

Thank you for joining the weekly webinar!

We are admitting audience members from the waiting room.

**Please allow a few moments for the webinar to begin.**



# HEALEY ALS Platform Trial

Weekly Q&A – July 6, 2023



## Healey & AMG Center

Sean M. Healey & AMG Center for ALS  
at Massachusetts General Hospital



The AMG Foundation

# Guest Speaker



**Bill Cho, MD PhD**  
Head of Clinical Science



# ABBV-CLS-7262 for ALS

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HEALEY ALS Platform Trial  
Regimen F



# Calico Life Sciences in collaboration with AbbVie

## Calico

**Founded** by Google (now Alphabet) and Art Levinson in 2013

**Mission:** To understand human aging and develop therapies for age-related disorders, including neurodegeneration

## abbvie

**Partnership with AbbVie**, a global biopharmaceutical company with a proven track record of developing medicines and solutions for people living with neuropsychiatric disorders such as Parkinson's Disease, schizophrenia, and depression



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# What is the Integrated Stress Response (ISR)?

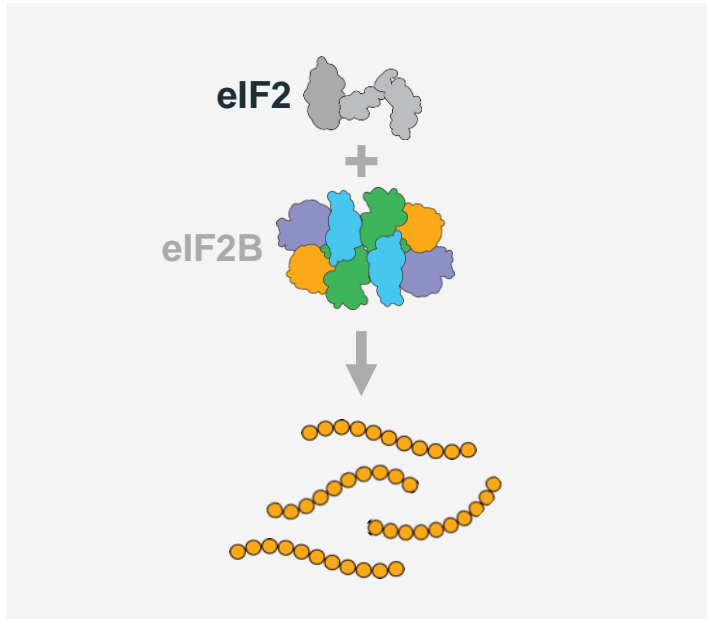


# The Integrated Stress Response (ISR)

2 key players:

