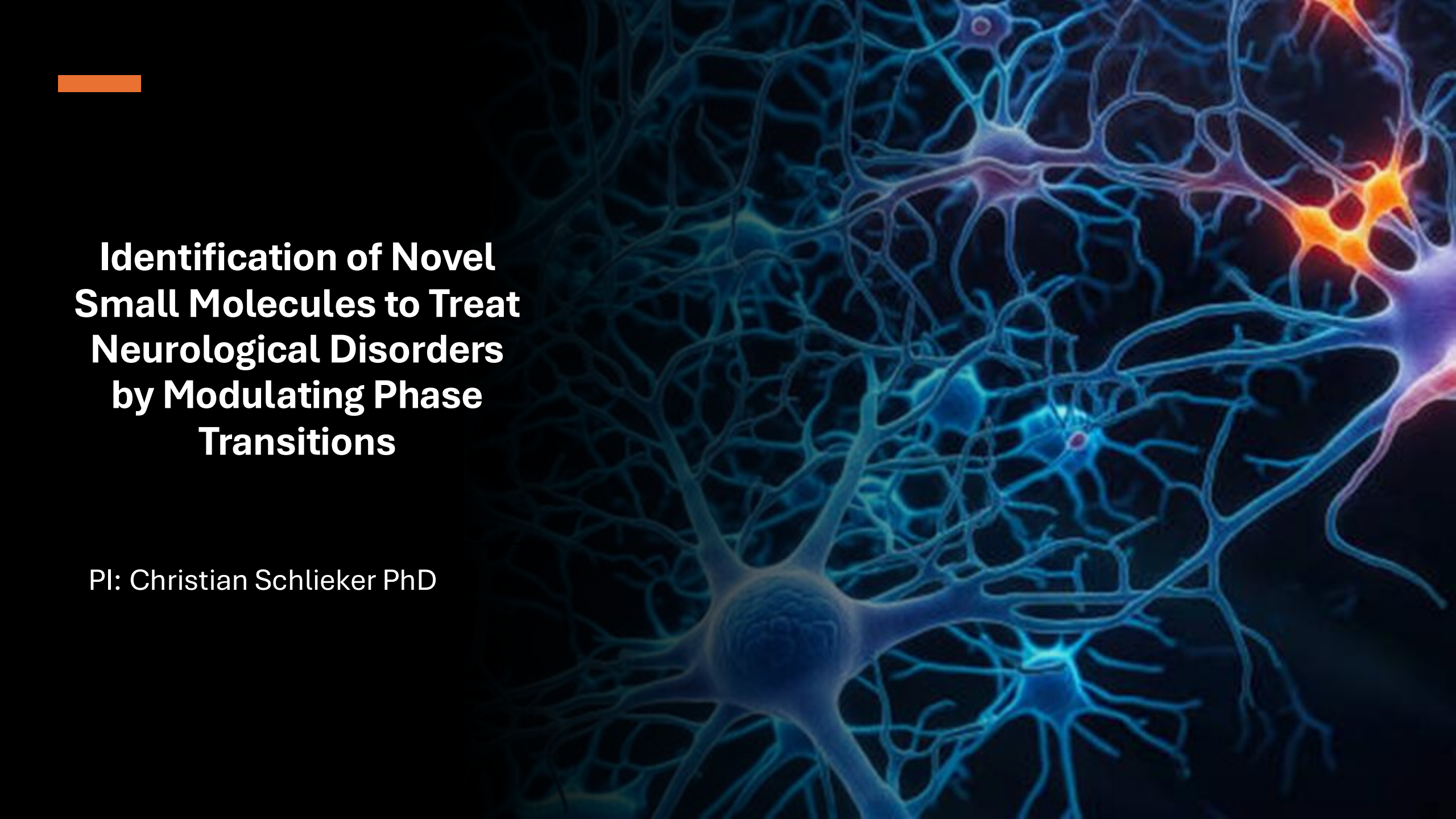
Identification of Novel Small Molecules to Treat Neurological Disorders by Modulating Phase Transitions

PI: Christian Schlieker PhD



The Team

Christian Schlieker, PhD
Professor of Molecular Biophysics and Biochemistry
Professor of Cell Biology

