Asyst Therapeutics

Transformative therapies for polycystic kidney disease

A small molecule drug candidate targeting the Ire1α-XBP1 pathway for treatment of polycystic kidney disease

Yale SCHOOL OF MEDICINE

Building a company focused on developing paradigm shifting strategies for ADPKD

- **Founded on unique insights into ADPKD biology**
  - Ire1-Xbp1 ER stress pathway is critical for the viability of cystic cells
  - Finding that is potentially synergistic with other strategies

- **Lead compound partially de-risked**
  - No adverse events in limited human trial
  - Efficacy demonstrated in two independent orthologous ADPKD mouse models
  - Method of use patent filed

Team

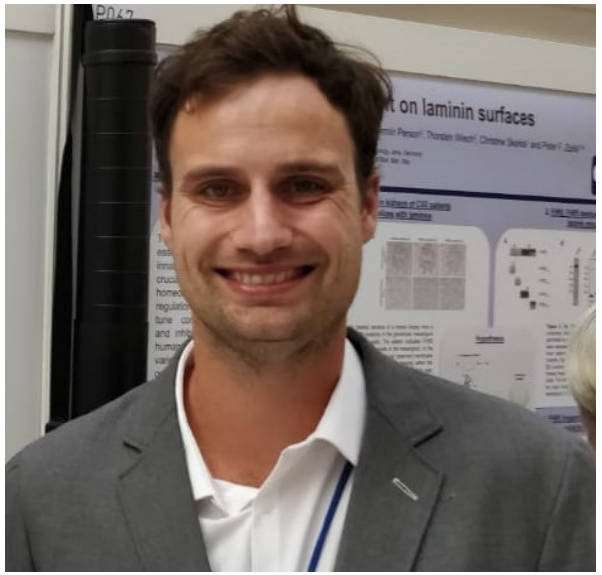
Stefan Somlo, MD

C.N.H Long Professor of Medicine and Genetics

Chief, Section of Nephrology

Sorin Fedeles, PhD, MBA

Research Faculty



Matteus Krappitz, MD, Dr. med.

Nephrologist

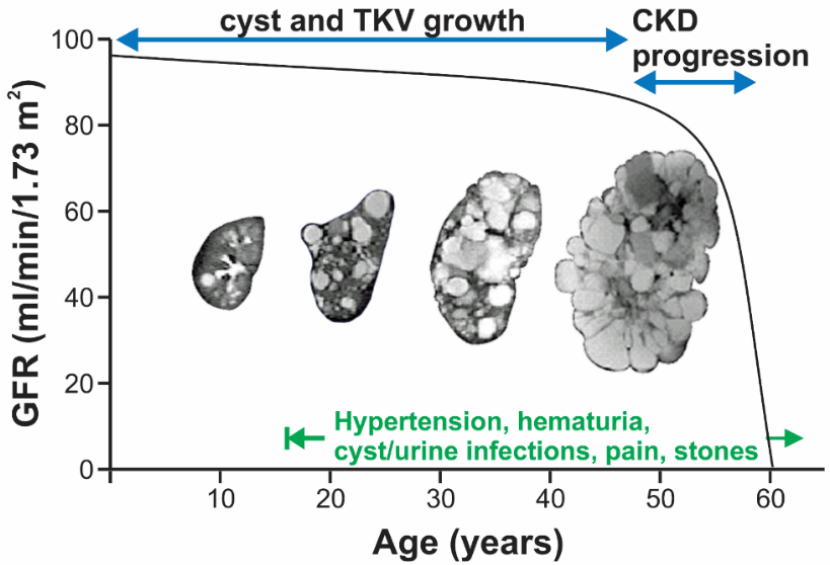
Rachel Gallagher, PhD

Research Faculty

Our team has extensive expertise in genetics, polycystic diseases, clinical nephrology, and performing translational research with transformative potential

