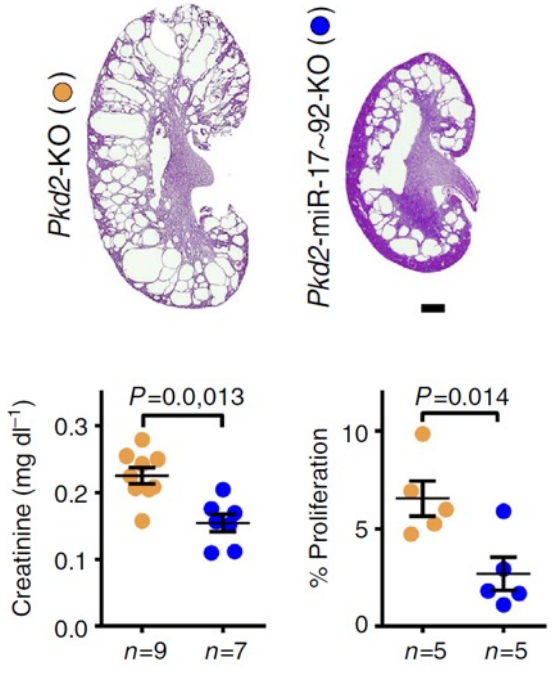
Pkd1-KO mice



Pkd1$^{F/RC}$ mice



Pkd2-KO mice



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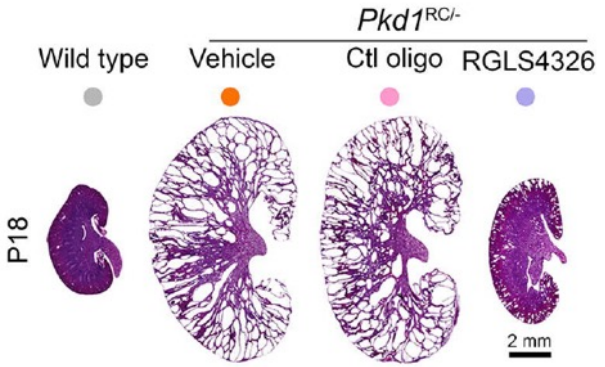
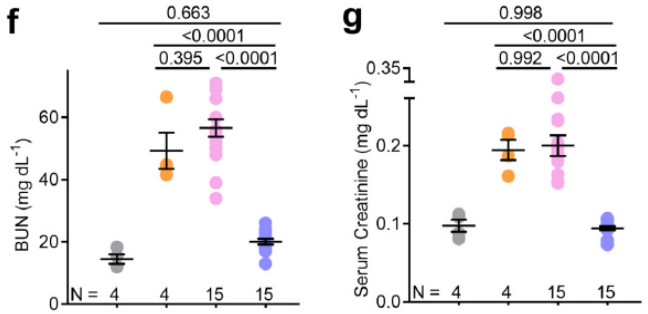
1, Patel (2013) PNAS; 2, Hajarnis (2017) Nat Commun; 3, Lee (2019) Nat Commun; 4, Lakhia (2022) Nat Commun.

Anti-miR-17 Treatment Reduces Kidney Cyst Growth in Multiple Disease Models.