Team Leader

Dylan Poch, BSc (Chem)
PhD candidate
Schlieker Lab

Pioneered HTS pipeline

Yulia Surovtseva, PhD
Director, YCMD

Longstanding Expertise in HTS

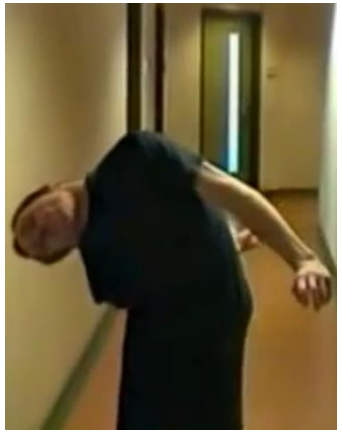
Anthony Koleske, PhD
Professor of Molecular Biophysics and Biochemistry
Professor of Neuroscience

Need for Effective Therapeutics to Treat Dystonia

Dystonia is the third most frequent movement disorder affecting **~250,000 US citizens**

Patients present with severe spasms, involuntary muscle contractions and twisted postures

There is **no cure** for dystonia and treatments (BOTOX, Deep Brain Stimulation) are inadequate



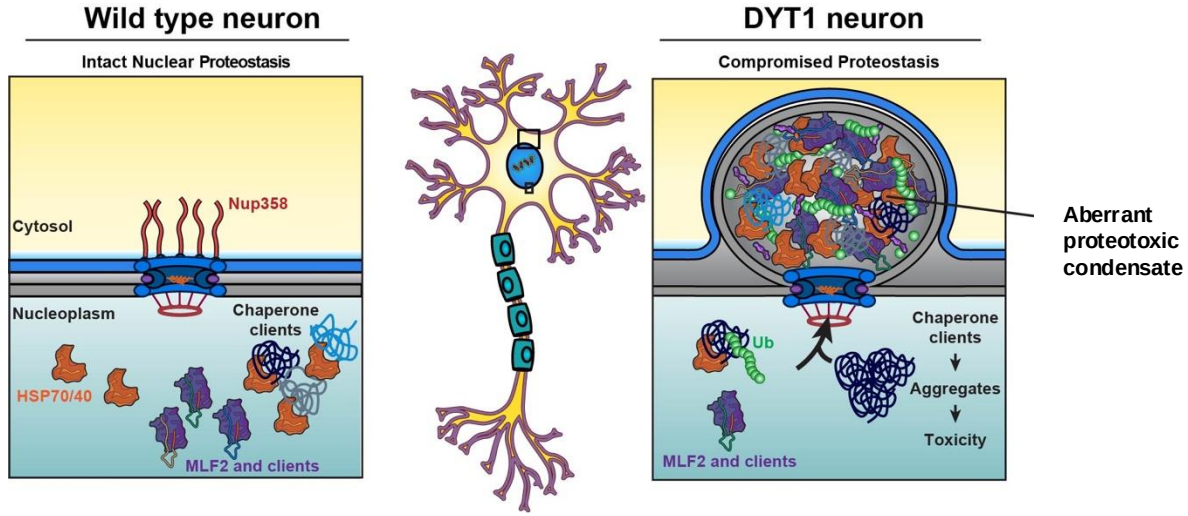
Opportunity for Innovation in Treatment Market

The current dystonia, ALS, and FTD treatment landscape is inadequate

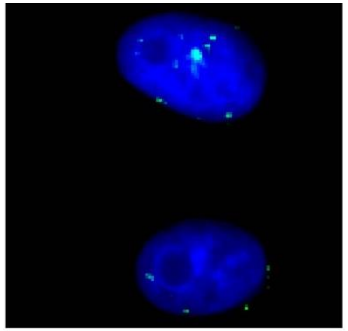
Disease	Estimated Prevalence	Estimated Market (2030)	Compound Annual Growth Rate (CAGR)
Dystonia	1.3 million	1.2 billion	5.1%
ALS	500,000	950 million	6.5%
FTD	1.2 million	450 million	5.1%

Combined estimated market opportunity > 2.6 billion (2030)

