Asyst Therapeutics

Transformative therapies for polycystic kidney disease

A small molecule drug candidate targeting the Ire1α-XBP1 pathway for treatment of polycystic kidney disease
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-α 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 Ire1-α, the activator of XBP1, with small molecules will have disease modifying outcomes in ADPKD

Genes involved in:
- Protein folding, processing, and degradation
- Redox homeostasis
- Autophagy
- Lipid biosynthesis
- Vesicular trafficking
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)

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

Kidney/body weight (%)

Vehicle

Inhibitor

*p=0.03

[Graph showing kidney/body weight comparison between vehicle and inhibitor]
Ire1α inhibitor has a better preclinical profile than Tolvaptan

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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cost</th>
<th>Time (months)</th>
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<tbody>
<tr>
<td>Develop lead molecule through CRO studies for <em>in vivo</em> PK/tox</td>
<td>$180,000</td>
<td>12</td>
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<tr>
<td>Medicinal chemistry combined with <em>in silico</em> drug design for generating new composition of matter (CRO)</td>
<td>$80,000</td>
<td>6</td>
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<tr>
<td>Test newly generated chemistry in early ADPKD models in-house</td>
<td>$40,000</td>
<td>6</td>
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Contact information

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