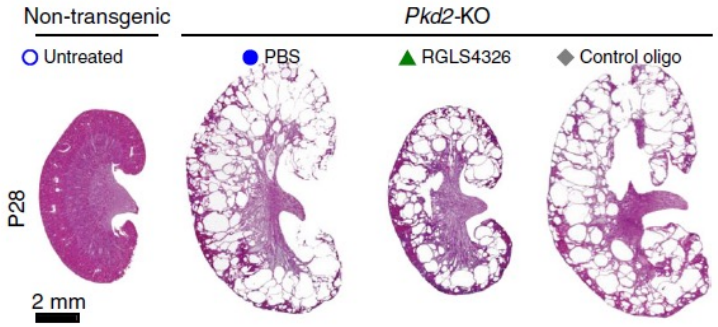
Pkd1/2 genes models

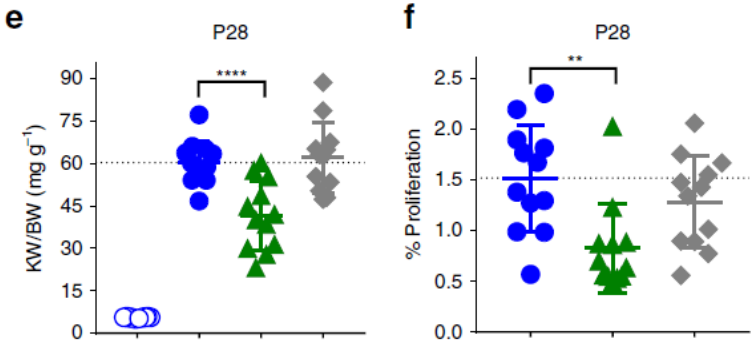
***Pkd1*$^{F/RC}$ mice**





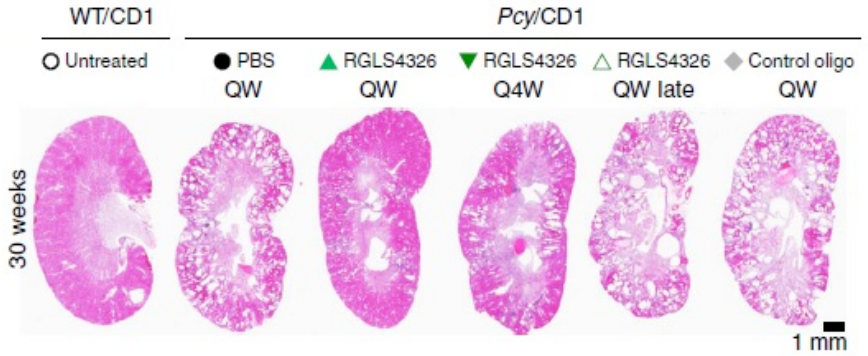
***Pkd2*-KO mice**



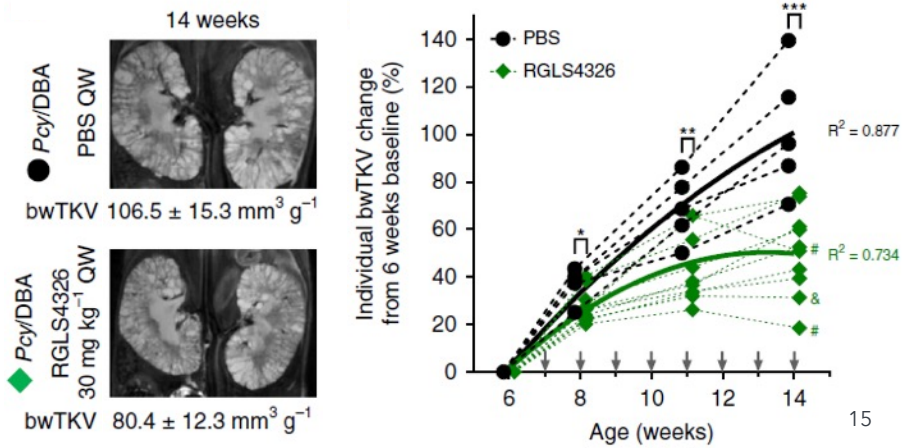


Non-Pkd gene models

***Pcy*/CD1 mice**

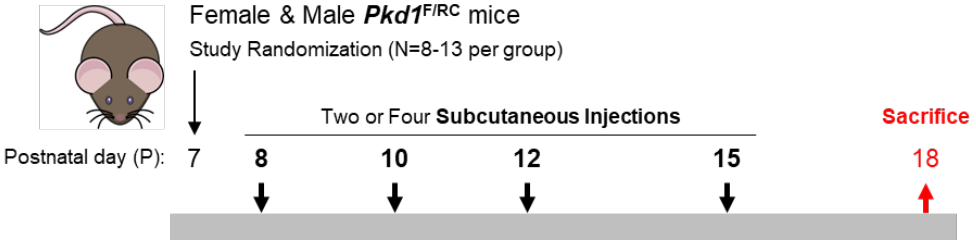


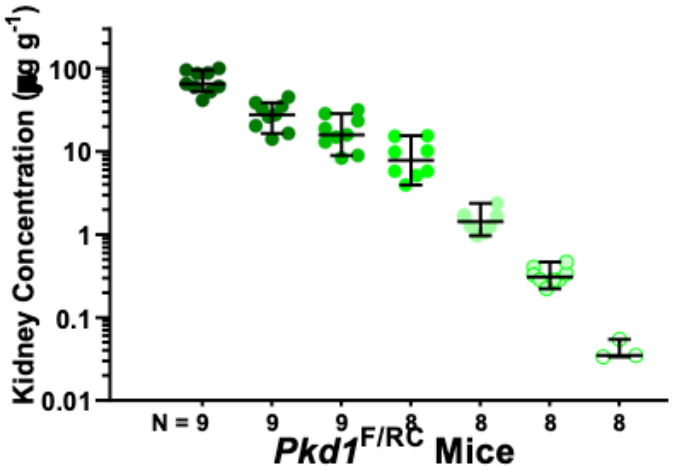
***Pcy*/DBA mice**

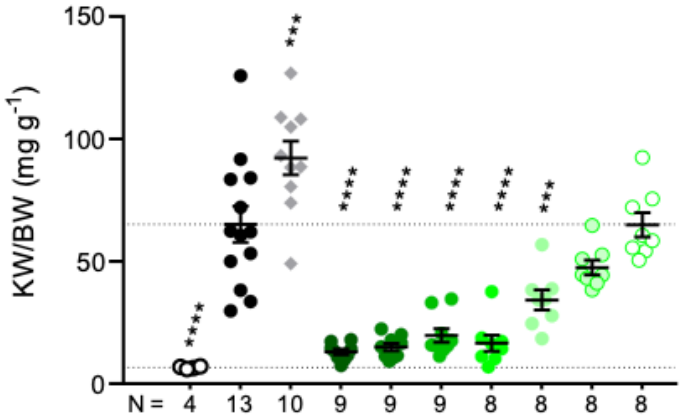


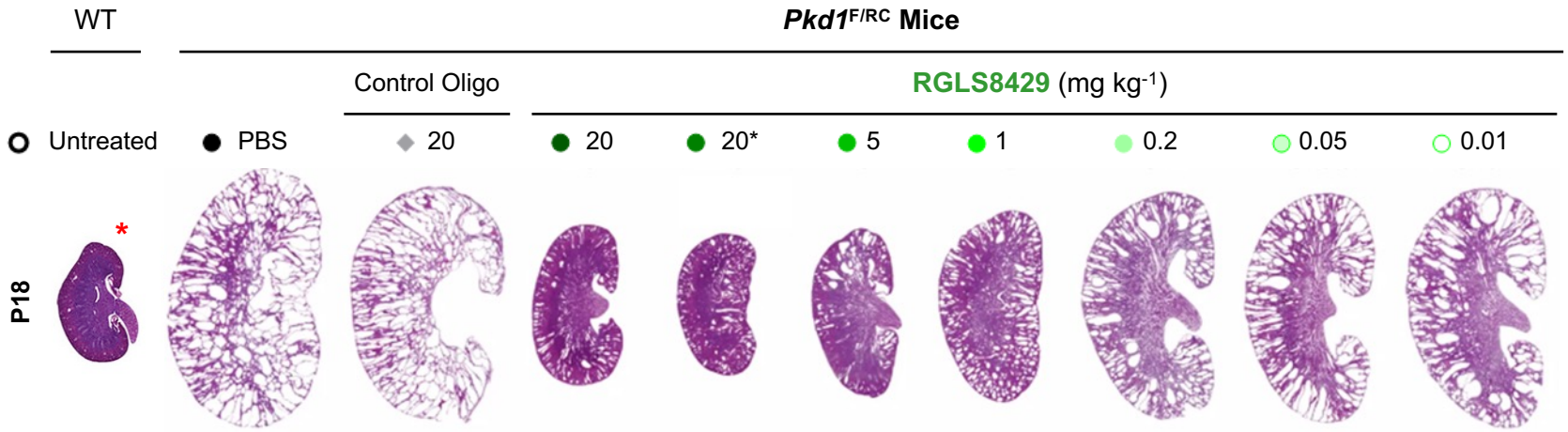
1, Lakhia (2022) Nat Commun; 2, Lee (2019) Nat Commun;

Anti-miR-17 Treatment Exhibits a Clear Dose Response.









