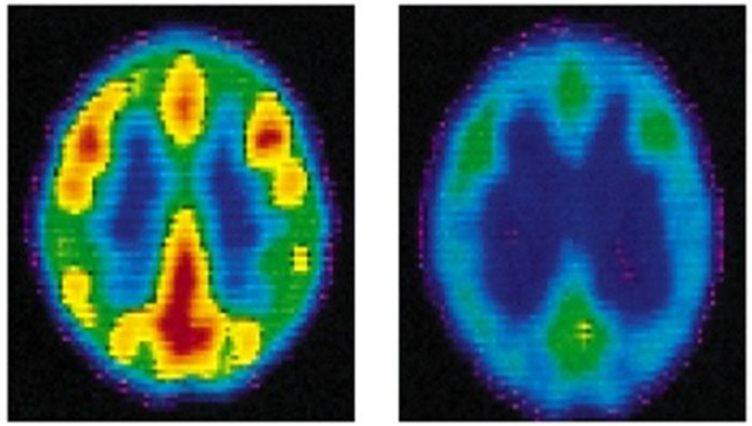
NCS1- A New Target for Mood Disorders

Barbara E. Ehrlich, Professor
Department of Pharmacology
Yale University

Primary Focus - Bipolar Disorder

- 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



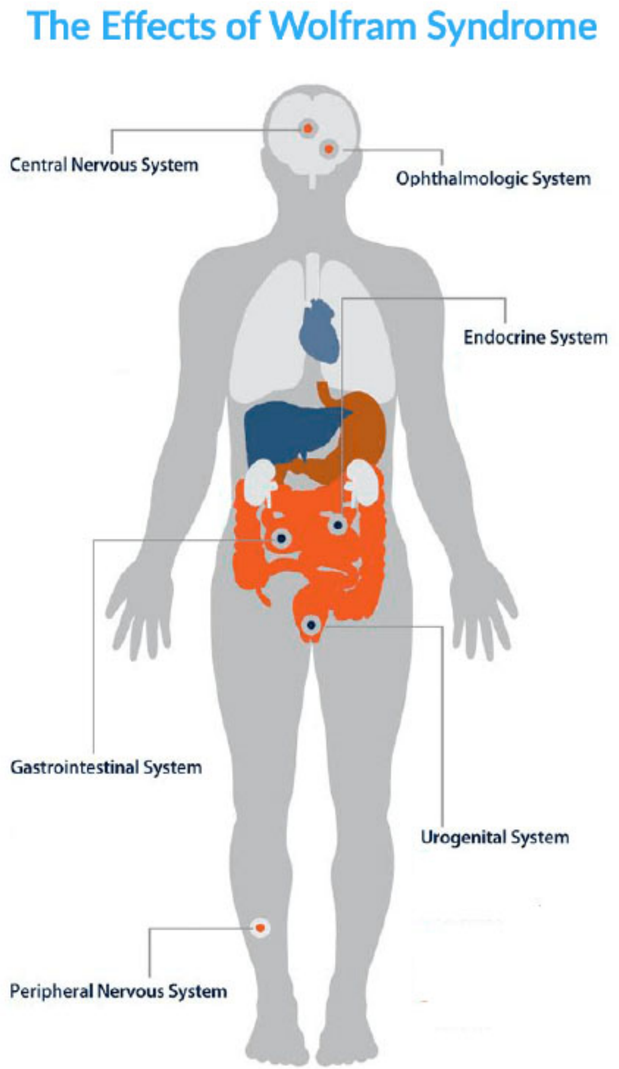
Manic state

Depressed state

Baxter and Phelps, UCLA

Orphan Indication - Wolfram Syndrome*

- 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



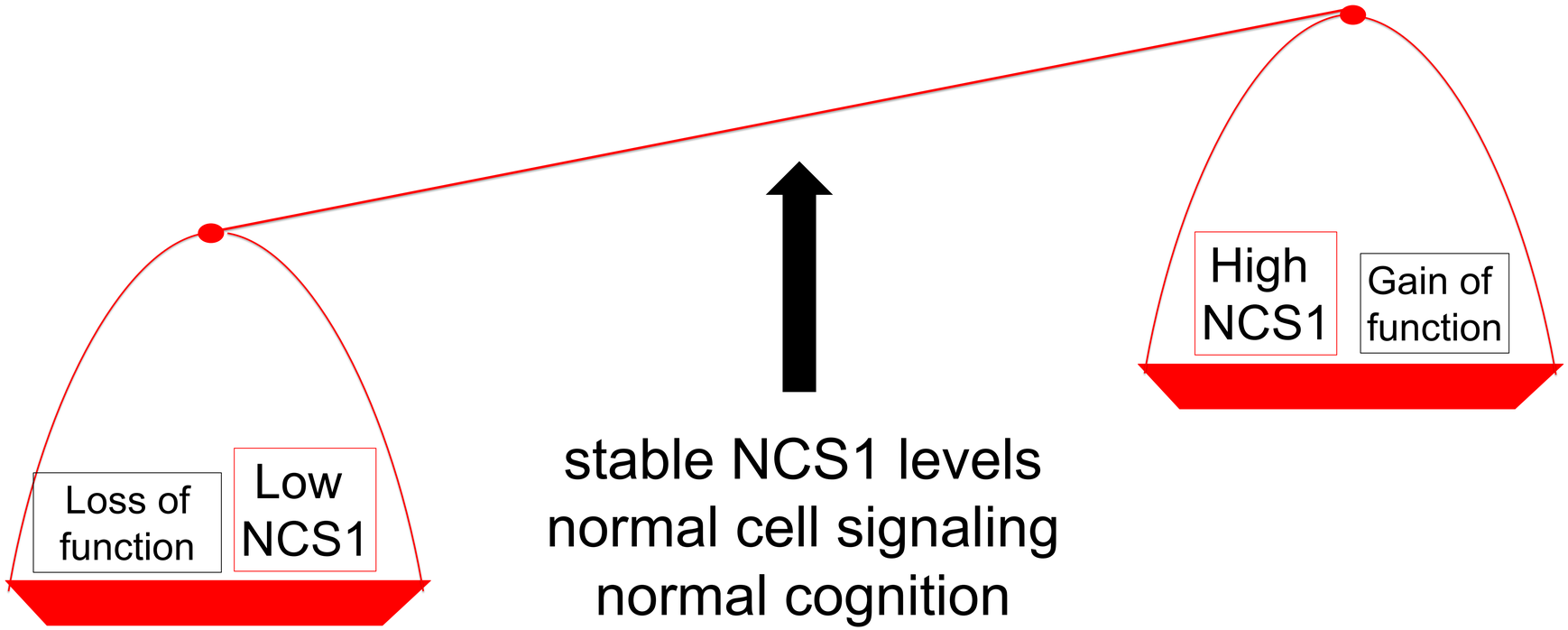
*DIDMOAD syndrome
*Diabetes insipidus-diabetes mellitus-optic atrophy-deafness syndrome

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



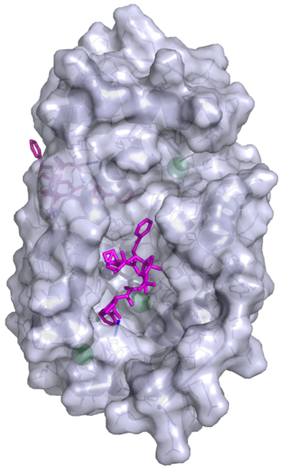
NCS1 is a Target for Drugs by Candidate Approach

- 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

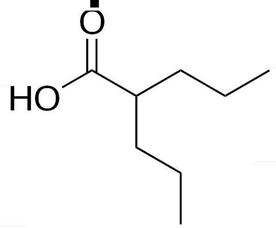


NCS1 crystal structure with paclitaxel docked in binding pocket

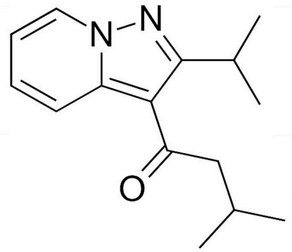
NCS1 is a Target for Structure Based Drug Design

