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

Barbara E Ehrlich, PhD

Professor of
Pharmacology
Yale University

Science Lead
Expert in calcium signaling
and regulation by NCS1

barbara.ehrlich@yale.edu

Zhiyao Lu, PhD

Blavatnik Fellow in Life
Science Entrepreneurship

Operations

zhiyao.lu@yale.edu

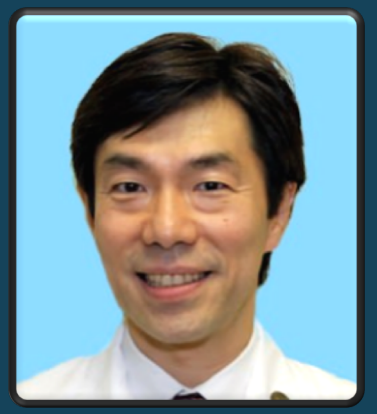
David Lewin, PhD

Sr. Assoc. Dir. Bus. Dev.
Yale, OCR

Advisor/IP Management

david.lewin@yale.edu

Clinical Partner



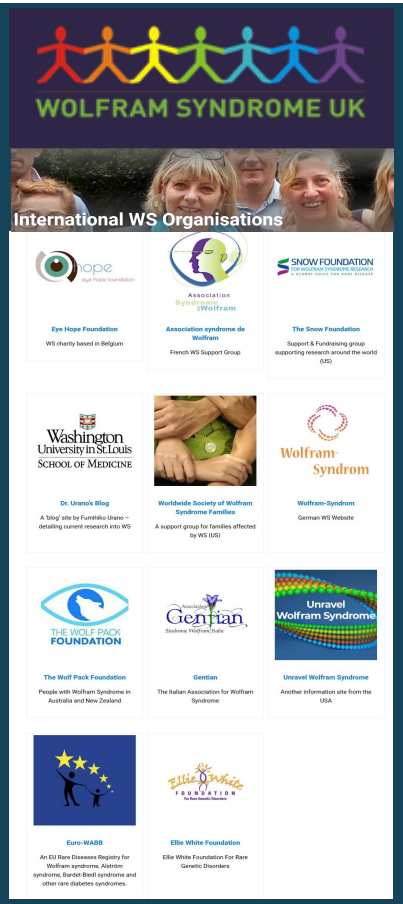
Fumihiko Urano, MD, PhD

Professor of Medicine at
Washington University in St. Louis

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

Wolfram syndrome, a devastating orphan disease

SNOW FOUNDATION FOR WOLFRAM SYNDROME RESEARCH
A GLOBAL VOICE FOR RARE DISEASE



Global Patient Advocacy

Typical Disease Trajectory:

Symptom	Diabetes mellitus	Neurodegeneration Blindness Deafness	Neurological losses	Death
Age (Yrs)	6	6-15	10-30	30
Current SOC	Insulin	Glasses & Hearing aids	Urinary catheter But no other Rx	