*P8 & P12 Injections only; All others P8, P10, P12 & P15 Injections

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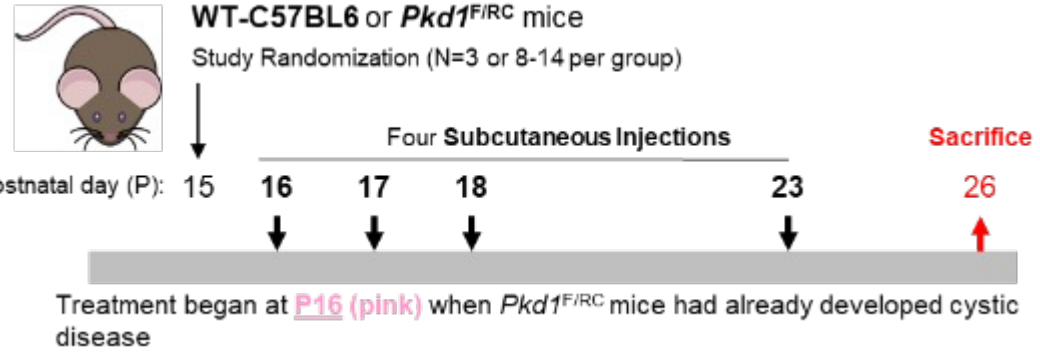
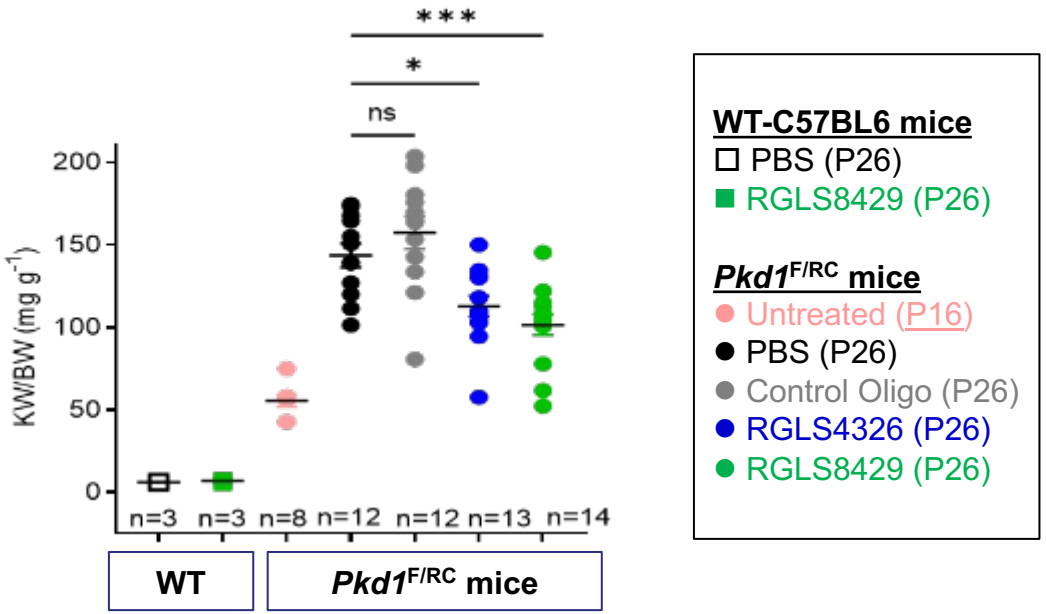
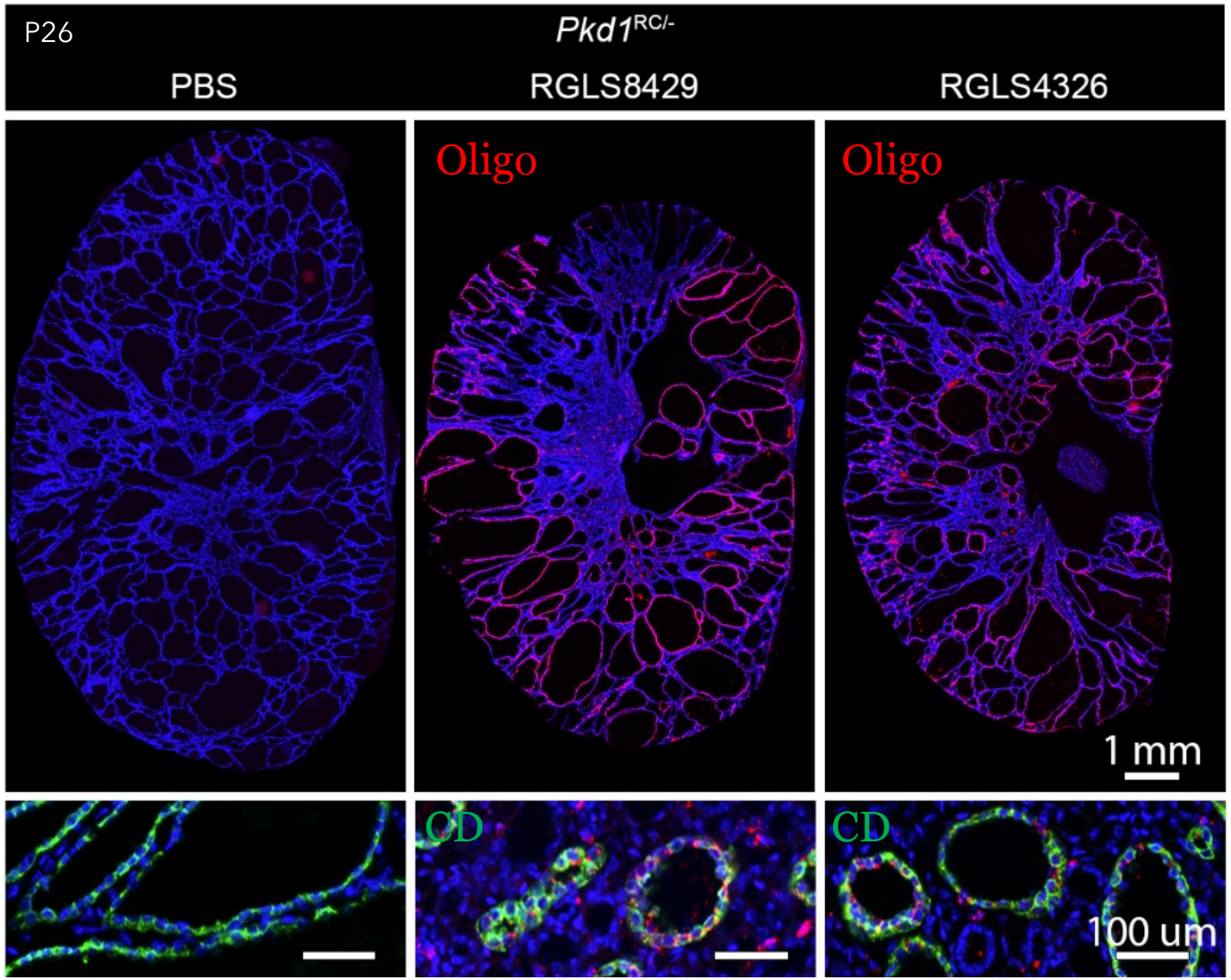
Anti-miR-17 Oligo Localizes to Kidney Cyst Epithelium and Confers Efficacy in *Pkd1*$^{F/RC}$ ADPKD Mice.





