HEALEY ALS Platform Trial

Weekly Q&A – March 16, 2023

HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

TACKLE ALS "DON'T BE SORRY LETS BEAT THIS"

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

I AM ALS

TAMBOURINE

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

ALS ONE

RUN2REVIVE MIND · BODY · POTENTIAL

Berry Consultants Statistical Innovation

1850 MELIORA

ucb

biohaven pharmaceuticals

CLene NANOMEDICINE

prilenia

THE ARTHUR M. BLANK FAMILY FOUNDATION

BASEBALL WINTER MEETINGS SAN DIEGO 2019

SEELOS THERAPEUTICS

Calico

DENALI THERAPEUTICS

AMG The AMG Foundation

Guest Speaker

Nicholas Maragakis, MD
Platform Trial Site Investigator
Johns Hopkins University, MD

ALS ASSOCIATION

MDA® Muscular Dystrophy Association

Our ALS Care Team

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Occupational Therapist

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Senior Research Program Manager

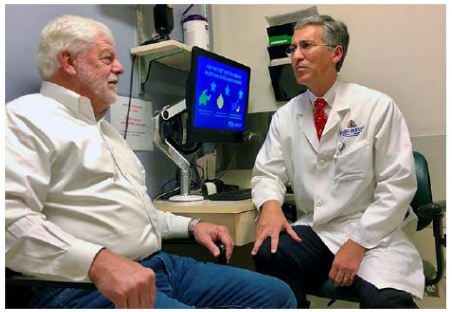
Amy Tesch
Research Program Coordinator

Weiyi Mu, Sc.M. ›
Genetic Counselor

David McEvoy Cromwell, M.D. ›
Gastroenterologist

EXPLORING NEW THERAPIES

BRINGING TREATMENT TO ALS PATIENTS



JOHNS HOPKINS
MEDICINE

ALS CLINICAL TRIALS UNIT








The HEALEY ALS Platform Trial is a unique opportunity to advance science

DNA – whole genome sequencing

Neurofilaments –for all regimens

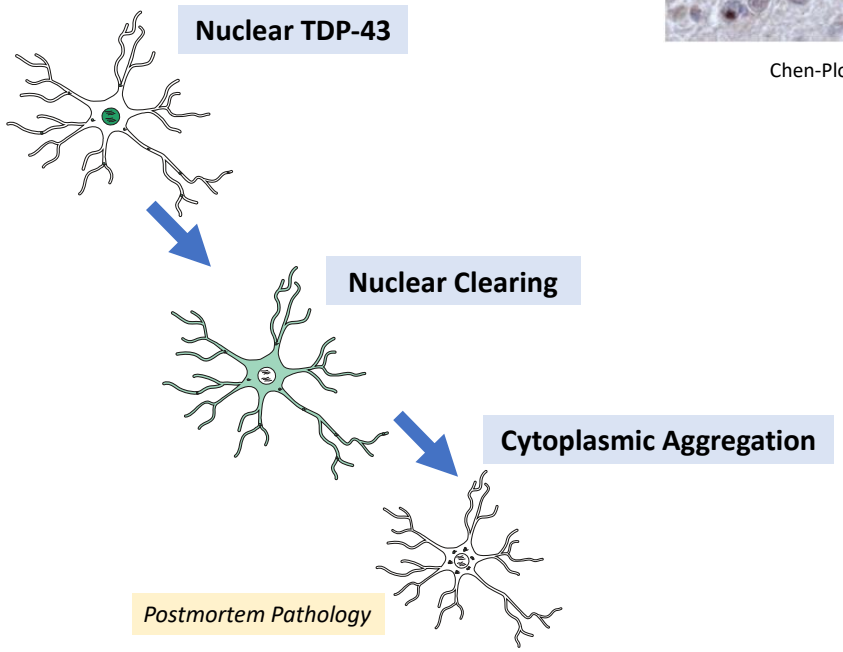
Biomarkers **(Blood, Urine, CSF)** – several drug-specific biomarkers

Speech Analysis – emerging digital biomarker

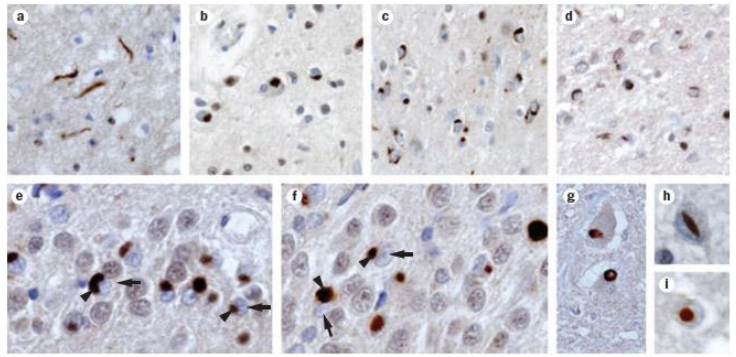
Home Spirometry – critical during the pandemic