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

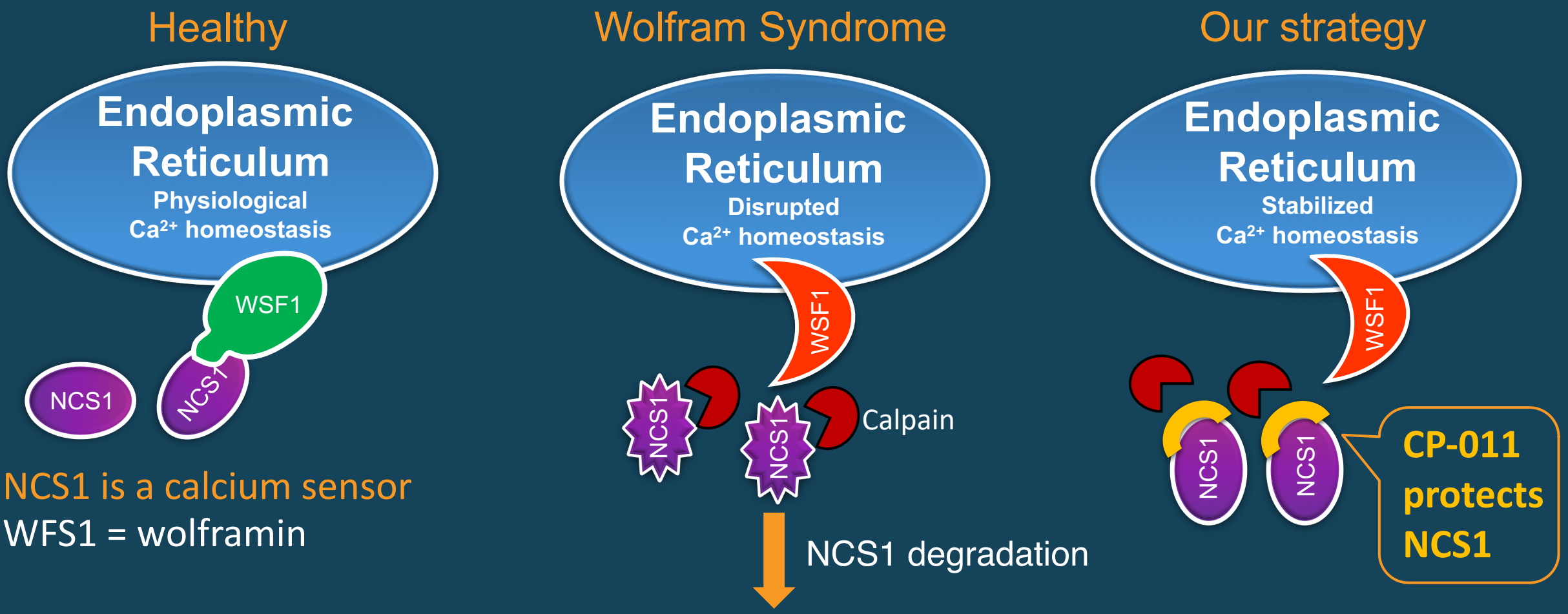
× sodium valproate (NCT03717909 - recruiting):
- Repurposed drug, GABA modulator, unclear mechanism of efficacy
- PI: Dr. Barrett, University of Birmingham, UK

✓ 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)