WT-C57BL6 mice
- ☐ PBS (P26)
- ■ RGLS8429 (P26)

***Pkd1*$^{F/RC}$ mice**
- ● Untreated (P16)
- ● PBS (P26)
- ● Control Oligo (P26)
- ● RGLS4326 (P26)
- ● RGLS8429 (P26)



Immunofluorescence (IF) Imaging:
RGLS: Anti-Oligo Antibody
DBA: Collecting Duct (CD) Marker

Ramalingam 2023; unpublished

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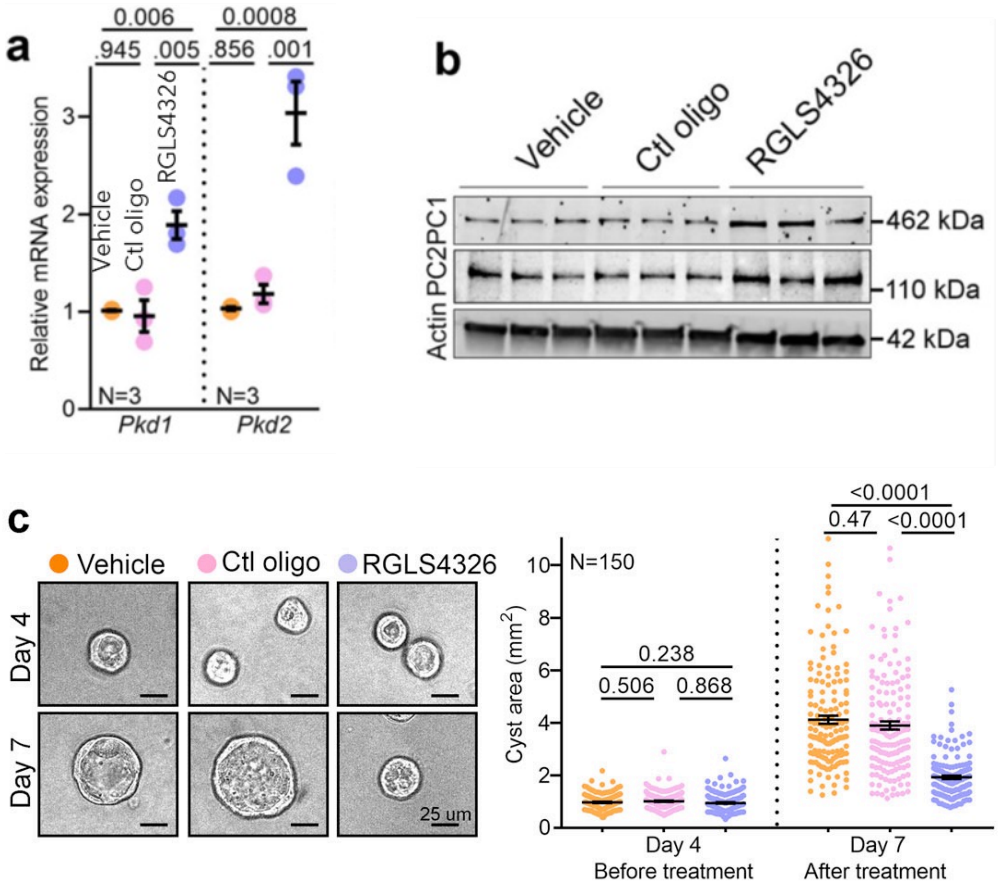
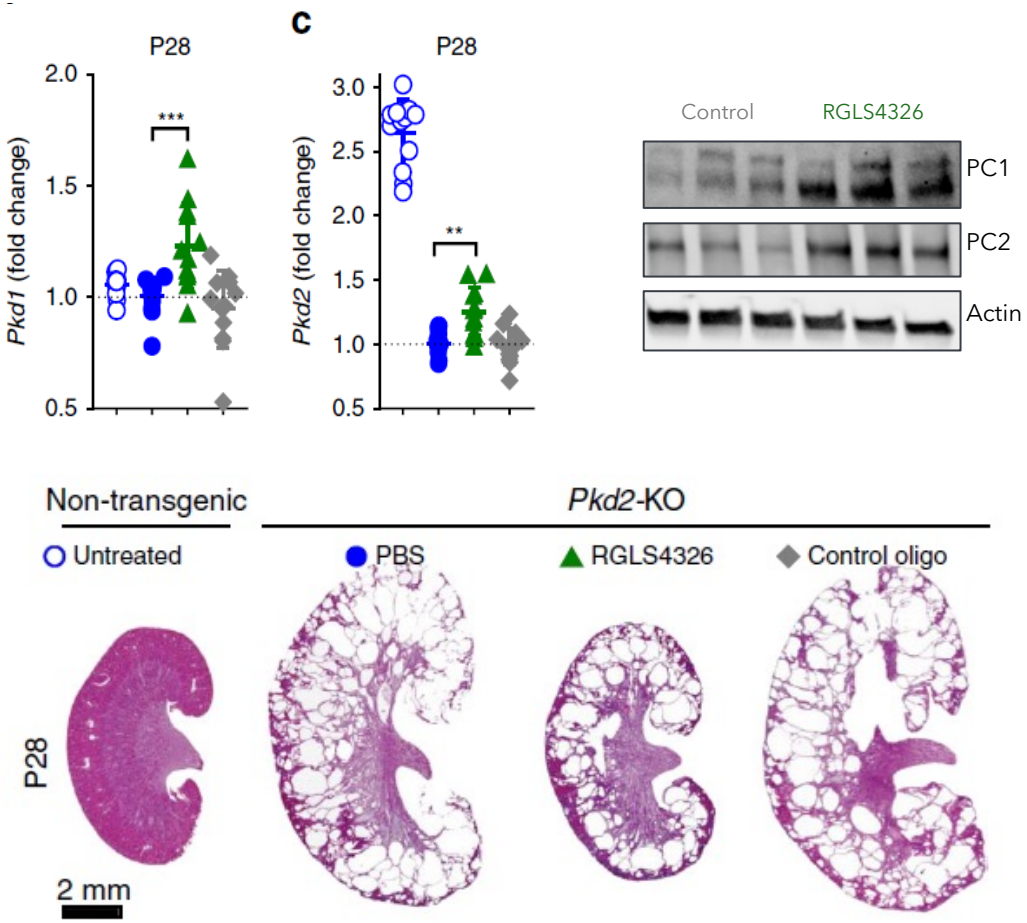
Anti-miR-17 Treatment Increases Polycystin Levels and Confers Anti-cyst Activity in ADPKD Models.

Mouse ADPKD Cysts



Pkd2-KO mice



Lakhia (2022) Nat Commun; Lee (2019) Nat Commun.

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RGLS8429 Development.

RGLS8429: Engineered to Block the Action of miR-17 in ADPKD.