NCS1 functionally binds drugs at defined sites

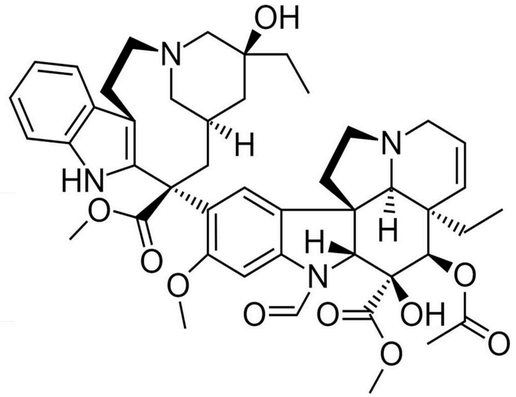
Valproate



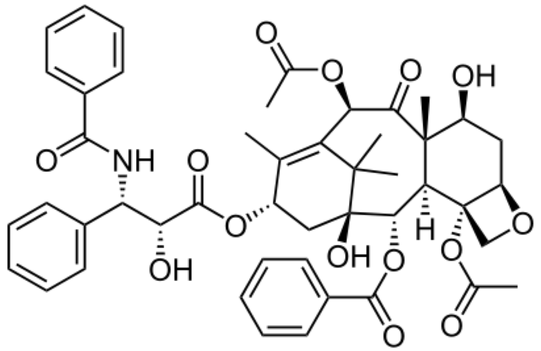
Ibudilast



Vincristine



Paclitaxel



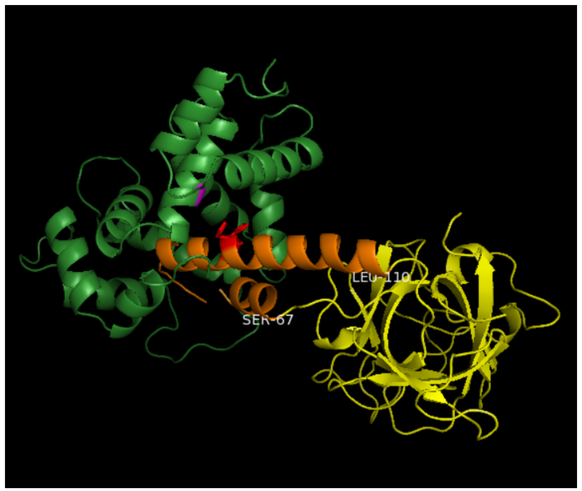
Immediate Starting Point for Medicinal Chemistry

NCS1 is a Target for High Throughput Screening (HTS)

NCS1 functionally binds proteins at defined sites

Proteins that bind: InsP3 receptor, dopamine receptor, wolframin

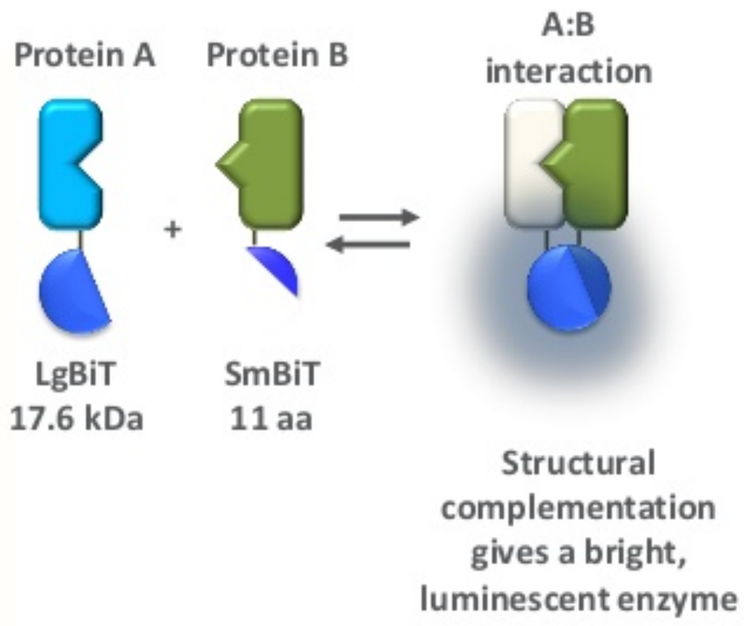
Critical binding residues identified



Green = NCS-1, pink residue = AA_1
Yellow/orange = InsP3R1 (1-225),
red residues = AA_2 & AA_3