Reduction of Aberrant Phase Transitions Could Prevent Dystonia

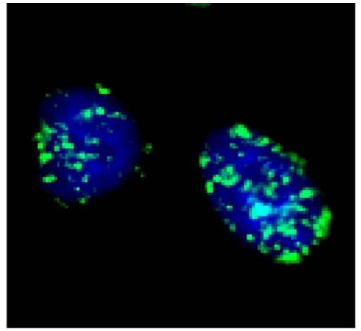


Healthy Cell



MLF2-GFP

Aberrant proteotoxic condensate



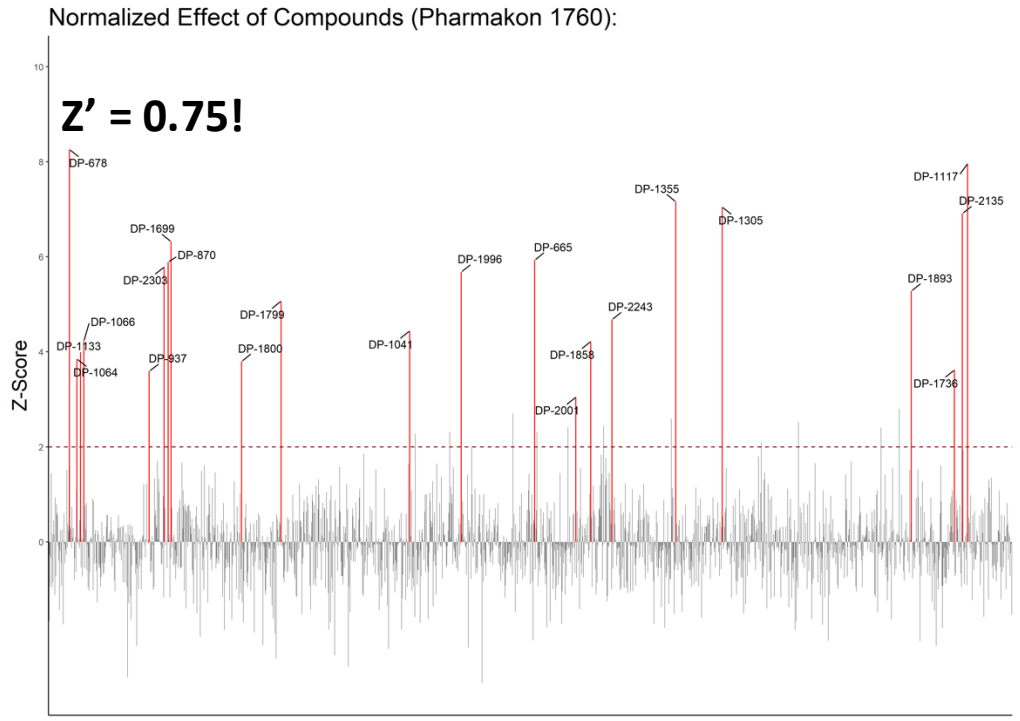
MLF2-GFP

Aberrant phase transitions create proteotoxic condensates that are drivers of dystonia pathology.

We identified MLF2 and DNAJB6 as Dystonia biomarkers for precision monitoring of phase transitions

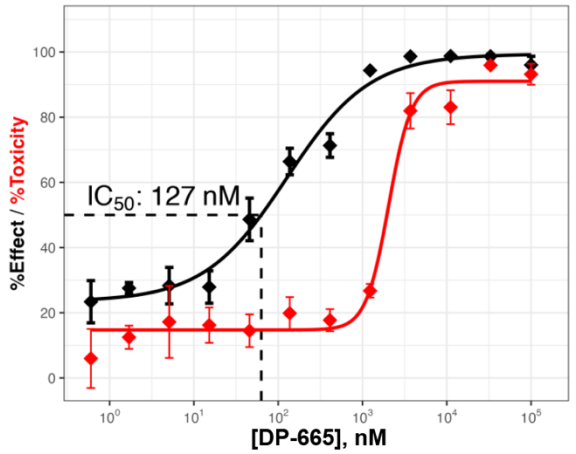
Reduction of aberrant phase transitions could restore protein homeostasis to prevent or modulate dystonia severity