Oligonucleotide built with specificity against miR-17

- Directly binds to key seed region on miR-17
- Prevents miR-17 engagement with target mRNA
- Strong evidence of efficacy in vitro and in vivo

Preferential delivery to organ of choice and favorable kinetics for Q2W delivery

- Short, naked oligo confers preferential delivery to kidney compared to liver, plasma and other compartments
- $T_{1/2}$ ~10 days in tissue enabling every-other week subcutaneous injection

Favorable safety & tolerability profile

- Low potential for off-target effects via aptamer or nucleotide binding
- Chronic tox in mouse complete *(NOAEL = top dose)*
- Ph1 SAD in healthy subjects was safe and well-tolerated

Early evidence of benefit using key pharmacodynamic and disease marker *(polycystin)* in ongoing Ph1b

- Initial 1 mg/kg dose demonstrates increases in PC1 & PC2
- Additional 2 & 3 mg/kg cohorts underway

Orphan Drug Designation: Granted by FDA Q2 2022

Accelerated Approval Possible with Successful Ph2 Trial: Total Kidney Volume generally accepted as an appropriate surrogate for clinical benefit

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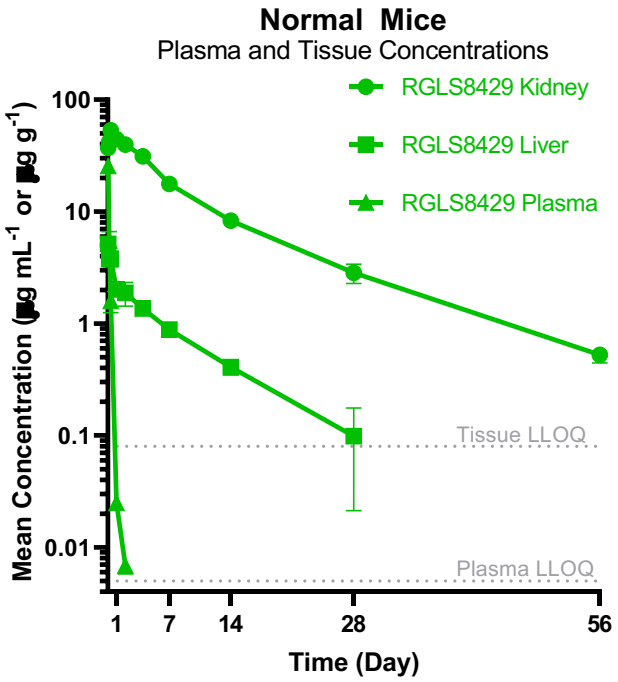
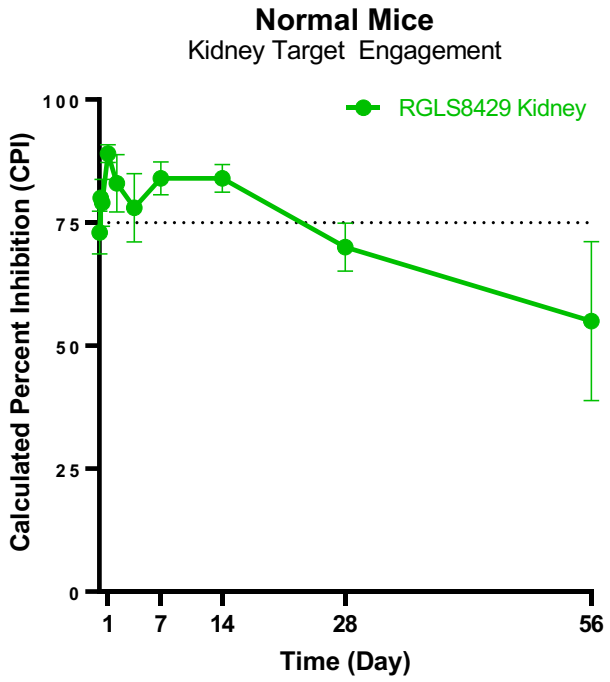
RGLS8429 Preferentially Distributes to Kidney and Demonstrates Strong Target Engagement.





WT-C57BL6 mice received a single subcutaneous injection of RGLS8429 at 30 mg/kg

Manuscript in Preparation

Clinical PK mirrors nonclinical models and supports every-other week dosing

- Plasma concentrations show rapid absorption followed by rapid clearance
- RGLS8429 is metabolically stable; primary route of excretion via kidney
- Anticipated kidney tissue $T_{1/2}$ ~10 days based on nonclinical sampling
- Extrapolation from mouse and monkey models supports max (~80%) miR-17 inhibition in humans between 2-3 mg/kg

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RGLS8429 has Favorable Safety Profile in Preclinical Toxicity Studies.

- **SC administration** in the clinical formulation, 150 mg/mL in 0.3% saline, is supported by nonclinical local tolerability study conducted in rabbits
- **Well tolerated in mice in a 6-month toxicity study**, with no-observed-adverse-effect-level (NOAEL) of 300 mg/kg dosed subcutaneously (SC) once-every-two-weeks (Q2W)
- **Well tolerated in non-human-primates (NHP) in a 3-month toxicity study**, with NOAEL of 150 mg/kg dosed SC once-weekly (QW). Chronic toxicity study (9-months) in NHP initiated Q4-2023
- **No CNS or renal toxicity** observed in either species
- **Low potential for off-target effects** via receptor inhibition
- Has shown **no potential for genotoxicity** and **no evidence of mitochondrial toxicity**
- Has **minimal potential** for adverse effects on platelets and **low risk** for pro-inflammatory activity