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

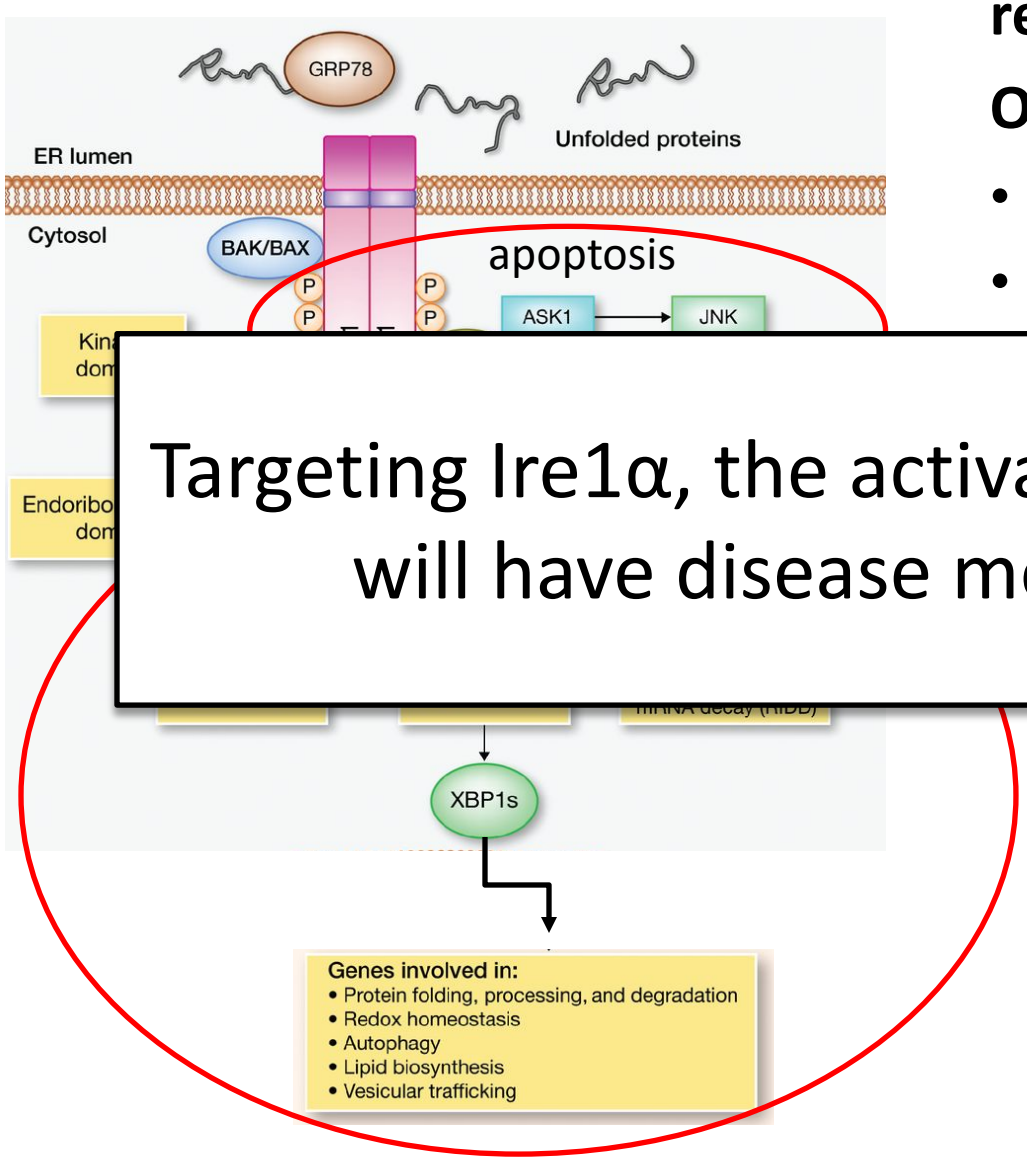
- ADPKD affects >600,000 in US population; 12.5 M worldwide
- ~4% of prevalent End-Stage Renal Disease (ESRD)
- ADPKD has **orphan condition designation** (2012) with estimated prevalence in US 1:2,000