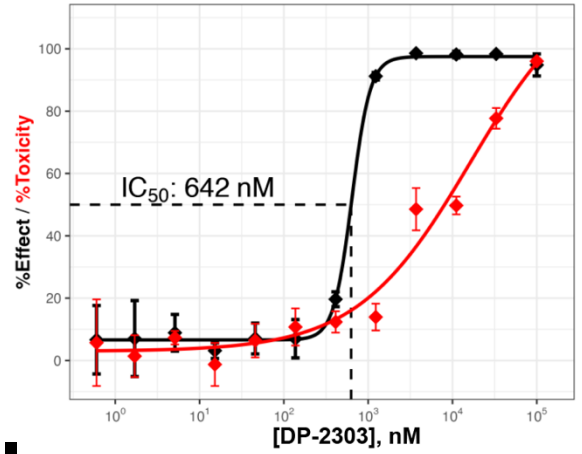
HTS assay, Validation in Cells and Animal Model



(1) Established Robust HTS Assay

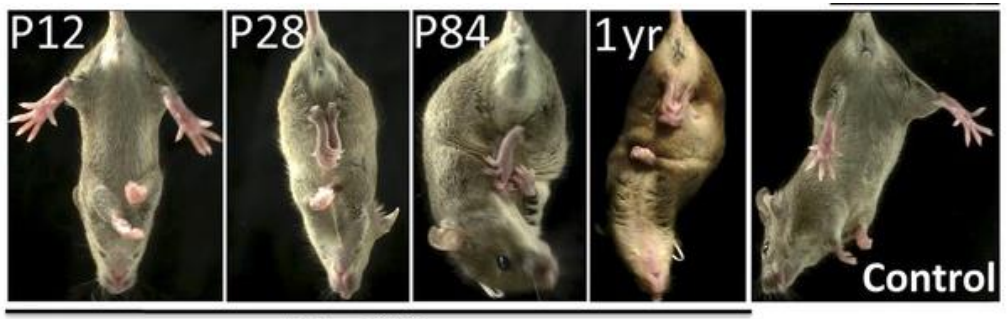
Potent reduction of proteotoxicity





(2) Validated Compounds *In Vitro*

(3) Available established *In Vivo* model

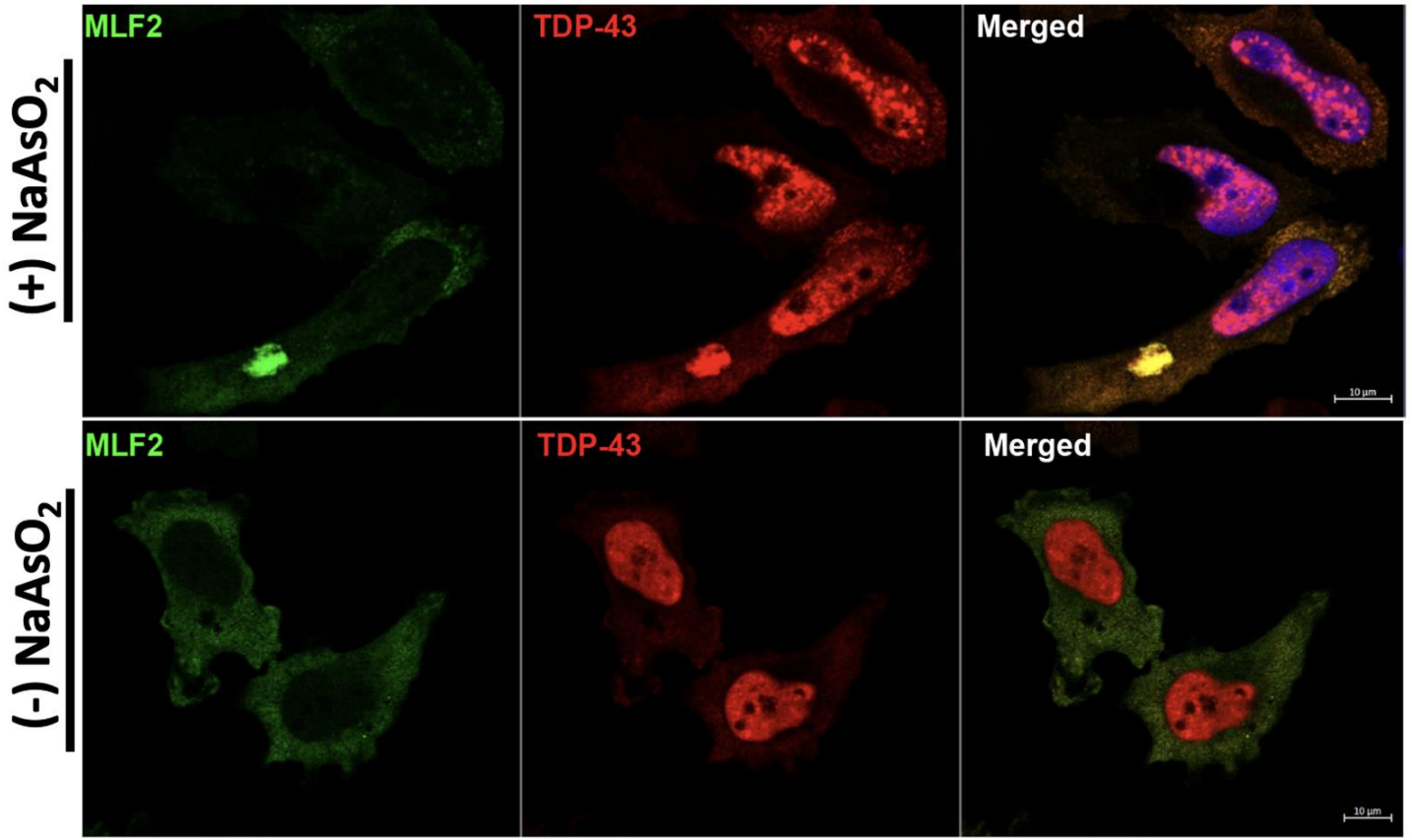


Pappas et al., eLife https://doi.org/10.7554/eLife.08352

Aberrant Phase Transitions Occur in ALS and FTD

Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) are terminal neurodegenerative diseases with no cure

MLF2 acts as **a Novel Biomarker** for Stress Granules of ALS/FTD



Project Timeline

Progress since 2023

Screen with MLF2 Biomarker

15,000+ compounds screened

Result: Several hits identified and validated

Completed

Milestone 1

Expand to New Chemical Matter

1. Screen 50,000+ compounds

2. Source & validate screen-actives, clustering/SARs

3. Establish dose/response & toxicity in cell-based DYT1 and ALS/FTD models

$80,000 total

Milestone 2

Evaluate Efficacy of Lead Compounds

1. Perform functional assays for cellular protein homeostasis and phase separation **$50k**

2. Test compounds in animal model **$120k**

3. Initiate target identification **$150k**

~$2M core funding (pathomechanism)