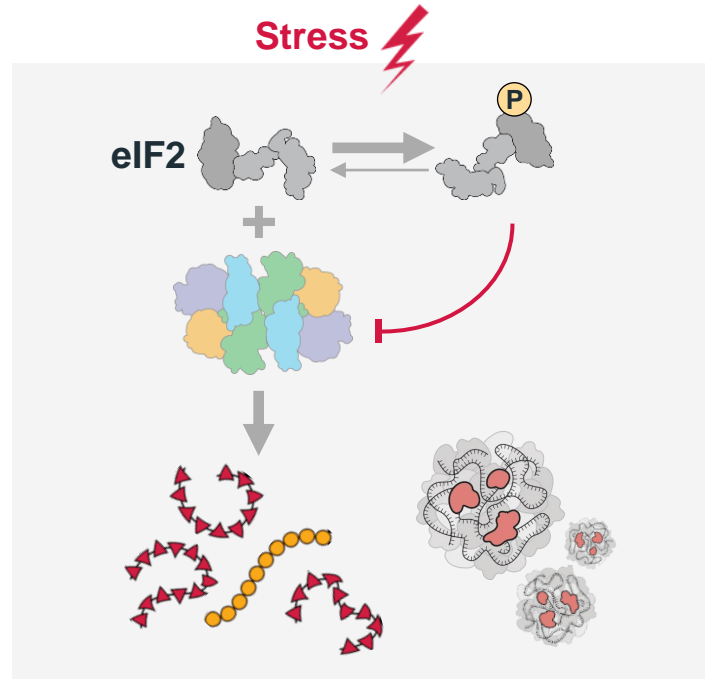


No ISR



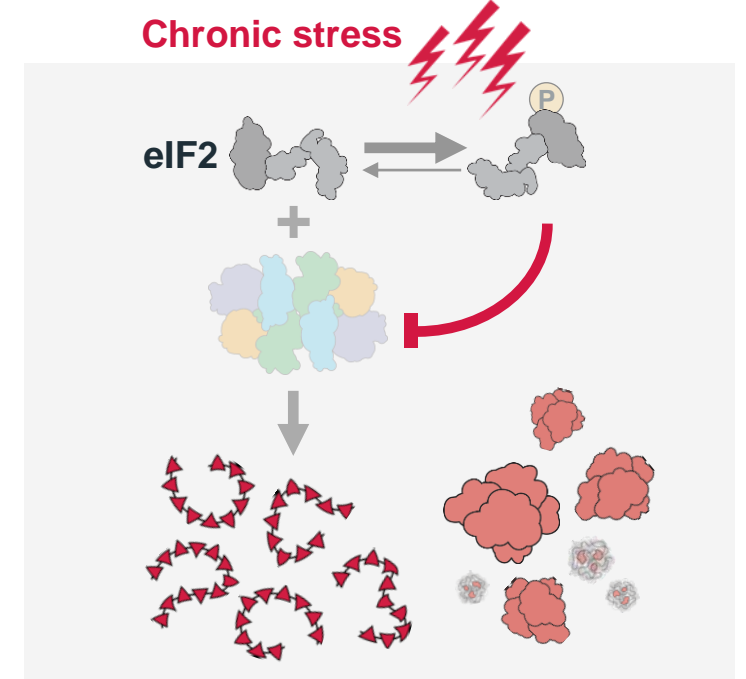
Normal protein synthesis

Transient ISR



Reduced protein synthesis  
Production of stress proteins  
Formation of TDP-43 stress granules

Persistent ISR



Lack of essential proteins  
Toxic levels of stress proteins  
Build-up of TDP-43 aggregates  
**Cell death**

## LEGEND



Normal proteins



Stress proteins



Stress granules



TDP-43

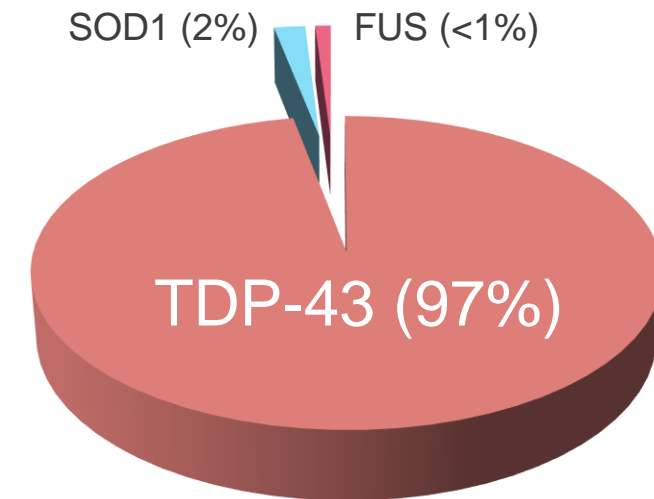
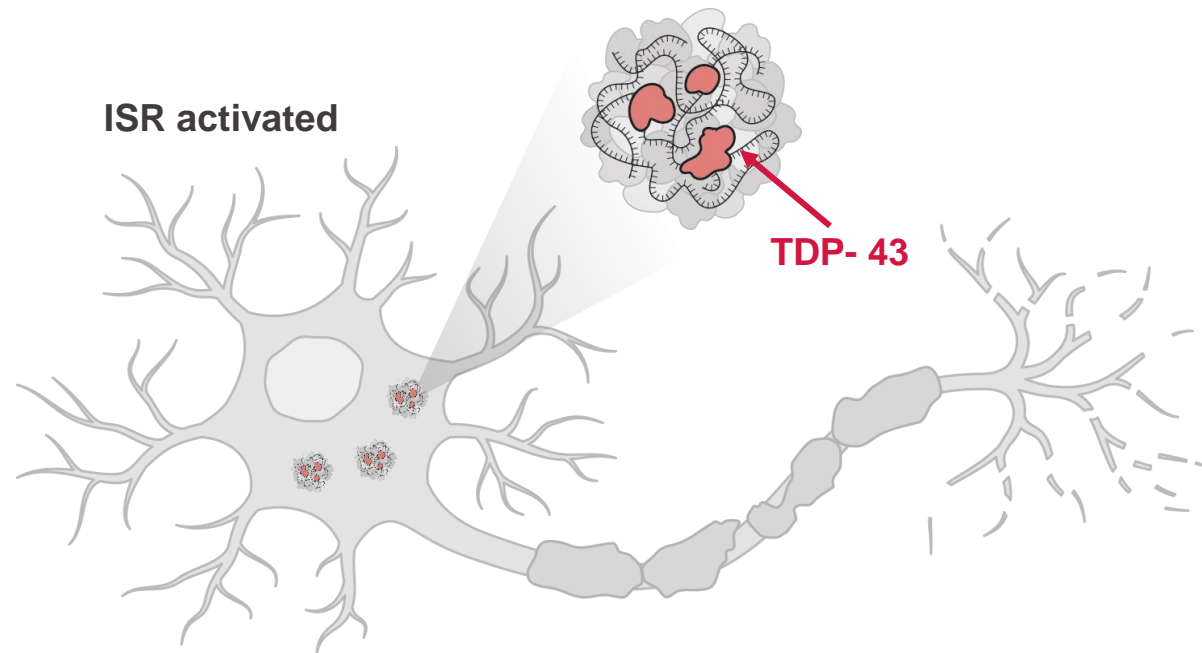