Protein-protein Interaction

split renilla luminescence assay

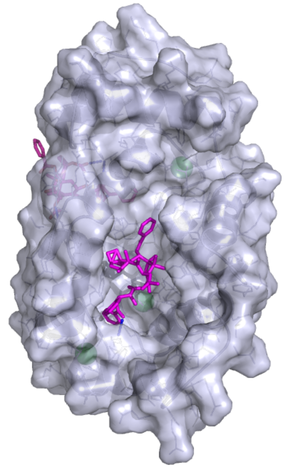


Nguyen and Ehrlich, in preparation 2018
Boehmerle et al, PNAS 2006

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



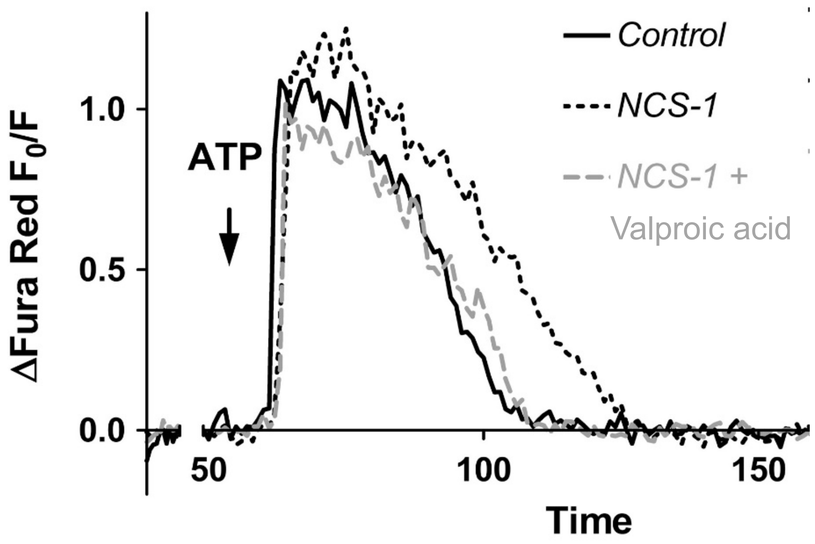
NCS1 crystal structure with paclitaxel docked in binding pocket