One **approved therapy**: Tolvaptan (Jinarc) – approved April, 2018

- Targets low level proliferation and secretion in cysts originating from collecting duct
- **Limitations:**
  - Uncertain long-term efficacy
  - Adverse effects: liver toxicity (Hy's law), polydipsia/polyuria (~6L/day)
  - Not tolerated by all patients
  - Only indicated for patients at high risk for rapid progression

Ire1-XBP1 pathway

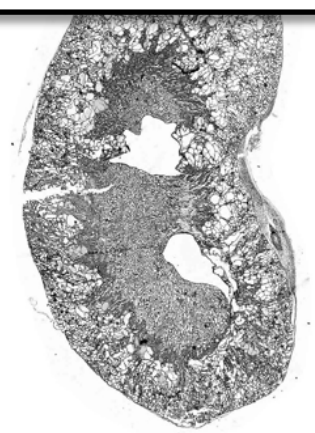


Ire1α activates XBP1 as part of the unfolded protein response (UPR)

Our research has shown that:

- XBP1 is **not** required for kidney homeostasis
- XBP1 is **not** upregulated in ADPKD models

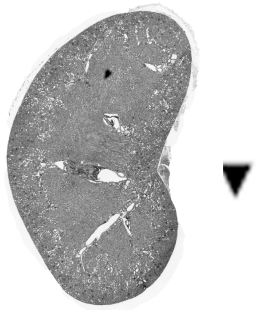
Targeting Ire1α, the activator of XBP1, with small molecules will have disease modifying outcomes in ADPKD



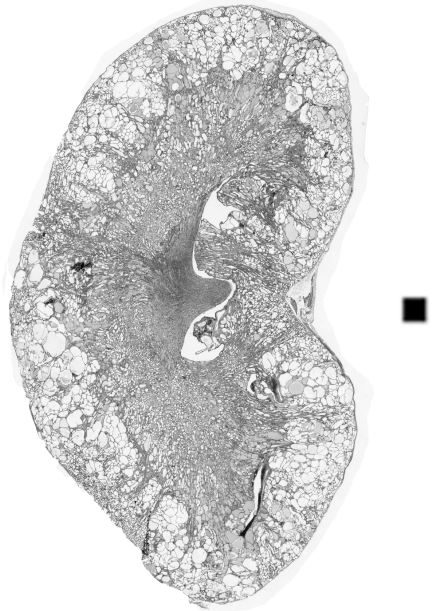
Ire1α inhibitor prevents cyst growth in preclinical models (1)

- Prevented cysts in preclinical studies with orthologous gene models of ADPKD
  - Early onset rapid model (data not shown)
  - Adult onset with PC1 missense mutation in trans with loss of function