TDP-43 aggregates



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# TDP-43 aggregates are a hallmark of ALS pathology





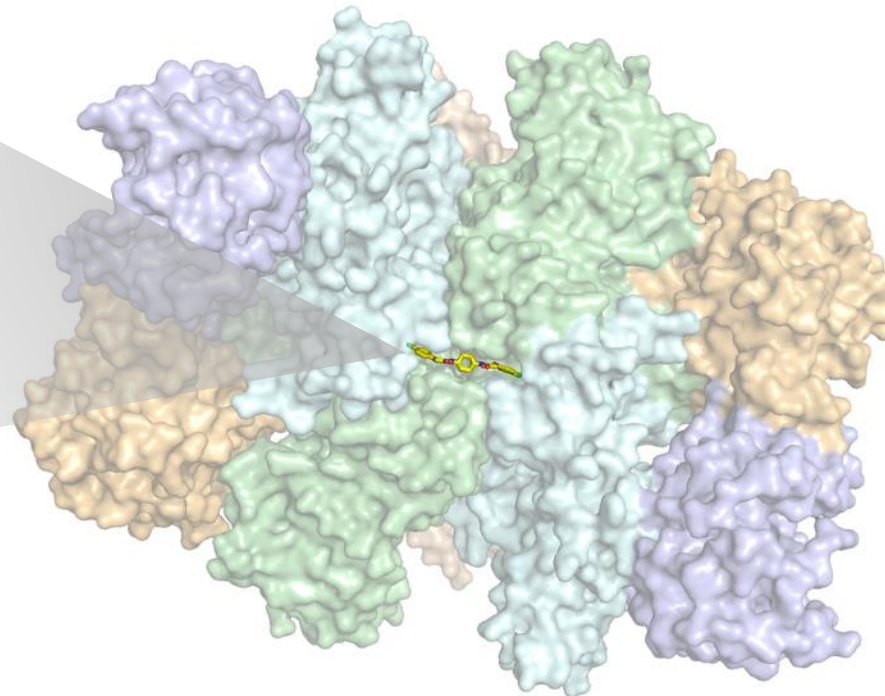
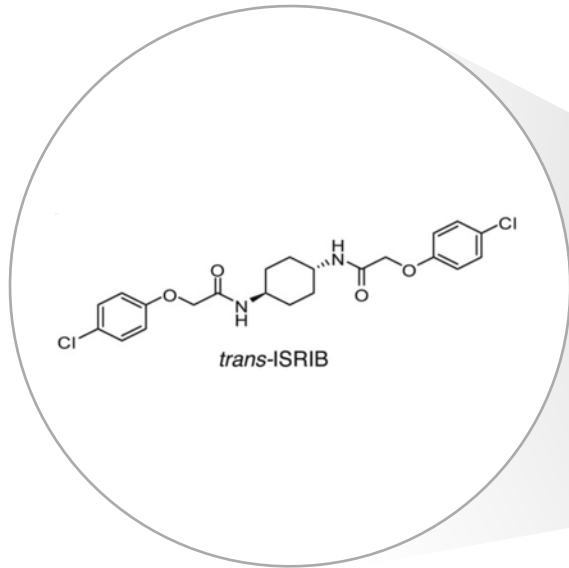


