NCS1- A New Target for Mood Disorders

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Bipolar Disorder = severe mood swings

- ~6 million adults in US have bipolar disorder
- 1 in 5 commits suicide
- Lithium works but there are serious safety issues
Wolfram syndrome = fatal genetic disorder

- Homozygous mutation –
  - Incidence 1:100,000 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

* DIDMOAD syndrome
* Diabetes insipidus-diabetes mellitus-optic atrophy-deafness syndrome
Neuronal Calcium Sensor 1 (NCS1) Is a Target for New Drugs

NCS1 is disregulated in disease
- NCS1 is high in the brain of bipolar disorder patients
- NCS1 is low in Wolfram Syndrome patients

The Goal is to develop drugs that maintain the balance

Gain of function
- High NCS1

Loss of function
- Low NCS1

stable NCS1 levels
- normal cell signaling
- normal cognition
NCS1 is a Target for Drugs by Candidate Approach

- Crystal structure is known
- NCS1 binds proteins at defined sites and influence function
- **Candidate drugs bind and influence function**
  - Paclitaxel degrades NCS1 function
  - Lithium maintains NCS1 function

**NCS1 is Druggable**

NCS1 crystal structure with paclitaxel docked in binding pocket
NCS1 is a Target for Structure Based Drug Design

NCS1 functionally binds drugs at defined sites

Valproate  Ibudilast  Vincristine  Paclitaxel

Immediate Starting Point for Medicinal Chemistry
NCS1 is a Target for High Throughput Screening (HTS)

NCS1 functionally binds proteins at defined sites
Proteins that bind: InsP3 receptor, dopamine receptor, wolframin

Critical binding residues identified

Protein-protein Interaction
split renilla luminescence assay

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

LgBiT
17.6 kDa

SmBiT
11 aa

Structural complementation gives a bright,
luminescent enzyme

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

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

Drug Validation
- Path to optimized lead is established
- NCS1 and WFS1 knock out mice are available for validation

NCS1 crystal structure with paclitaxel docked in binding pocket
Functional assays in cells and mice

Calcium signals in cells

Drug resets response

Behavioral testing in mice

Anxiety – open field test
Memory - Novel object recognition test
Depression - forced-swimming test

Schutze and Ehrlich, in preparation 2018
Use of Blavatnik Resources

**Award Funding**
- Candidate drugs
- Structure Based Design
- HTS & Virtual Screens

**Objective 1**
- Lead compounds

**Objective 2**
- Lead Identification

**Objective 3**
- Lead Qualification
- Cell assays
- Mouse assays

**Seed Funding**

18-24 months
Use of Blavatnik Resources
Charles River Proposal

Screen for Lead Compound: $180K, 6 months

- Phase 0: Expression and purification of InsP3R (1-225) protein
- Phase 1: Development and validation of TR-FRET
- Go/No-go decision point
- Phase 2: Pilot screen of 5,000 Lead-like library compounds and 2,200 compound validation set
- Go/No-go decision point
- Phase 3: Primary screen of remaining compounds from the Lead-like library selected from screening (150,000)
- Hit Compound Selection - I
- Phase 4: Hit Confirmation
- Hit Compound Selection - II
- Phase 5: Potency determination as 10-point curves, using TR-FRET assay from Phase 1 LC-MS purity analysis on all compounds tested

Lead testing: $100K, 4 months

- Secondary Assay Testing: NanoBiT and FLIPR assays
- Kinetic solubility
- Hepatic microsomal stability: half-life/intrinsic clearance format (2 species; human and mouse/rat)
- MDR1-MDCK: effective efflux ratio

Post Blavatnik path

- Cellular assay (primary neurons) Ca^{2+} signaling
- In Vivo PK / PD (brain and plasma)
- In Vivo Efficacy
- Non GLP Tox. Study

Quotes obtained from 3 CROs - project is tenable - choices available
Primary goal is clinically feasible
A new and safer compound to treat bipolar disorder

Global bipolar market valued at $5 Billion in 2016

https://www.grandviewresearch.com

Current drugs available: toxic, poor efficacy, or both
Current trials lack novel compounds, mainly drug combinations