Drug Validation

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

Functional assays in cells and mice

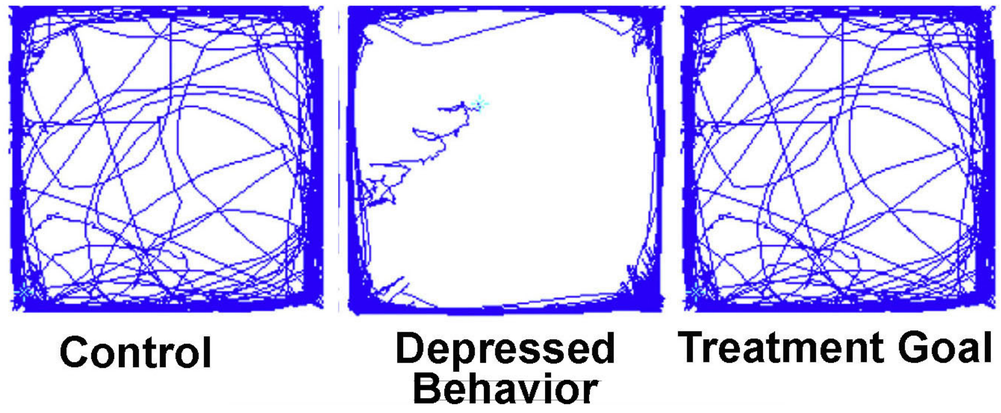
Calcium signals in cells



High NCS1 increases signal

Drug resets response

Behavioral testing in mice



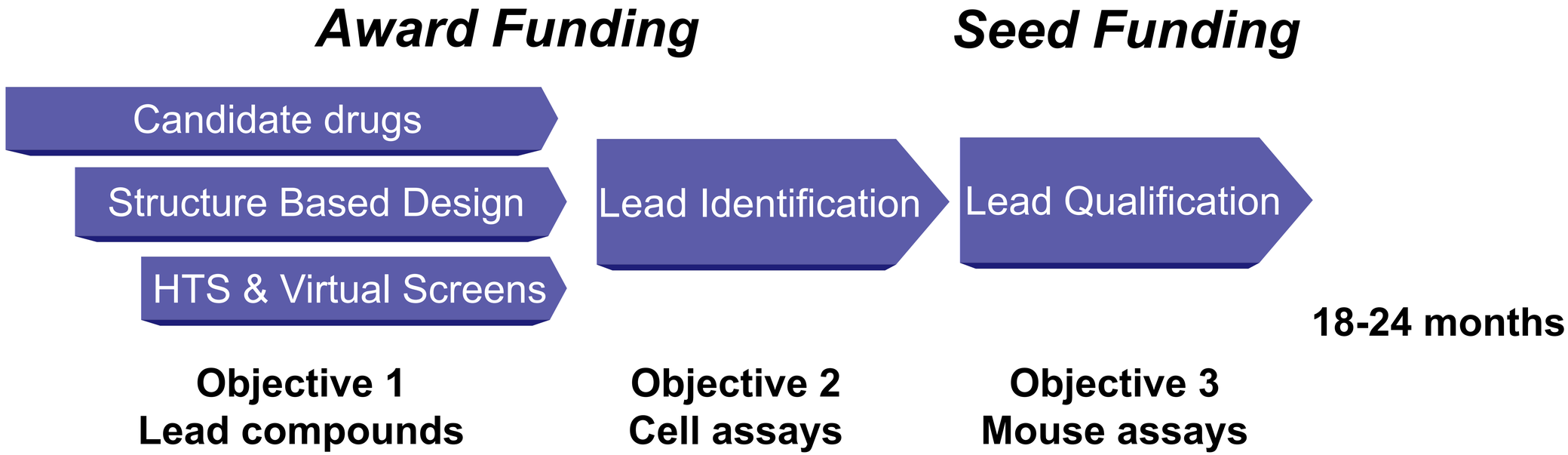
Anxiety – open field test

Memory - Novel object recognition test

Depression - forced-swimming test

Schutze and Ehrlich, in preparation 2018

Use of Blavatnik Resources



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 form 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
- Selection Point

Quotes obtained from 3 CROs

- project is tenable

- choices available

Competitive Landscape