# Can the ISR be inhibited?



# The first ISR inhibitor, ISRIB

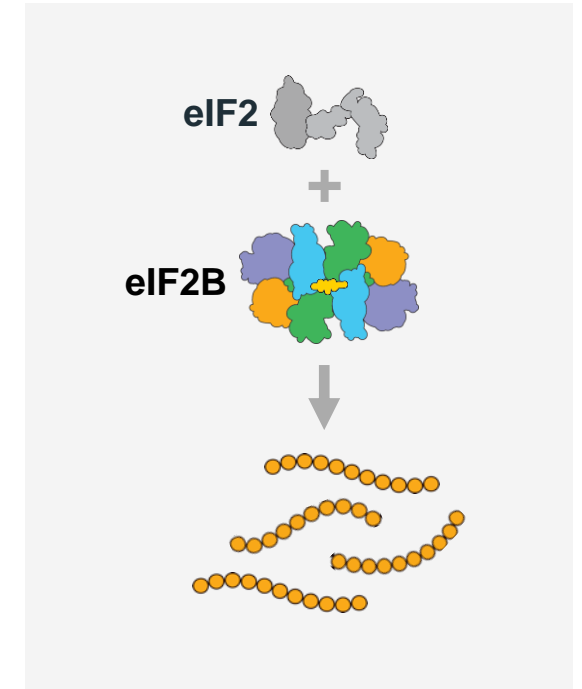
ISRIB bound to Human eIF2B



ISRIB binds to eIF2B in the central pocket

Increases the enzymatic activity of eIF2B

Makes eIF2B less sensitive to stress



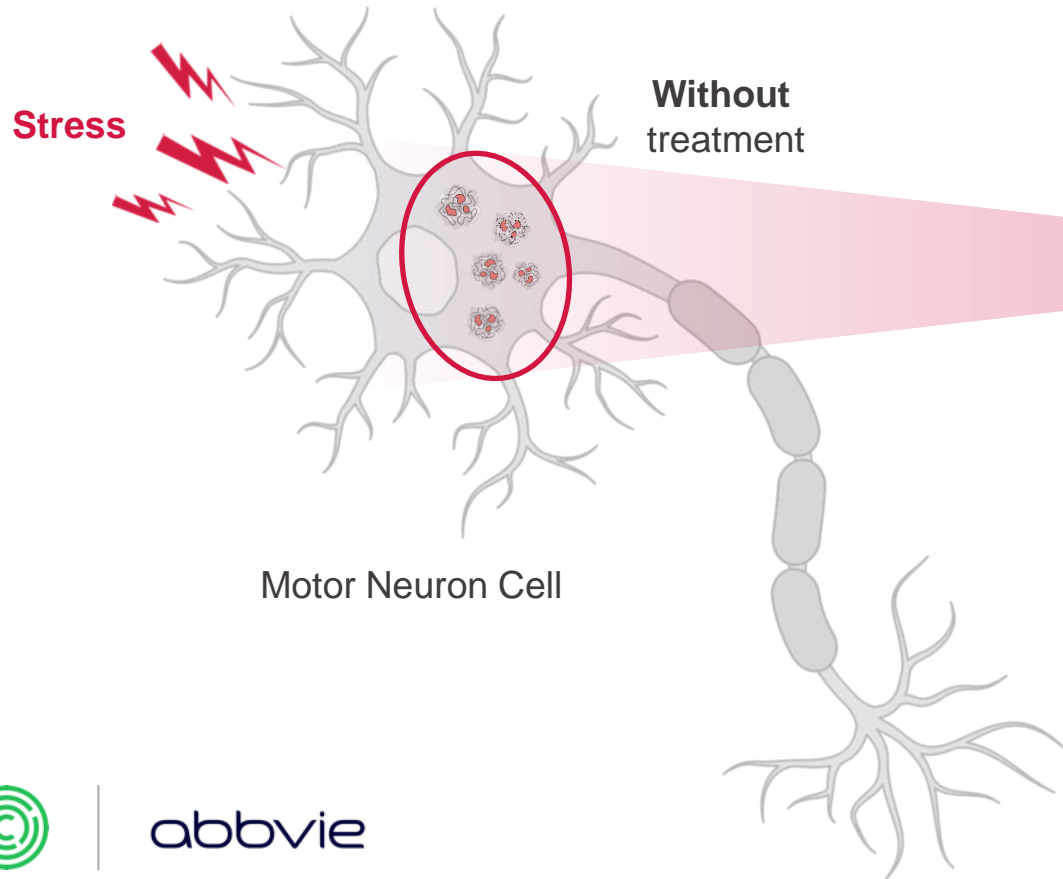
Discovered at UCSF by **Carmela Sidrauski** Principal Investigator  
Calico Life Sciences LLC



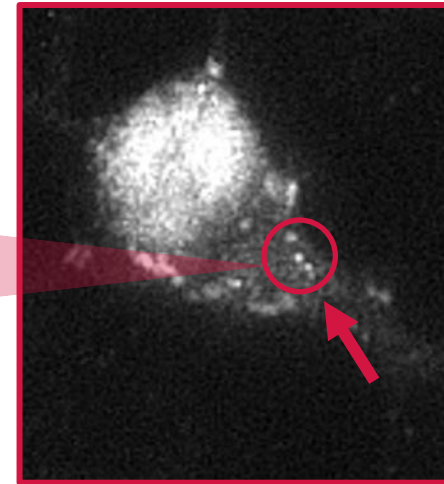
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# eIF2B activators dissolve TDP-43 stress granules in human motor neurons