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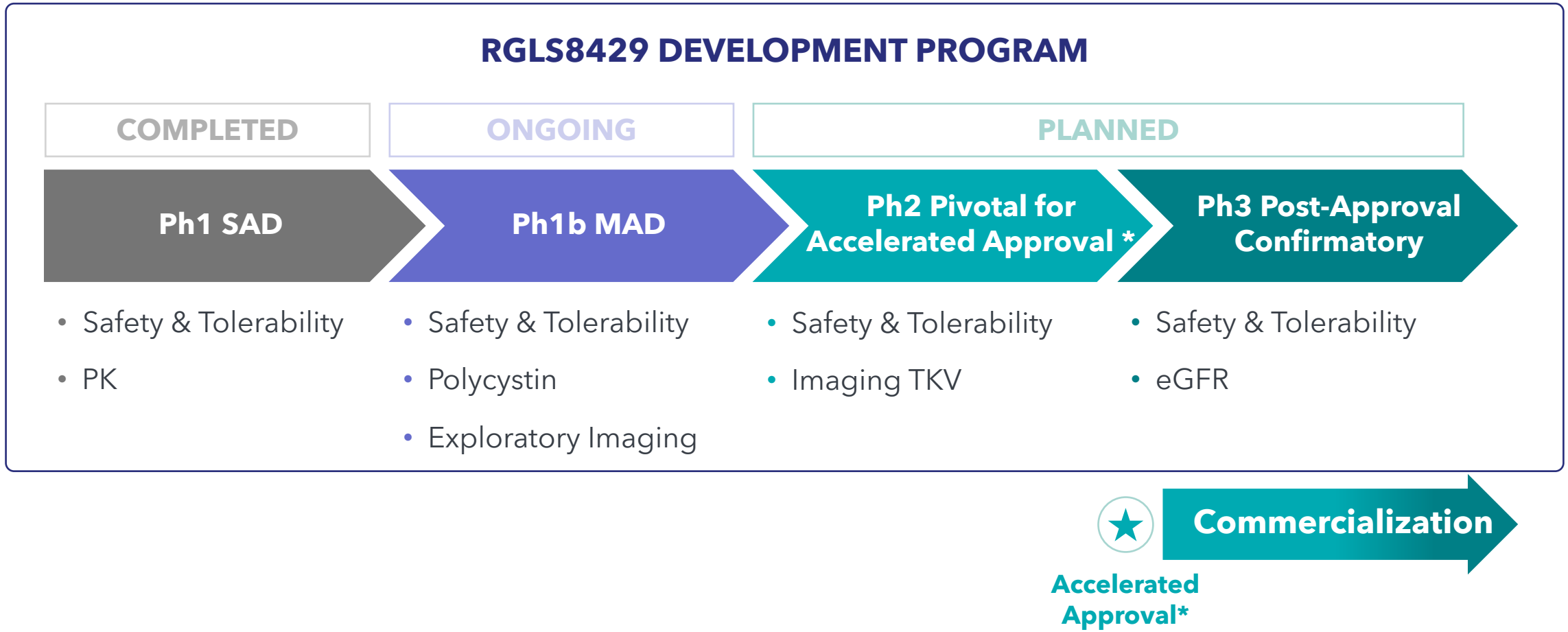
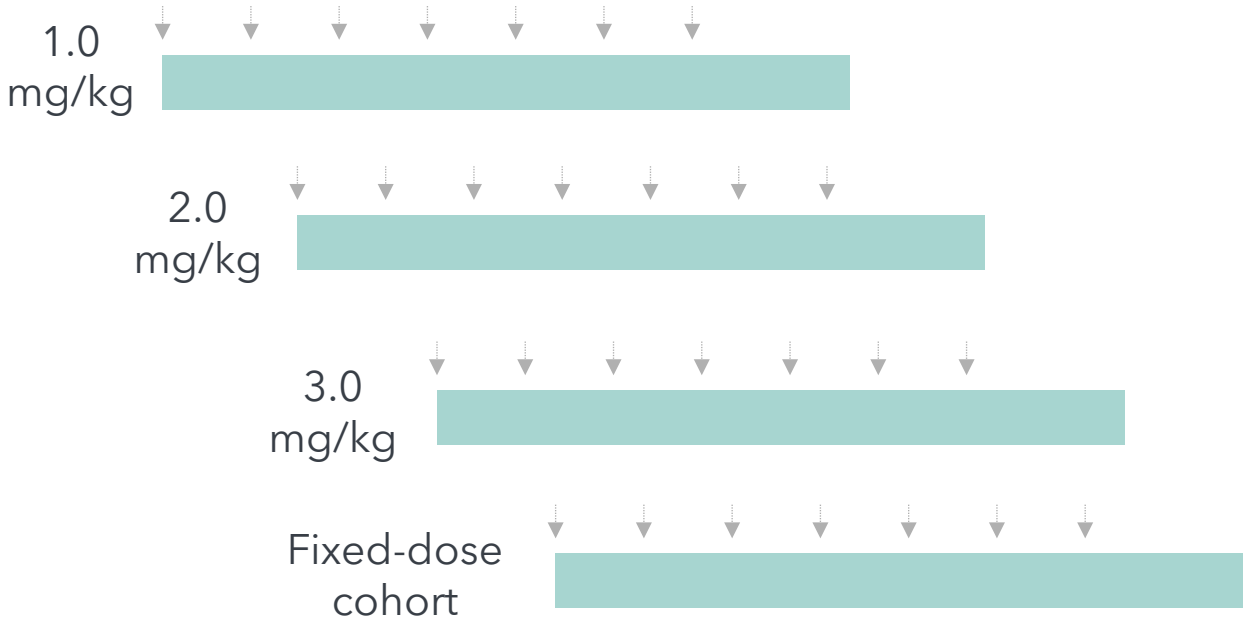
Planned RGLS8429 Clinical Development Based on Accelerated Approval.



TKV = total kidney volume; eGFR = estimated glomerular filtration rate

*Subject to confirmation with FDA

Multiple Ascending Dose in Patients with ADPKD to Evaluate Safety, PK, PD (Biomarkers), eGFR, and TKV.



STUDY DESIGN

- **Cohorts 1-3**
  - ADPKD Patients
    - Mayo Imaging Class 1C, 1D or 1E
    - eGFR 30-90 mL/min
  - 12 subjects per cohort
  - Randomized 3:1 (RGLS8429:Placebo)
  - 3-month dosing (Q2W x 7)
  - Safety, PK, PD/biomarkers, eGFR, TKV, and novel cyst imaging analysis (TCN, TCV and CPSA)
- **Cohort 4**
  - ~16 subjects
  - Open label, single arm fixed dose to compare PD

Cohort 2 topline data on track for Q1 2024

Cohort 3 topline data anticipated mid-2024

EXPECTATIONS

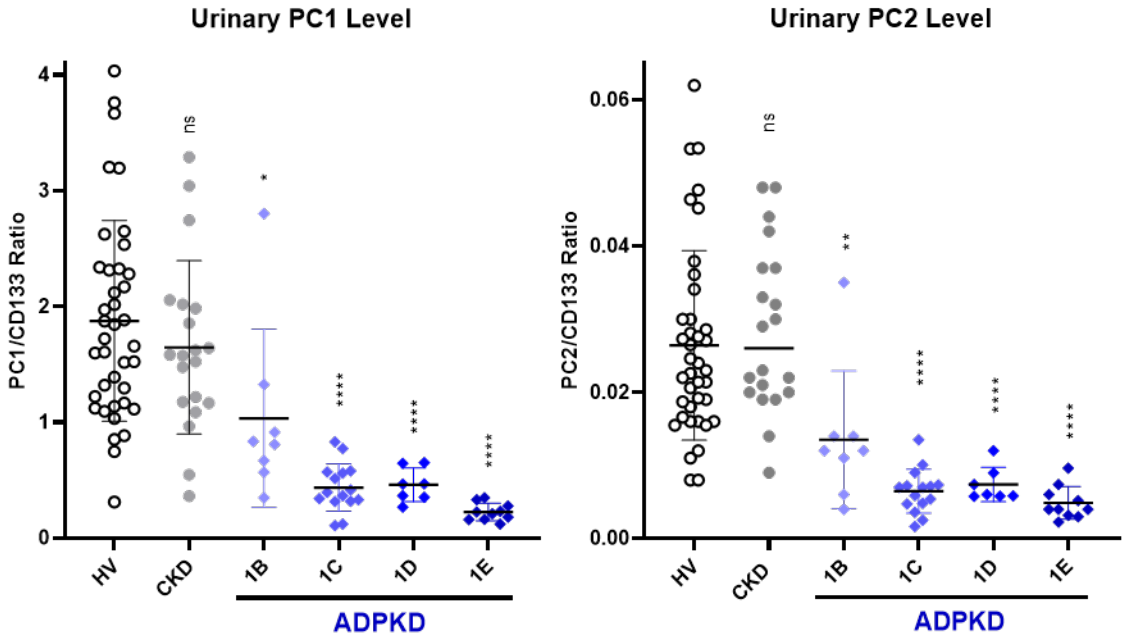
- Clear increase in PC1 & PC2 with dose response
- Experience with using novel imaging markers ahead of Ph2

TCN = total cyst number ; TCV = total cyst volume ; CPSA = cyst-parenchyma surface area

PC1 & PC2 Provide the Key Pharmacodynamic Readout in Phase 1b.