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 ***Series A/Partner Funding***

Expression of interest from:
Janssen Pharmaceuticals, CMIC Holdings, Bioasis, Taconic, Osmol Therapeutics

Barbara E Ehrlich
Professor
Yale University

Co-Founder

OSMOL

A better treatment for mood disorders

Prevention of chemotherapy induced peripheral neuropathy

Venture Backed with Series A: IND Planned for Q4’18

Barbara E. Ehrlich, Professor
Department of Pharmacology
Yale University
333 Cedar St
New Haven, CT 06511-8066

203 737 1158
barbara.ehrlich@yale.edu

Extra slides

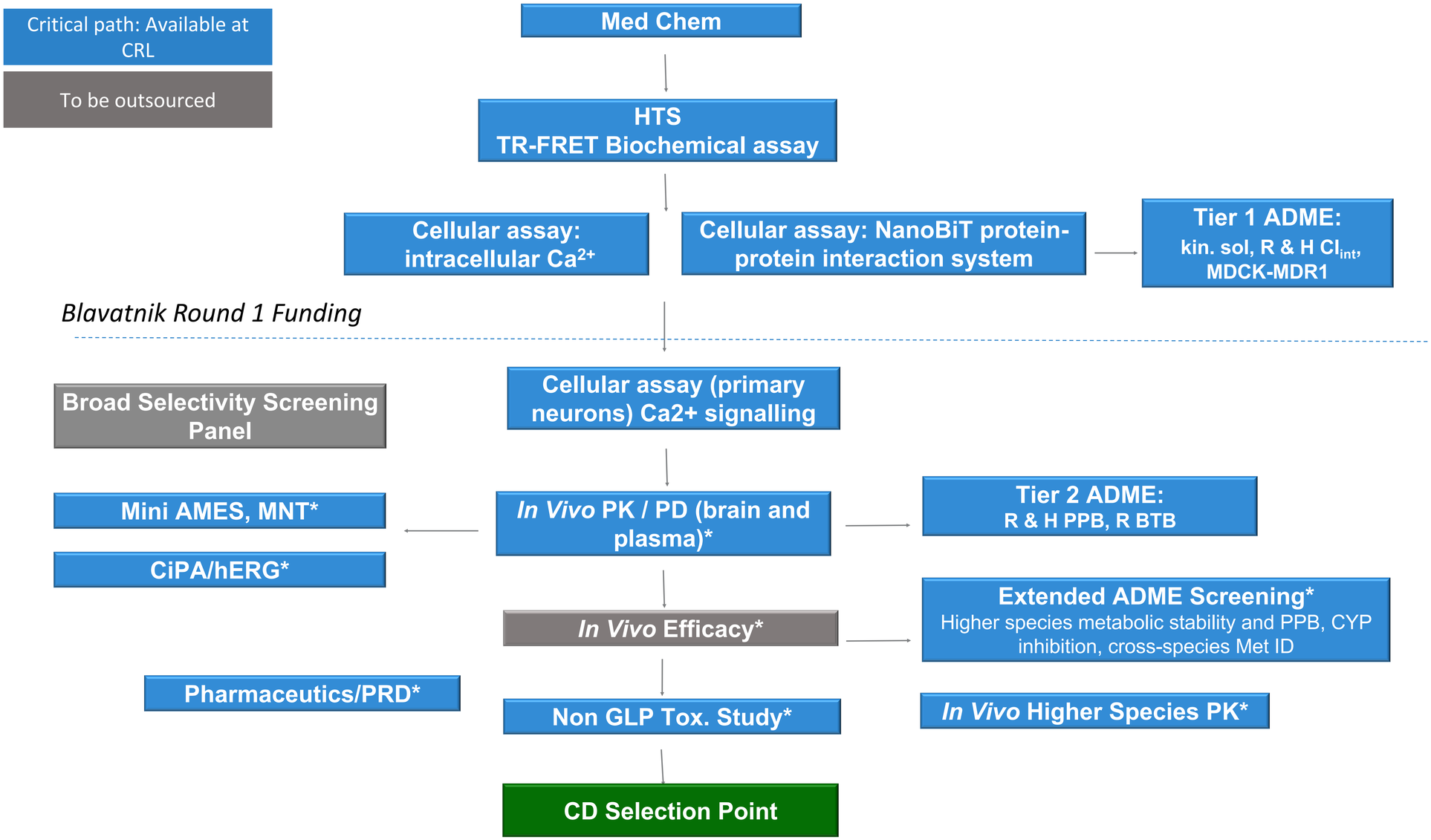
Examples where both loss of function (LOF) and gain of function (*GOF*) lead to disease