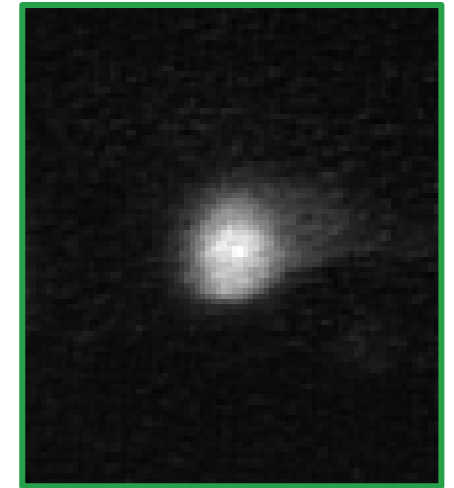
Activating the ISR drives TDP-43 into stress granules



TDP-43 Staining of Stressed Human Motor Neurons in Cell Culture



Without treatment



With treatment

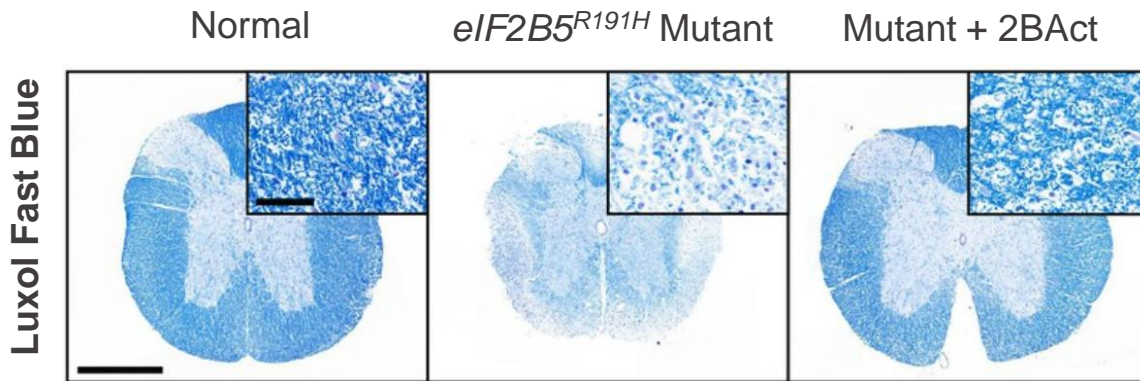
IN VITRO EXPERIMENT



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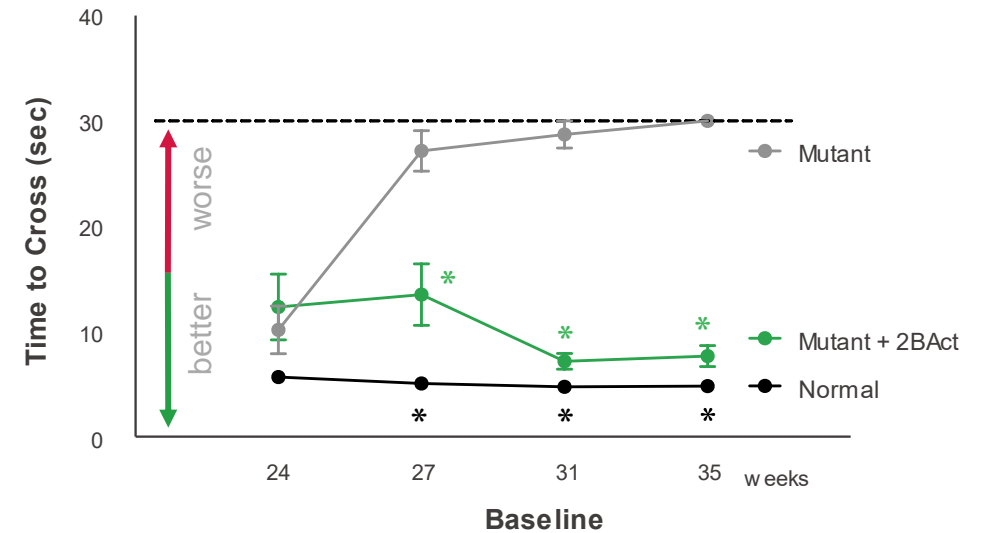
# eIF2B activators rescue mice from neurological deficits caused by a persistent ISR in the brain and spinal cord