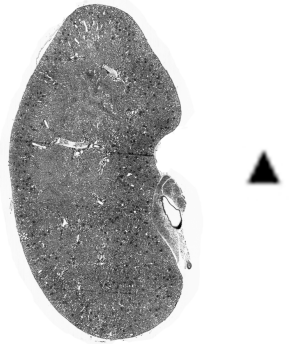
Wild type



***Pkd1* adult cystic model**



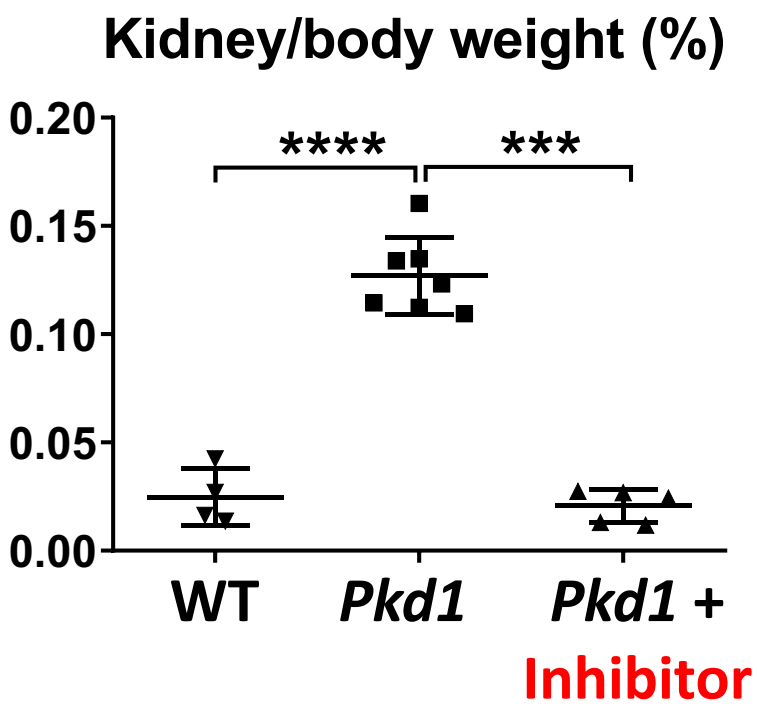
***Pkd1* adult model + Inhibitor**

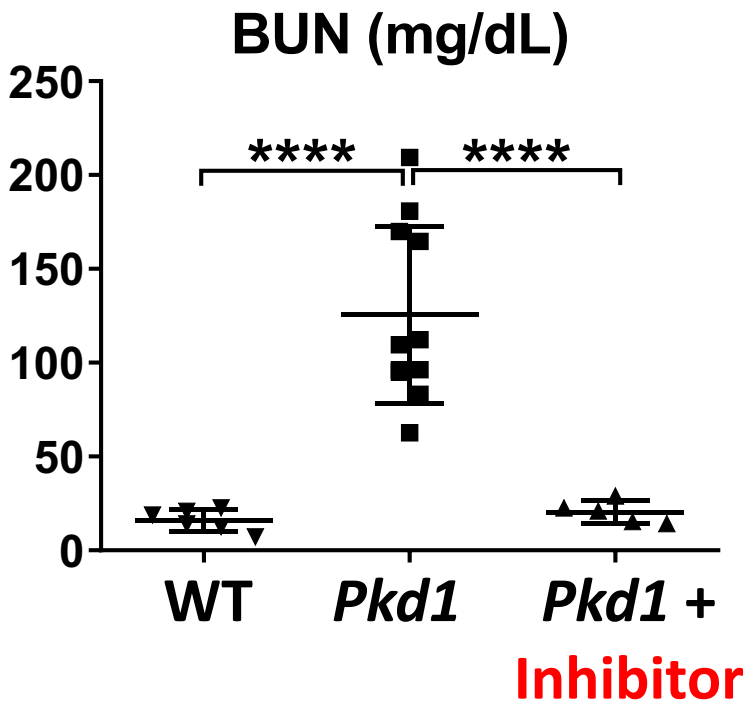


Inhibitor:
0.5 mg/kg IP
once every 2 weeks
from 6-18 weeks age

Ire1α inhibitor prevents cyst growth in preclinical models (2)

- No apparent systemic toxicity (body weight)
- Reduced cyst growth (kidney/body weight ratio)
- Normalized kidney function (blood urea nitrogen [BUN])
- Enhanced apoptosis specifically in cyst cells with PC1 mutation