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



Yale Professor and Co-Founder of Osmol Therapeutics

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

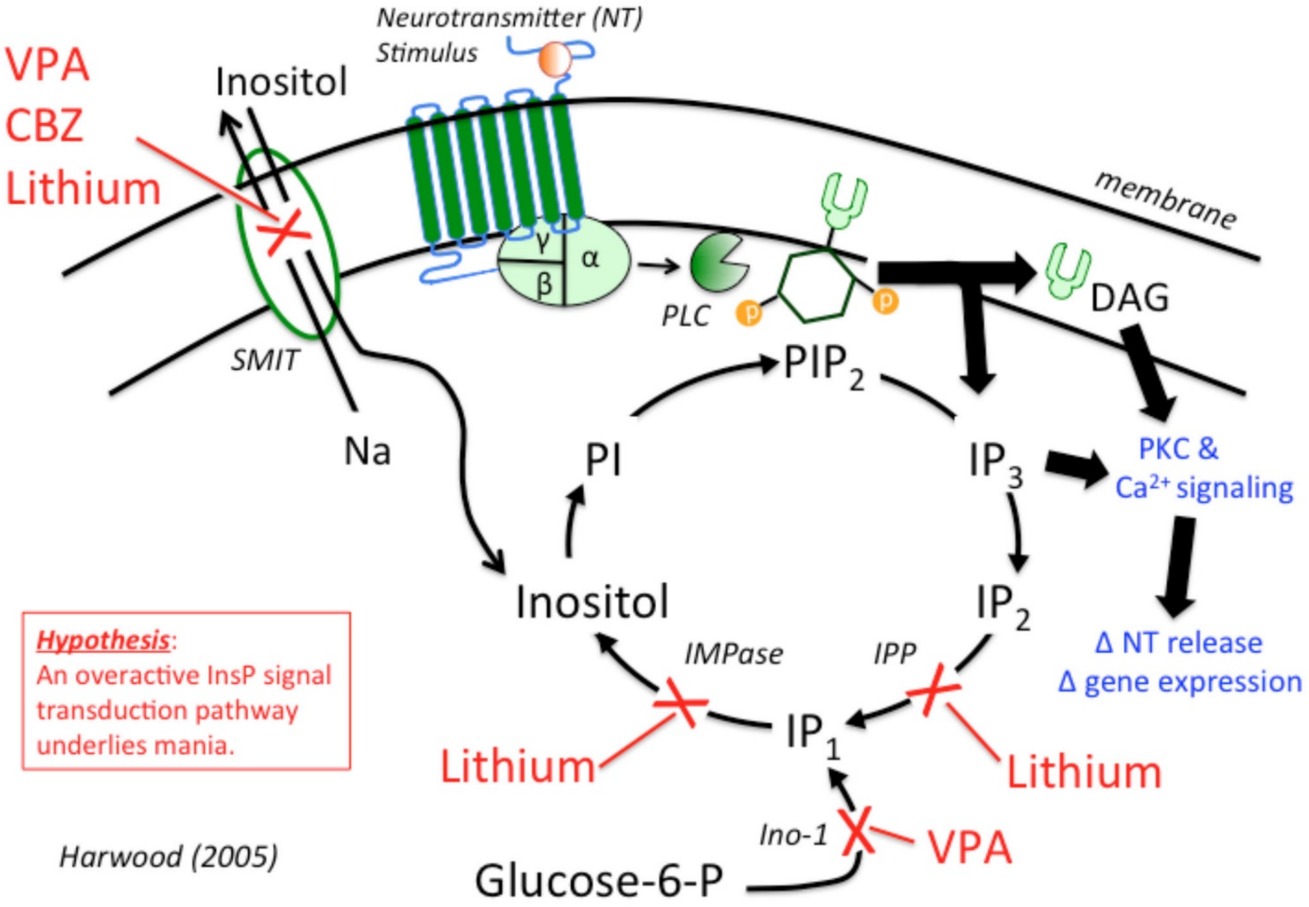
Post-Doctoral Fellow Albert Einstein College of Medicine, Bronx, NY (1980-86)
Properties of cardiac and Paramecium calcium channels