2BAActivator preserves the white matter in the spinal cord



Wong et al., eLife 2019

2B Activator improves motor function and balance<sup>#</sup>



\* $p \leq 0.00001$  vs. *eIF2B5<sup>R191H</sup>* Mutant

<sup>#</sup>as measured by time to cross a balance beam

Sadowski et al., 2019; SFN, Chicago, IL poster



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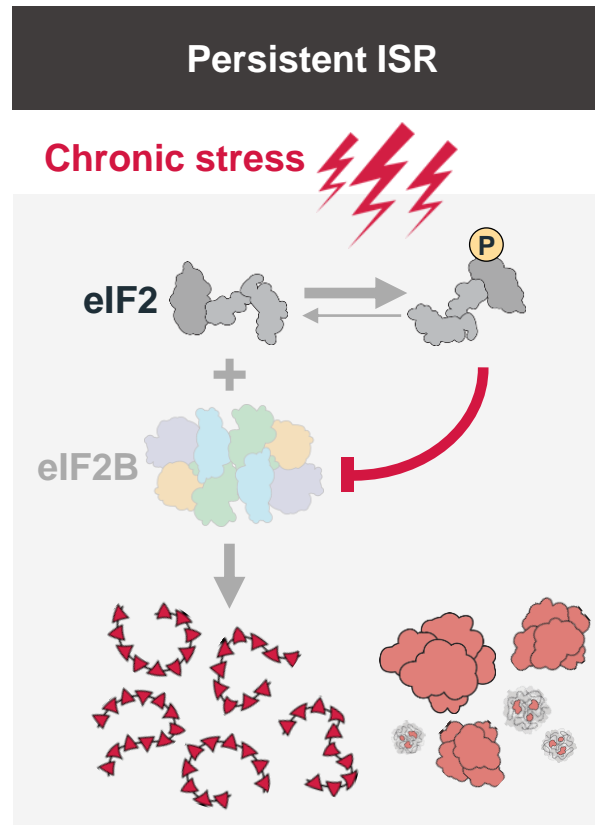
IN VIVO (MOUSE) EXPERIMENT

# How can eIF2B activators potentially treat ALS?



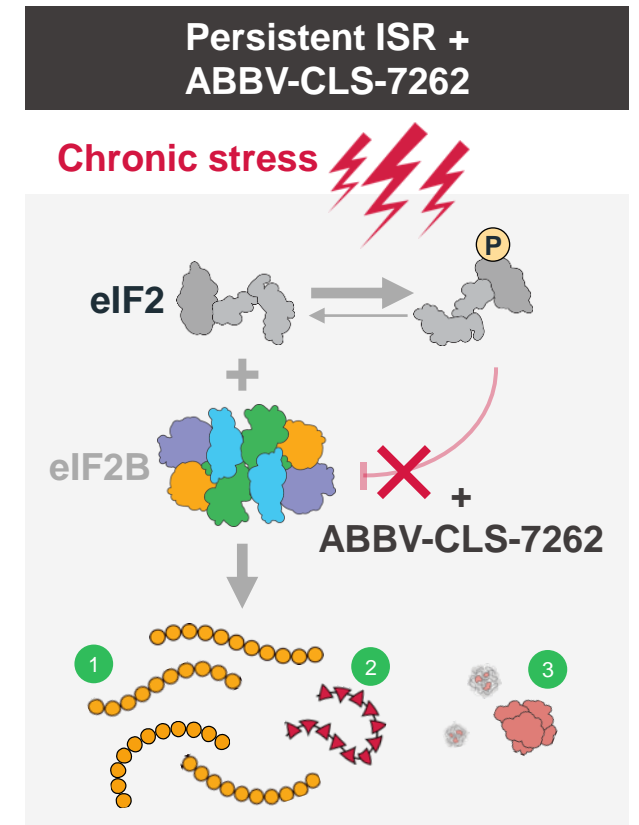
# eIF2B activators may help motor neurons survive harmful stress conditions by:

- 1 Restoring normal protein production in stressed nerve cells
- 2 Reducing stress proteins that may lead to nerve cell death
- 3 Dissolving stress granules that may lead to TDP-43 aggregates



↓ Synthesis of essential proteins  
 ↑ Stress proteins to toxic levels  
 ↑ Build-up of TDP-43 aggregates

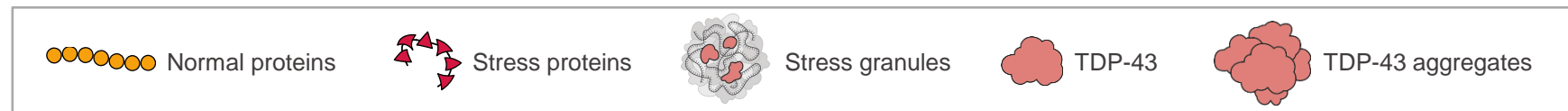
**Cell death  
 Neurodegeneration  
 ALS**



↑ Protein synthesis  
 ↓ Stress proteins  
 ↓ Further TDP-43 sequestration

**Improve cell function**

**LEGEND**



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A photograph of a family walking outdoors on a paved path. In the center, a man with glasses and a mustache is seated in a wheelchair, smiling. Behind him, a woman with short blonde hair is walking and smiling. To the right, a young girl in a plaid shirt is walking and looking towards the man in the wheelchair. The background shows trees and a bright, sunny day. The entire image is overlaid with a semi-transparent green filter.

