Re-Purposing Drugs for the Treatment of Polycystic Kidney Disease:

Partnership with the Polycystic Kidney Disease Foundation

PKD Models:  *pcy* and *jck* Mice, PCK Rat

PreClinOmics, Inc.
PKDF Goals

The Accelerating Treatments to Patients (ATP) Initiative

• A comprehensive, integrated research and development program that represents the core of our work.
• ATP was launched in 2010 to speed up development of treatments which could slow or stop the progression of PKD.
  o Scientific Meetings
  o Tissue Donation
  o Core Research Grant
  o **Drug Repurposing**
  o PKD Outcomes Consortium
  o Clinical Trial Awareness Program
• Each of the programs within ATP is important and interconnected.
• PreClinOmics chosen as the preferred CRO for colony maintenance and conduct of efficacy studies.
Rodent Models

- **jck** (C57Bl/6J-nek8jck): a mouse model of slowly progressing renal cystic disease associated with the same gene that causes human nephronophthisis type 9. Renal cysts in this mouse develop in multiple regions of the nephron and is more severe in male mice. These mice are bred at PreClinOmics.

- **pcy (CD-1-pcylusm)**: a mouse model of slowly progressive renal cystic disease associated with the same gene that causes human nephronophthisis type 3. Renal cysts in this mouse initially develop in the collecting tubules but other segments of the nephron become cystic as disease progresses. Male and female mice are similarly affected. These mice are bred at PreClinOmics.

- **PCK (PCK/Crl-Pkhd1pck/Crl)**: a rat model of the slowly progressive form of autosomal recessive PKD with a mutation in the same gene that causes human ARPKD (PKHD1). This model displays significant kidney and liver cyst development similar to most patients with PKD. This allows an evaluation of treatment efficacy for both kidney and liver pathology. (Model maintained at Charles River Labs)

- There are many models of polycystic kidney disease, but the 3 outlined above have been designated the primary models that the PKDF was interested in pursuing based on their collective translational power.
General Study Design: *jck* Mouse

- Male *jck* mice 4 weeks of age
- Body weight and feed intake recorded weekly
- Test substances are administered for 5 weeks (oral gavage or admixed in the diet)
- Endpoints measured:
  - Cyst volume and fibrosis in kidney
  - Kidney weight
  - Serum BUN
  - Concentration of test article in blood
  - Other analyses relevant to cellular mechanism may be included
Reference Compound Validation: *jck* Mouse

- Based on published literature and preliminary in-house work, the CDK inhibitor, roscovitine, was selected as the positive control for all studies in *jck* mice.
- Representative cumulative data obtained with roscovitine in this model are shown below:

![Diagram showing reduction in renal cyst volume with roscovitine](image)

- Roscovitine elicited a significant reduction in renal cyst volume compared to vehicle in *jck* mice.
Study Design: *pcy* Mouse

- Male *pcy* mice 4 weeks of age
- Body weight and feed intake recorded weekly
- Test substances are administered for 10 weeks (admixed in the diet)
- Endpoints measured:
  - Cyst volume and fibrosis in kidney
  - Kidney weight
  - Serum BUN
  - Concentration of test article in blood
  - Other analyses relevant to target may be included
Reference Compound Validation: \textit{pcy} Mice

- Based on published literature and preliminary in-house work, the vasopressin antagonist, tolvaptan, was selected as the positive control for all studies in \textit{pcy} mice.

- Representative cumulative data obtained with tolvaptan in this model are shown below:

- Tolvaptan significantly reduced renal cyst volume compared to vehicle in \textit{pcy} mice.
General Study Design: PCK Rat

- Male PCK rats 4 weeks of age
- Body weight and feed intake recorded weekly
- Compound administered for 12 weeks (oral gavage or admixed in the diet)
- Endpoints measured:
  - Cyst volume and fibrosis in kidney and liver
  - Kidney and liver weight
  - Serum BUN, ALT, AST, Bilirubin
  - Concentration of test substance in blood
  - Other analyses relevant to cellular mechanism may be included
Reference Compound Validation: PCK Rat

- Based on published literature, the PPARγ agonist, pioglitazone, was selected as the positive control for all studies in PCK rat.
- While measures of renal function are included in the study, the primary endpoint is cyst volume quantification by histology.
- Representative cumulative data obtained with pioglitazone in this model are shown below:

- Pioglitazone induces a significant reduction in renal cyst volume compared to vehicle in PCK rats.