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

Inositol depletion hypothesis & Bipolar Disorder

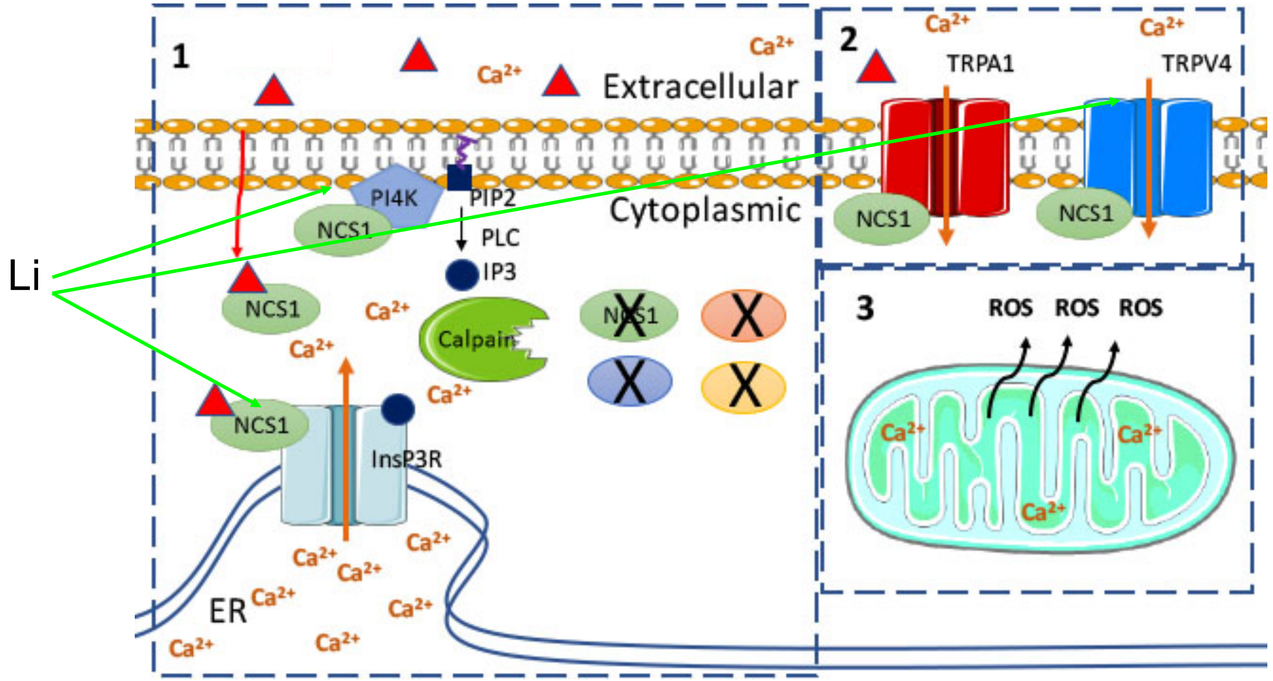


Hypothesis:
An overactive InsP signal transduction pathway underlies mania.