**Has ABBV-CLS-7262  
been given to people?**



# Results from the first study in healthy people



ABBV-CLS-7262, our eIF2B activator, has been given to over

**100**

HEALTHY VOLUNTEERS

**ABBV-CLS-7262** can be administered by mouth once a day

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**Adverse events** were non-serious, and mild to moderate in severity

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**ABBV-CLS-7262** increased eIF2B activity and inhibited the ISR as expected by its mechanism of action

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The drug entered the cerebrospinal fluid (CSF) and was present at concentrations hypothesized to activate eIF2B

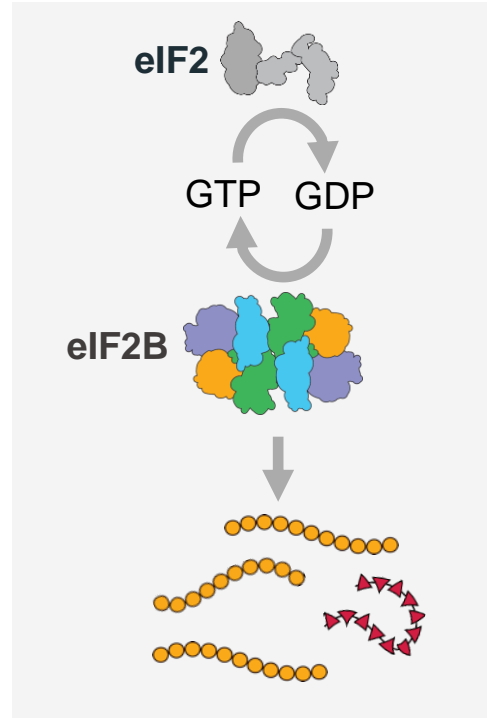
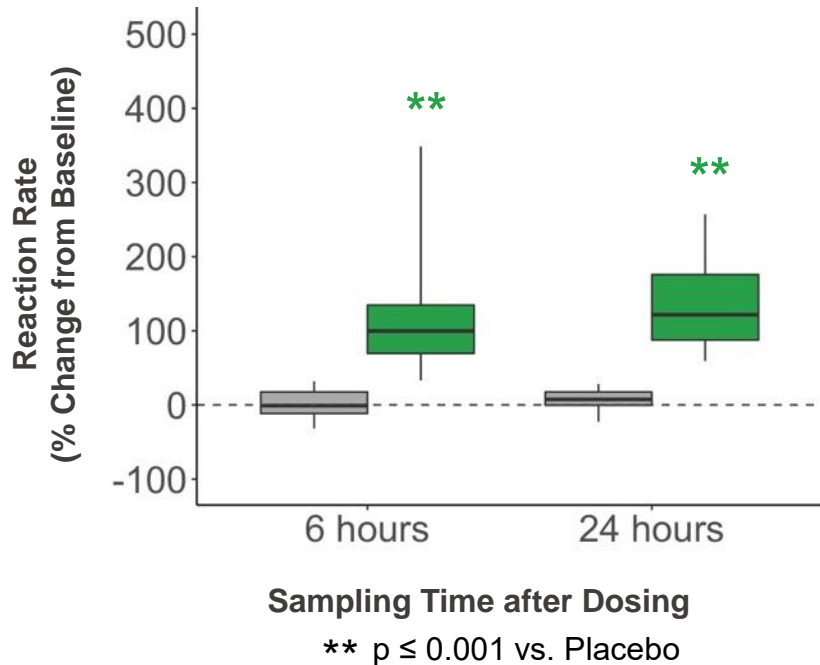


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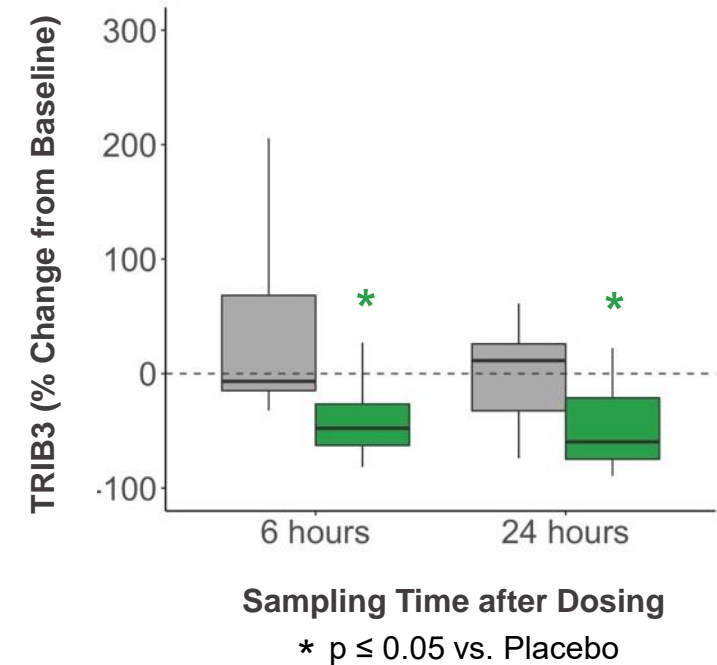