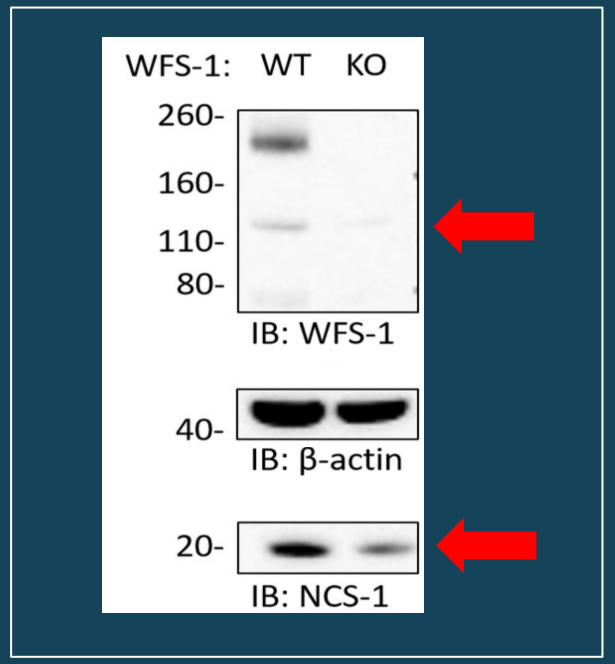
NCS1 is a calcium sensor

WFS1 = wolframin

Loss of NCS1 →Ca^{2+} dysregulation → Disease

Validation of role of NCS1 in Wolfram syndrome

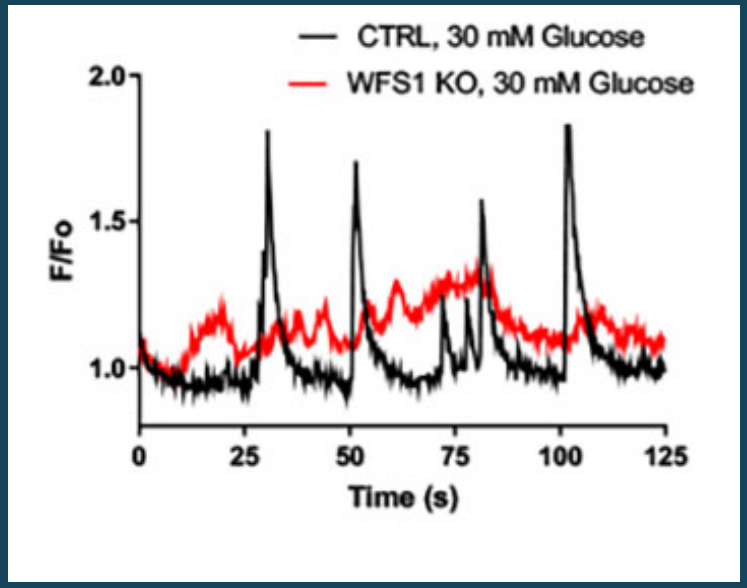
WFS1 KO (Wolfram syndrome) mouse brain has low NCS1