Harwood (2005)

Mechanisms

NCS-1 functionally interacts with several signaling pathways

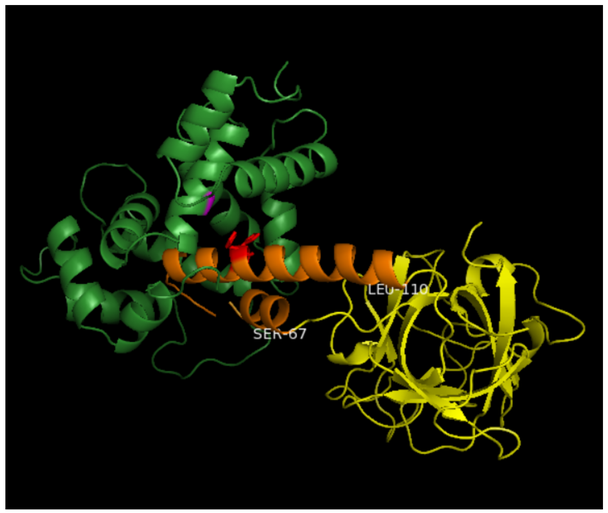


= potential target compounds

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



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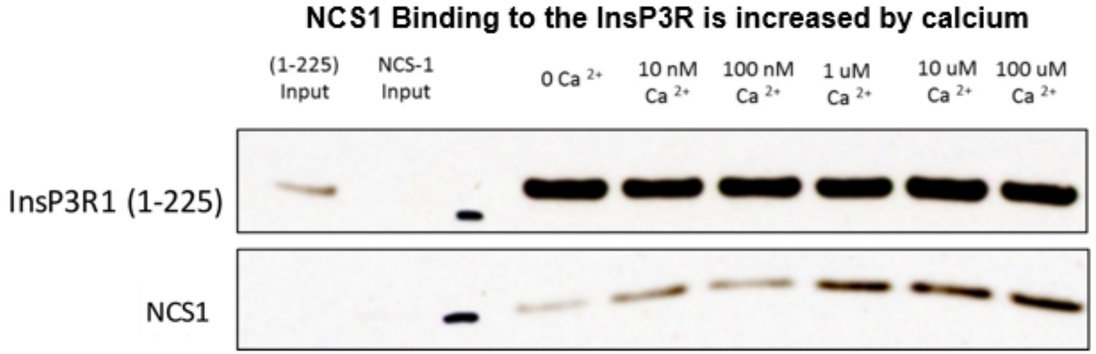
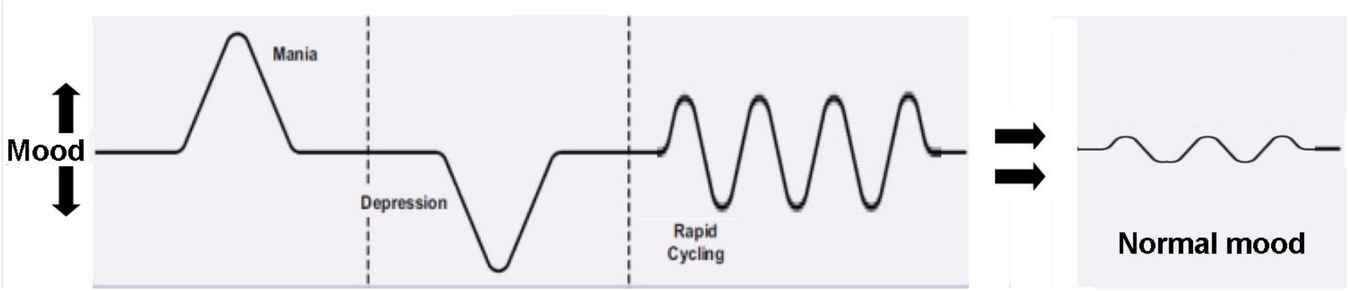
Yellow/orange = InsP3R1 (1-225),
red residues = AA_2 & AA_3

We identified critical functions using biochemical methods and cell signaling properties



Nguyen and Ehrlich, in preparation 2018
Boehmerle et al, PNAS 2006


April 23, 2018
People
EXCLUSIVE
My Battle With Bipolar Disorder
"I lived in denial and isolation"
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
KATE GOSSELIN
LOOKING FOR LOVE AGAIN—ON REALITY TV!
Brad Pitt
DATING A PROFESSOR?
LADY ANTEBELLUM'S
Hillary Scott
MEET MY MIRACLE BABIES!


Mood
Mania
Depression
Rapid Cycling
Normal mood