# ABBV-CLS-7262 increases eIF2B activity and inhibits the ISR in blood cells collected from trial participants

ABBV-CLS-7262 enhances the enzyme activity of eIF2B



ABBV-CLS-7262 suppresses the ISR stress gene TRIB3



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Placebo

ABBV-CLS-7262

**Has ABBV-CLS-7262 been  
given to people with ALS?**



# Preliminary blinded safety information from an ongoing study in people with ALS

The most frequent adverse events possibly related to ABBV-CLS-7262 or placebo were\*:



ABBV-CLS-7262  
has been given to

31

PEOPLE WITH ALS

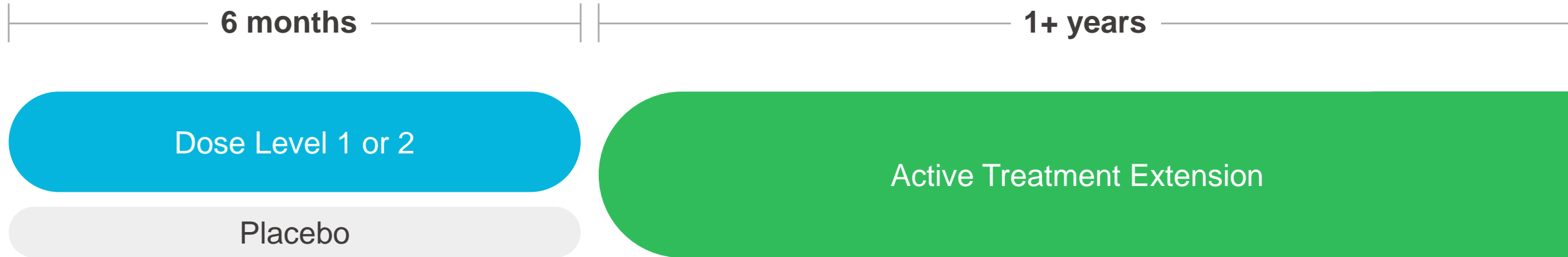
Some participants have been  
treated for more than a year



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\*As of 08 Jan 2023; Study data remains blinded and includes adverse events for participants who may have received placebo for four weeks

# We are excited that ABBV-CLS-7262 is part of the Healey ALS Platform Trial as Regimen F



ABBV-CLS-7262 will be taken by mouth once daily

Participants will be randomly assigned to receive ABBV-CLS-7262 or placebo in a 3:1 ratio

Participants will be randomized to 1 of 2 dose levels, **both of which are hypothesized to activate eIF2B**

Participants may receive ABBV-CLS-7262 for approximately 1 year



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MGH is the Sponsor of the study  
Calico is the Regimen Industry Partner  
AbbVie is the manufacturer of ABBV-CLS-7262

**In summary...**



# ABBV-CLS-7262 is ready to be evaluated as a new potential treatment for ALS

## Problem



ISR is activated in ALS

ABBV-CLS-7262 is a potent inhibitor of the ISR by binding to, and activating, eIF2B

Aggregates of the protein TDP-43 are observed in most ALS cases

ABBV-CLS-7262 dissolves stress granules containing TDP-43 which may reduce formation of new TDP-43 aggregates

Drugs tested in ALS clinical trials must have their intended biological effect in people

Blood cells from people given ABBV-CLS-7262 show increased eIF2B activity and reduced ISR

The right dose needs to be administered in clinical trials

ABBV-CLS-7262 was measured in the CSF at levels hypothesized to activate eIF2B

The understanding of ALS is incomplete

CSF and blood samples will improve our understanding of the ISR in ALS and may identify people most likely to respond to ABBV-CLS-7262



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The background is a solid green color with a white maze pattern. The maze consists of concentric, irregular circular paths that spiral outwards from the center. The word "Questions" is written in a bold, white, sans-serif font in the center of the image.

**Questions**

Learn more about Calico  
and our clinical trials:

[calicolabs.com/patients](https://calicolabs.com/patients)



**Watch this video explaining the  
ISR and its connection to ALS ...**