NCS1- A New Target for Wolfram Syndrome

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Orphan Indication - Wolfram Syndrome*

- Wolfram syndrome = fatal genetic disorder
- Homozygous patients
  - Incidence 1:200,000 in North America
  - Blindness, deafness, mood disorders
  - Death in early 30’s
- Heterozygous patients –
  1% of US, 8-fold higher mood disorders
- No available treatment – palliative care only
  Potential market - $500 million

*DIDMOAD syndrome
*Diabetes insipidus-diabetes mellitus-optic atrophy-deafness syndrome
Neuronal Calcium Sensor 1 (NCS1) is Degraded in Wolfram Syndrome

- NCS1 is low in Wolfram Syndrome patients
- Loss of NCS1 decreases cell signaling and behavior
- Candidate drugs re-set NCS1 cell signaling and behavior

Behavioral testing in mice

Control | Depressed Behavior | Treatment Goal

NCS1 is a Druggable Target
NCS1 is a Target for Structure Based Drug Design

- Crystal structure is known
- NCS1 functionally binds drugs at defined sites

Immediate Starting Points for Medicinal Chemistry
Critical Binding Residues Identified

- Green = NCS-1, pink residue = AA₁
- Yellow/orange = InsP3R1 (1-225), red residues = AA₂ & AA₃

Protein-protein Interaction

split renilla luminescence assay

Proteins that bind: wolframin, InsP3 receptor, dopamine receptor

NCS1 functionally binds proteins at defined sites

Nguyen and Ehrlich, in preparation 2018
Boehrmerle et al, PNAS 2006
Target Product Profile (TPP) and in vivo Validation

Drug Properties
- Maintain NCS1 levels and function
- Oral use
- Non-toxic and safe for long term use
- Cross blood brain barrier
- Membrane permeable

Drug Validation
- Path to optimize drug lead is established
- WFS1 and NCS1 knock out mice are available for validation
Milestones and Funding Plan

**Award/Grant Funding**
- Candidate Drugs
- Structure Based Design
- HTS & Virtual Screens

  **Objective 1**
  - Lead compounds

**Seed Funding**
- Lead Identification
- Lead Qualification

  **Objective 2**
  - Cell assays
  - Mouse assays

  **Objective 3**
  - 18-24 months

**Series A/Partner Funding**
- Lead Optimization
- IND Enabling

  **IND Candidate**
  - 24 months

  **Open IND**
  - 18 months
Competitive Landscape

- No available treatment – palliative care only
- **First in class drug** for Wolfram Syndrome
- Suitable for orphan disease application (approx. 1000 patients in US)
- **Market expansion to carriers of mutation with mood disorders**
6 million adults in US have BP = severe mood swings
1 in 5 commits suicide
NCS1 levels affected in BP
All available BP drugs: toxic, poor efficacy, or both
Current trials lack novel compounds, mainly drug combinations
Global bipolar market valued at $5 Billion in 2016

https://www.grandviewresearch.com
Our new compound will treat Wolfram Syndrome and mood disorders
NCS1- A New Target for Wolfram Syndrome

Center Pharm

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Impact: 1. First in class drug for orphan disease
2. Novel treatment for mood disorders
   (millions of sufferers)

Potential Market: $500 million in 5 years for orphan disease
$5 billion per year for mood disorders
Prize money will be spent on registration to attend an industry conference for example, Bio2018 (Boston; early June)
I will have the opportunity to meet with companies to discuss partnering