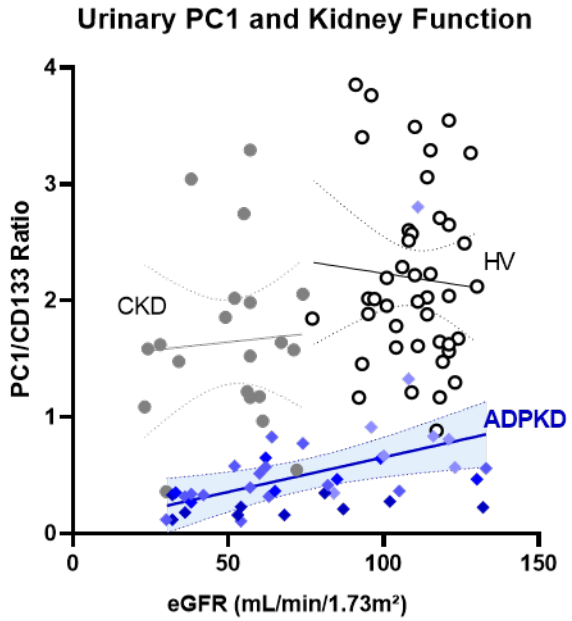
DIRECT MEASURE OF ANTI-miR-17 MOA AND CORRELATION WITH CLINICAL DISEASE

Protein levels inversely correlated with MIC

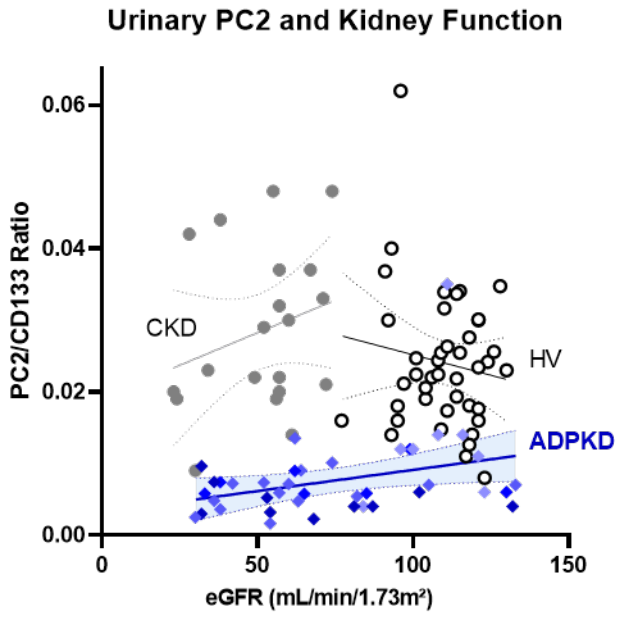


MIC, Mayo Imaging Classification;
Updated from Lee et al. (2022) FASEB-PKD Conference Presentation, Manuscript in preparation;
HV, Healthy volunteers; CKD, Chronic Kidney Disease (non-ADPKD);
*p-values, One-way ANOVA compared to HV with Dunnett's correction

Protein levels correlated with eGFR



Simple Linear Regression (95% CI):
HV: R^2=0.004, p=0.685;
CKD: R^2=0.004, p=0.799;
ADPKD: R^2=0.1735, p=0.008



Simple Linear Regression (95% CI):
HV: R^2=0.020, p=0.369;
CKD: R^2=0.007, p=0.272;
ADPKD: R^2=0.114, p=0.033

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Manuscript in Preparation

Cohort 1: Baseline Characteristics are Balanced Across Groups.

Baseline Characteristics	RGLS8429 N=9	Placebo N=3
Age (years) mean (SD)	52 (12)	42 (13)
Female n (%)	5 (56%)	2 (67%)
White n (%)	9 (100%)	3 (100%)
BMI mean (SD)	30 (5)	30 (4)
Prior tolvaptan use in prior 3 months n (%)	2 (22%)	0
eGFR (mL/min/1.73m$^{2)}$) mean (SD)	47 (20)	42 (9)
htTKV (mL/m) mean (SD)	1698 (737)	2091 (502)
Mayo Class n (%)		
1C/1D/1E	5 (56%) / 3 (33%)/ 1 (11%)	0 / 2 (67%)/ 1 (33%)
Genetic Mutation		
PKD1/PKD2/Other/Negative#	5 (56%) / 3 (33%) / 0/1 (11%)	2* (67%) / 0 /1* (33%)/1 (33%)

*One subject positive for PKD1 and other

#Among all 18 genes within the PKDNext-expanded panel:*COL4A1, GANAB, HNF1B, PKD1, PKD2, PKHD1, PRKCSH, TSC2, NOTCH2, OFD1, SEC61A1, VHL, DNAJB11, IFT140, SEC63, LRP5, ALG8, SEC61B*

Cohort 1 Safety and PK Results.

- Well tolerated
- Majority of TEAEs were Grade 1 or 2
- One SAE of appendicitis not related to study drug
- No clinically significant changes in laboratory values, vitals, and ECGs
- No AE's leading to early withdrawal

- PK results are similar to results seen for RGLS4326
- No accumulation observed in plasma or urine with repeat dosing.
- AUC plasma exposure in patients nearly twice that of healthy volunteers and consistent with ~ 35% reduction in renal excretion.
- Plasma to tissue modeling suggests 1mg/kg is less than half of dose response curve