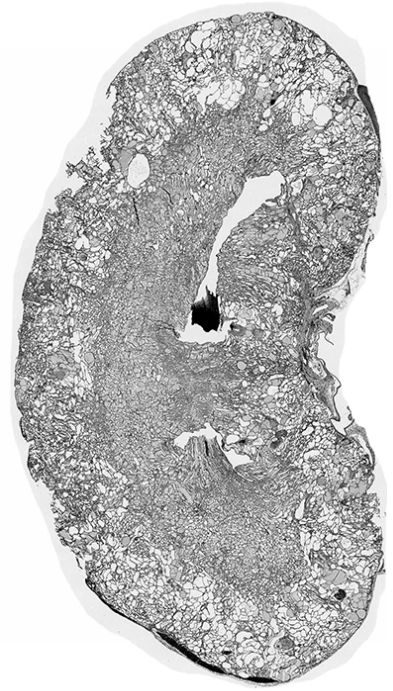




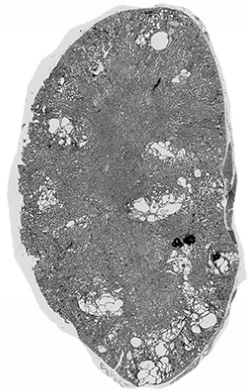
Ire1α inhibitor improves disease progression in a second adult ADPKD model

- Adult onset model with complete loss of function
- Treatment started immediately after gene inactivation (from 6 to 18 weeks)

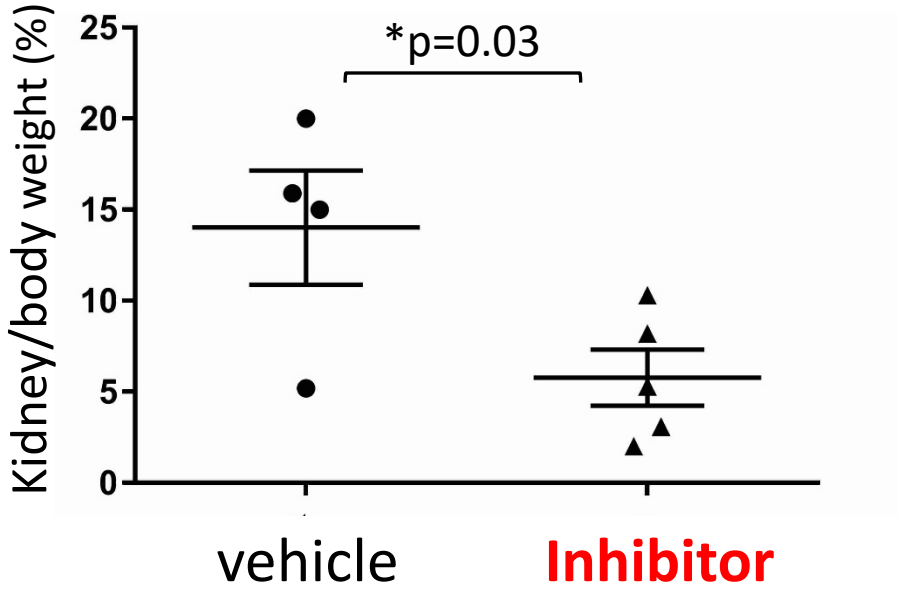
Vehicle



Inhibitor



Inhibitor: 0.5 mg/kg IP, 1x/week



Ire1α inhibitor has a better preclinical profile than Tolvaptan

	Ire1α inhibitor	Tolvaptan
Cysts start by somatic second hit mutations Cyst cells are recessive for PKD genes	Specifically targets cyst cells for apoptosis with no effect on heterozygous non-cyst cells	Reduced proliferation and/or secretion in cysts Aquaresis in normal collecting duct
Adult preclinical animal models	Adult ADPKD model (Pkd1RW/flox) 12 weeks of treatment 18 week-old at sacrifice >75% decrease in KW/BW ratio	Adult ADPKD model (Pkd1RC/RC) 20 week treatment 24 week-old at sacrifice ~24% decrease in KW/BW ratio [Hopp et al, 2015, JASN]

Current Development Plan

Activity	Cost	Time (months)
Develop lead molecule through CRO studies for *in vivo* PK/tox	$180,000	12
Medicinal chemistry combined with *in silico* drug design for generating new composition of matter (CRO)	$80,000	6
Test newly generated chemistry in early ADPKD models in-house	$40,000	6

Contact information

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