Clinical Candidate CP-011 for Wolfram Syndrome

- Lethal orphan indication with no therapeutic standard of care
- Novel MOA for first-in-class small molecule CP-011
- Animal POC is gating to pre-IND meeting
- Clinical trial for CP-011 possible within 12 months of gating POC
Our Team

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KOL in Wolfram research & clinical trials
Maintains the international patient registry

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Clinical Partner

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Wolfram syndrome, a devastating orphan disease

Typical Disease Trajectory:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Diabetes mellitus</th>
<th>Neurodegeneration</th>
<th>Neurological losses</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blindness</td>
<td>Deafness</td>
<td></td>
</tr>
<tr>
<td><strong>Age (Yrs)</strong></td>
<td><strong>6</strong></td>
<td><strong>6-15</strong></td>
<td><strong>10-30</strong></td>
<td><strong>30</strong></td>
</tr>
<tr>
<td><strong>Current SOC</strong></td>
<td>Insulin</td>
<td>Glasses &amp; Hearing aids</td>
<td>Urinary catheter But no other Rx</td>
<td></td>
</tr>
</tbody>
</table>

Example patient: diagnosed with Wolfram syndrome at 7
He is insulin-dependent and has worsening vision and hearing, bladder issues requiring an indwelling catheter, aggression, anxiety, and obsessive thoughts.

Homozygous mutations = Disease: ~15,000 pts in US + EU
- Neurodegenerative disease
- Multisystem organ failure

Estimated societal costs are $3B/year
No disease-modifying therapy

Current clinical trials are for toxic agents or have unclear mechanisms of efficacy

- dantrolene sodium (NCT02829268 - recruiting):
  - Repurposed drug, severe liver toxicity
  - PI: Dr. Urano, University of Washington, St Louis

- sodium valproate (NCT03717909 - recruiting):
  - Repurposed drug, GABA modulator, unclear mechanism of efficacy
  - PI: Dr. Barrett, University of Birmingham, UK

Current trials validate clinical endpoints and trial design

CenterPharm biology reveals potential market expansion to Wolfram carriers’ genetically-defined mood disorders

1% population - attenuated symptoms, primarily mood disorders
CP-011 Novel MOA – Neuronal Calcium Sensor 1 (NCS1)

Healthy

Endoplasmic Reticulum
Physiological $\text{Ca}^{2+}$ homeostasis

NCS1 is a calcium sensor
WFS1 = wolframin

Wolfram Syndrome

Endoplasmic Reticulum
Disrupted $\text{Ca}^{2+}$ homeostasis

Loss of NCS1 $\rightarrow$ $\text{Ca}^{2+}$ dysregulation $\rightarrow$ Disease

Our strategy

Endoplasmic Reticulum
Stabilized $\text{Ca}^{2+}$ homeostasis

NCS1 is protected

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Validation of role of NCS1 in Wolfram syndrome

**WFS1 KO (Wolfram syndrome) mouse brain has low NCS1**

**WFS1 KO cells have attenuated Ca\(^{2+}\) response to acute glucose**

**NCS1 protein level responds to chronic glucose challenge**

**Western blot**

McLeod, Nguyen, Ehrlich, 2019

**Intracellular Ca\(^{2+}\) transients**

Nguyen, Ehrlich, 2019

**Western blot quantified**

Fischer, Nguyen, Ehrlich, 2019

WFS1 = wolframin

NCS1 = neuronal calcium sensor 1

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CP-011: Validated candidate for Wolfram syndrome Rx

In normal cells, wolframin protects NCS1 from calpain cleavage

CP-011 protects cells from high glucose-induced death
Clinical biomarker of early efficacy: blood glucose

IP Status: Yale patent appl. filed for CP-011 use expires 2039

CP-001: positive control

CP-011 = clinical candidate meets 1st in class oral TPP criteria (Kd < 500 nM)

CP-012 = ineffective analog of CP-011
In normal cells wolframin protects NCS1 from calpain cleavage.


CP-011 = clinical candidate meets 1st in class oral TPP criteria (Kd < 500 nM)

CP-012 = ineffective analog of CP-011

IP Status: Yale patent appl. filed for CP-011 use expires 2039.
Total of $300K for IND-enabling CRO work → ~18 months to filing IND

Now

- Assay development
- Target validation
- CP-011 Clinical candidate

Additionally...
- Clinical collaboration initiated
- Molecular target crystalized
- Animal model selected
- Clinical biomarkers identified
- Clinical endpoints established
- Regulatory exclusivity strategy identified

12 months
- Wolfram mouse in vivo validation of CP-011 MOA completion $250K

15-18 months
- Pre-IND regulatory activity, pre-IND meeting for CP-011 $50K

18-20 months
- Series A Funding File IND for Dr. Urano-led Phase 1b/2a of CP-011

24 months
- Interim indication of efficacy

36 months
- Analysis of clinical response to CP-011

Partnering

- **Commercial Interest:**
  - Bio2018 & Bio2019: 27 Non-Confidential Meetings
  - Multiple confidential follow-ups/meetings with 5 Pharma/biotechs – all waiting for in vivo results