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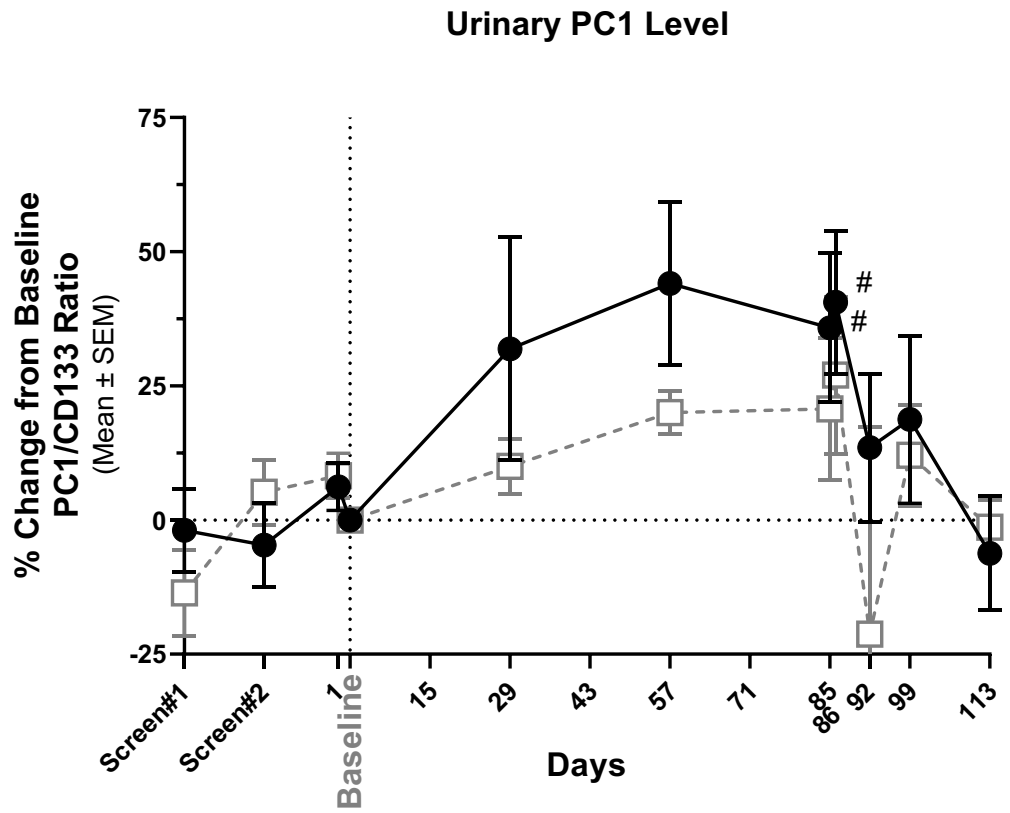
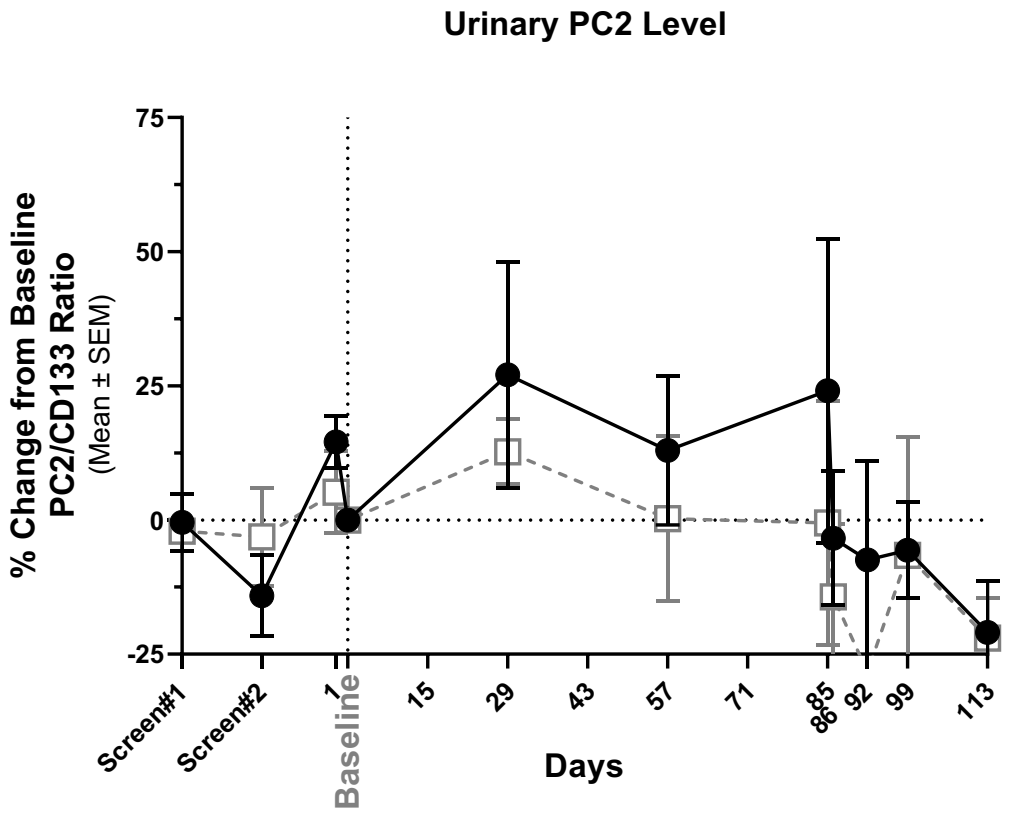
RGLS8429 Phase 1b Cohort 1:
POLYCYSTIN LEVELS INCREASED DURING TREATMENT WITH RGLS8429





● RGLS8429 (1 mg/kg Q2W x7) (Total N=9 subjects, with Mayo Class 1C/1D/1E=5/3/1)
□ Placebo (Q2W x7) (Total N=3 subjects, with Mayo Class 1C/1D/1E=0/2/1)

#, Change from Baseline for RGLS8429; Statistical Significance by Wilcoxon Sign-Ranked Test (alpha=0.05) at Day 85 and Day 86

Planning for Phase 2 and Phase 3.

REGULATORY PRECEDENT FOR ACCELERATED APPROVAL BASED ON PHASE 2 ENDPOINT

FDA has adopted an accelerated approval pathway in ADPKD

- Accelerated approval based on single pivotal trial demonstrating statistically significant reduction in TKV growth compared to placebo
- Requires confirmatory pivotal trial demonstrating statistically significant improvement in eGFR compared to placebo, which is conducted in the post-approval setting
- Multiple sponsors have confirmed this accelerated approval pathway with FDA

Phase 2 trial endpoint: TKV over 12 months

- N~300 subjects; placebo-controlled trial
- MRI for TKV at baseline and 12 months
- Patients continue blinded therapy for an additional 12 months (24 months total) and will contribute to the primary Ph3 endpoint of eGFR

Phase 3 trial endpoint: eGFR over 24 months

- N~600 subjects; placebo-controlled trial
- eGFR measures at baseline and several timepoints over 24 months
- Study begins enrolling pre-NDA and completes in post-approval setting

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Regulus Summary.

Anti-miR-17 approach addresses the key control mechanism of cystogenesis and proliferation in ADPKD

Phase 1b underway with cohort 1 data showing anticipated PD response (PC1 & PC2) and generally safe and well tolerated

Cohort 2 & 3 topline data readouts expected Q1 and mid-year 2024

Probability of RGLS8429 Phase 1b success is high and a streamlined path to approval exists

Significant market opportunity fueled by clear unmet need, targeted population, and orphan drug status

Additional research programs in kidney and CNS where microRNA play pivotal roles in disease pathogenesis

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Corporate Presentation.

January 2024