Western blot

McLeod, Nguyen, Ehrlich, 2019

WFS1 KO cells have attenuated Ca^{2+} response to acute glucose

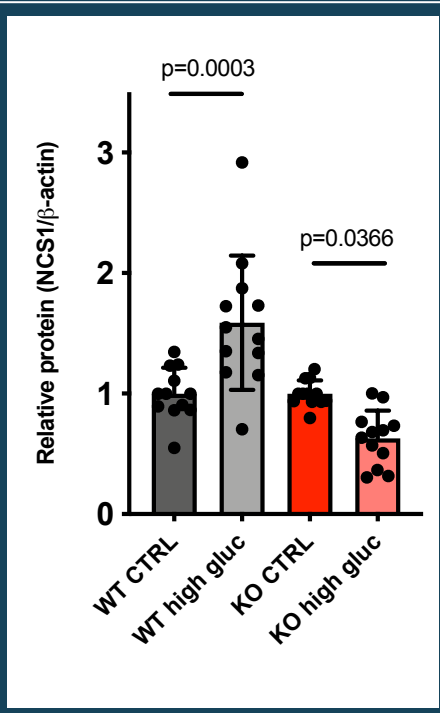


Intracellular Ca^{2+} transients

Nguyen, Ehrlich, 2019

WFS1 = wolframin
NCS1 = neuronal calcium sensor 1

NCS1 protein level responds to chronic glucose challenge

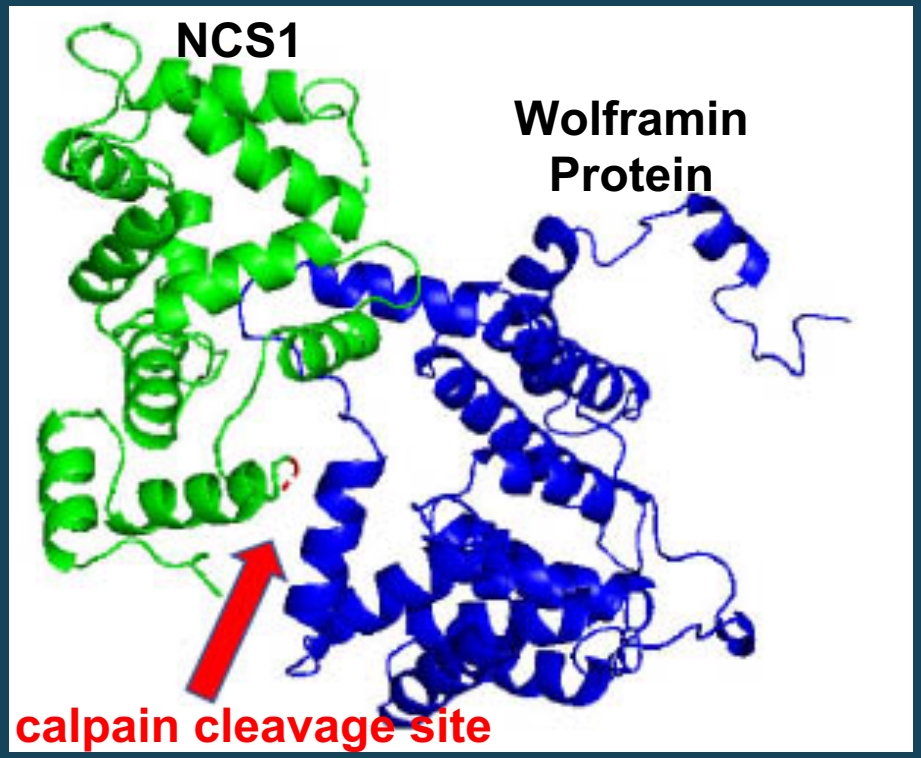


Western blot quantified

Fischer, Nguyen, Ehrlich, 2019

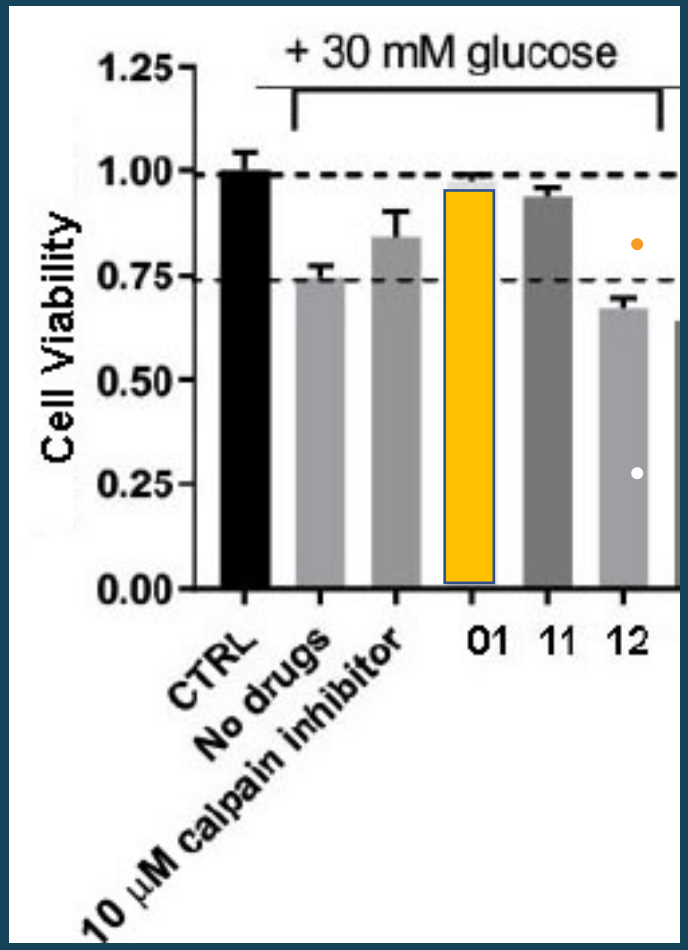
CP-011: Validated candidate for Wolfram syndrome Rx

In normal cells, wolframin protects NCS1 from calpain cleavage



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

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



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

CP-011: Validated candidate for Wolfram syndrome Rx

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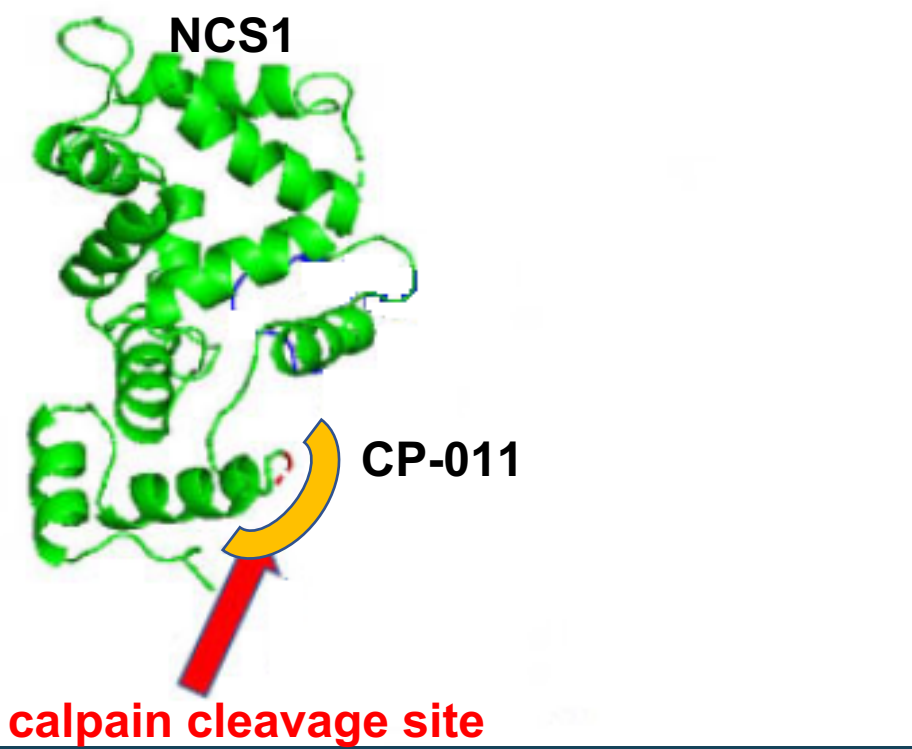