Budget Request: $300,000

CDMRP DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

DYSTONIA MEDICAL RESEARCH FOUNDATION

Key Publications from Our Lab

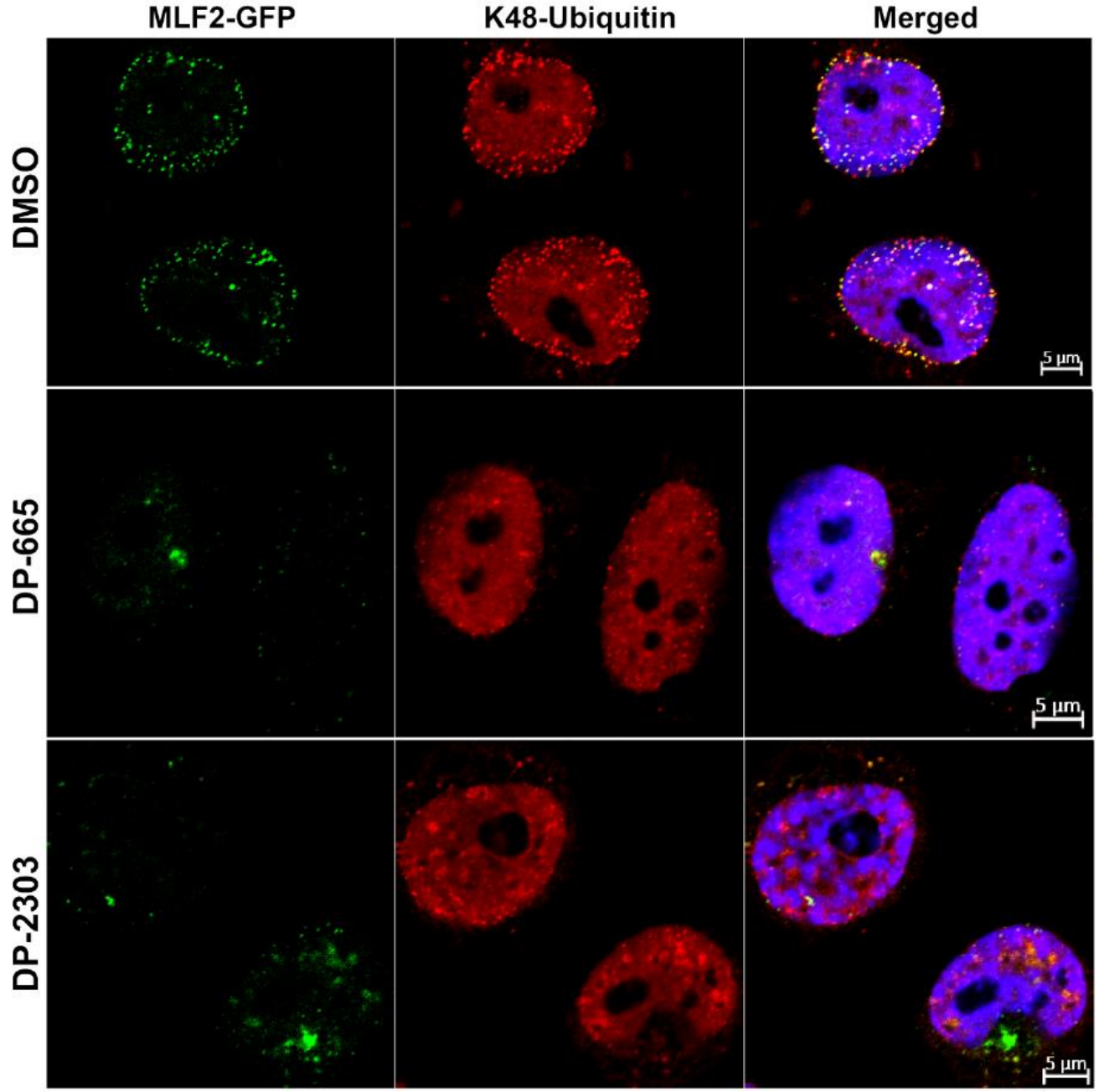
Key publications from my lab of relevance to this proposal:

- Definition of molecular defect underlying primary (DYT1) dystonia:
  Zhao et al. PNAS 2013
  Brown et al. PNAS 2014*
  *editorially highlighted by Nature Structural and Molecular Biology

- Identification of biomarkers and cellular defects
  Laudermilch et al. MBoC 2016
  Rampello et al. J Cell Biol 2020

- Discovery of aberrant phase separation/proteotoxicity as key driver for cellular pathology
  Prophet et al. Nature Cell Biol 2022*
  *editorially highlighted by NCB and Movement Disorders

Proteotoxic Condensates are Reduced Pharmacologically



Proof of Concept

Small molecules DP-665 & DP-2303 **decreases multiple condensate markers** *in vitro*

Current Treatments Focus on Relieving Symptoms

Class	Treatment	Route	Limitations
Botulinum toxin	BOTOX	Injection	• Requires treatments every 3-4 months • Administered at geographically limited, specialized centers • Not a cure
Surgery	Deep brain stimulation (DBS)	—	• Invasive procedures • Completed at geographically limited, specialized centers • Only helps a subset of patients • Not a cure
	Selective Denervation Surgery	—	
Medications	Anticholinergic Drugs (i.e trihexyphenidyl and benztropine)	Oral	• Only helps a subset of patients • Includes drug-related side effects (i.e. sedation) • Carries a risk of dependence (i.e. benzodiazepines) • Not a cure
	Muscle Relaxants (i.e baclofen)	Oral	
	Dopaminergic Agents (i.e levodopa and tetrabenazine)	Oral	
	Benzodiazepines (i.e clonazepam and diazepam)	Oral	

There is an **unmet need** to develop **oral medication** that **has potential to prevent disease onset or modulate severity**