Orphan disease application
First in class drug for Wolfram Syndrome
Potential market - $500 million
NCS1 Discovery Process
Post Blavatnik Funding Objectives

**Award/Seed Funding**
- Complete Lead Qualification
  - Acute in vivo Activity
  - Solubility/Permeability
  - Pharmacokinetics
  - Tissue distribution

**Series A/Partner Funding**
- Lead Optimization
  - Indication Specific
  - Optimize Drug Properties
  - Fit to Product Target
  - Possible Orphan

- IND Enabling
  - GLP/GMP Synthesis/Studies
  - Pre-IND Agency Interaction
  - Regulatory Docs

Expression of interest from:
Janssen Pharmaceuticals, CMIC Holdings, Bioasis, Taconic, Osmol Therapeutics
A better treatment for mood disorders

Prevention of chemotherapy induced peripheral neuropathy

Venture Backed with Series A: IND Planned for Q4’18
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Extra slides
Examples where both loss of function (LOF) and gain of function (GOF) lead to disease

Both LOF and GOF lead to disease for:
- K channels (epilepsy or long Q-T arrhythmia)
- RyR channels (muscular dystrophy or heart arrhythmias, malignant hyperthermia)
- SERCA pump (Darier’s Disease, Hailey–Hailey disease or cancer)

Many examples where target can utilize both antagonists and agonists to treat disease
- Estrogen receptor antagonists used to treat cancer
- Estrogen receptor agonists used to treat menopause

Lithium prevents swings into either mania or depression
Screening Cascade: Charles River

**Med Chem**

**HTS**
- TR-FRET Biochemical assay

**Tier 1 ADME**
- kin. sol, R & H Cl\(_{int}\)
- MDCK-MDR1

**Tier 2 ADME**
- R & H PPB, R BTB

**Extended ADME Screening**
- Higher species metabolic stability and PPB, CYP inhibition, cross-species Met ID

**In Vivo Efficacy**

**Critical path: Available at CRL**

**To be outsourced**

**Blavatnik Round 1 Funding**

**Broad Selectivity Screening Panel**
- Mini AMES, MNT*
- CiPA/hERG*
- Pharmaceuticals/PRD*

**Cellular assay (primary neurons) Ca2+ signalling**

**In Vivo PK / PD (brain and plasma)**

**In Vivo PK**

**Non GLP Tox. Study**

**In Vivo Higher Species PK**

**CD Selection Point**
Barbara E. Ehrlich, Ph.D
Professor of Pharmacology
Yale University

Education & Training
Sc.B. Brown University, Providence, RI. (1974)
Iodide transport in choroid plexus epithelium

Ph.D. University of California at Los Angeles (1979)
Lithium transport across membranes and the relationship to bipolar disease

Post-Doctoral Fellow Albert Einstein College of Medicine, Bronx, NY (1980-86)
Properties of cardiac and Paramecium calcium channels

Assistant Professor University of Connecticut, Farmington, CT (1986-1997)
Regulation of intracellular calcium signaling

Professor Yale University, New Haven, CT (1997-present)
Calcium signaling in polycystic kidney disease and peripheral neuropathy

Co-Founder Osmol Therapeutics (2017-present)
Develop pharmaceutical agents to prevent chemotherapy induced peripheral neuropathy
Worked with two VC firms and several Angel Investors
Proven ability to move ideas from the lab to the commercial space
Hypothesis:
An overactive InsP signal transduction pathway underlies mania.

Harwood (2005)
NCS-1 functionally interacts with several signaling pathways
The InsP3R binds to NCS1

NCS1 binds to the InsP3R (ITPR). Residues required for binding are known and calcium responsive

We identified critical residues using in silico docking and tested using biochemical methods

Green = NCS-1, pink residue = AA\textsubscript{1}
Yellow/orange = InsP3R1 (1-225), red residues = AA\textsubscript{2} & AA\textsubscript{3}

We identified critical functions using biochemical methods and cell signaling properties

Nguyen and Ehrlich, in preparation 2018
Boehmerle et al, PNAS 2006
My Battle With Bipolar Disorder

MARIAH CAREY OPENS UP

For the first time, the superstar singer-songwriter reveals her struggle with mental health. Why she kept it hidden for years—and how she’s healing.