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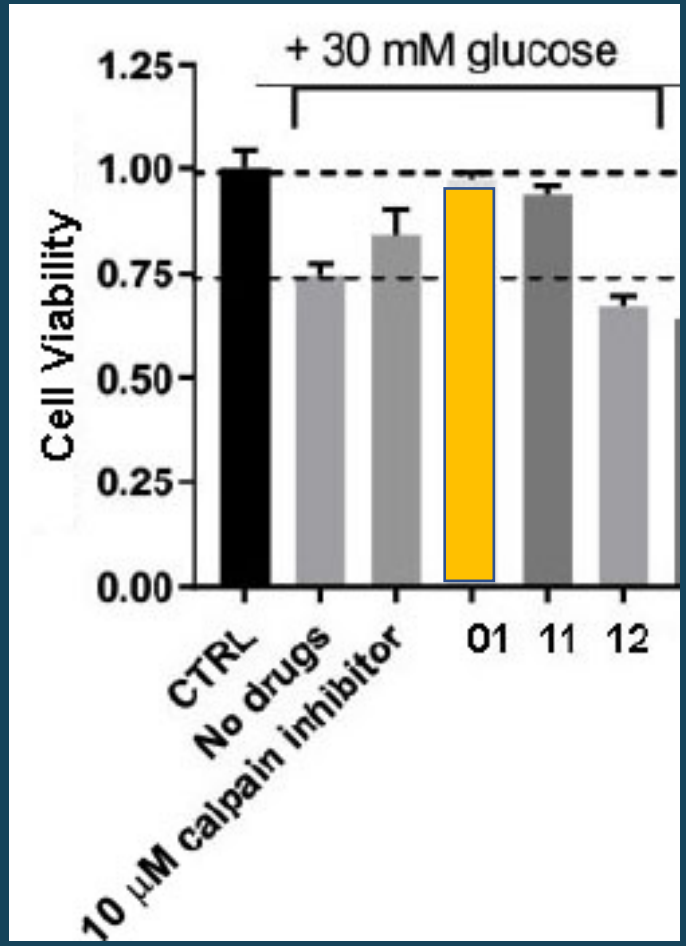

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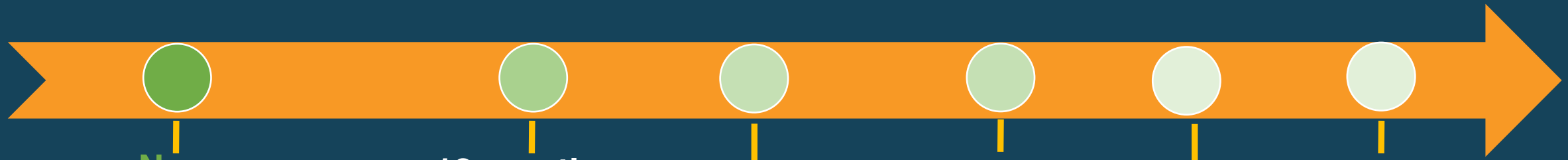
Total of **$300K** for IND-enabling CRO work → **~18 months to filing IND**



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