Additional biomarkers/outcome measures are being considered for upcoming regimens (e.g., new patient-reported outcomes; PBMCs for stem cell generation)

TDP-43 nuclear clearing is a pathological hallmark of most sALS: Loss of TDP-43 nuclear function leads to mis-regulation of hundreds of RNA species

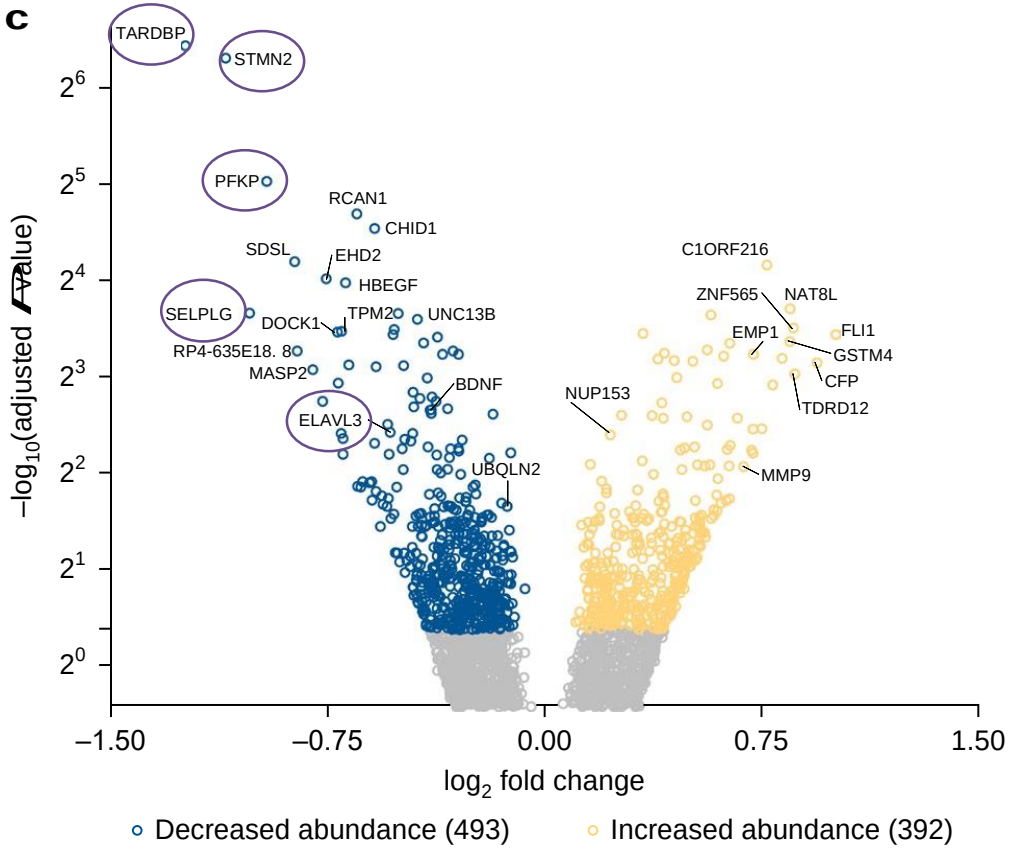


TDP-43 pathology in end-stage neurodegenerative disease



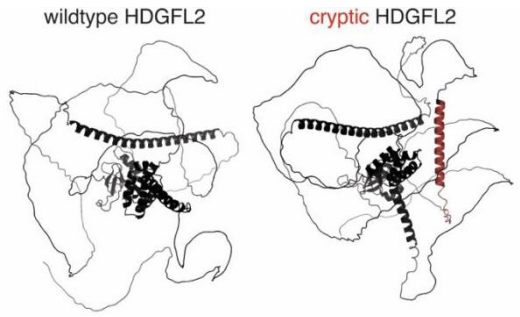
Chen-Plotkin et al (2010), *Nature Reviews Neurology*

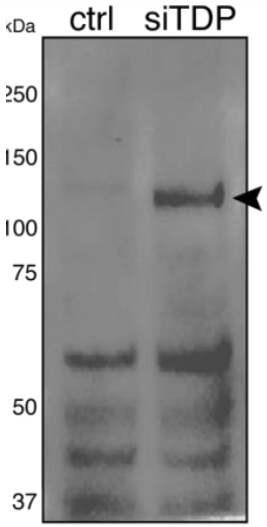
Defined set of altered RNAs with artificial TDP43 KD in human iPS MN



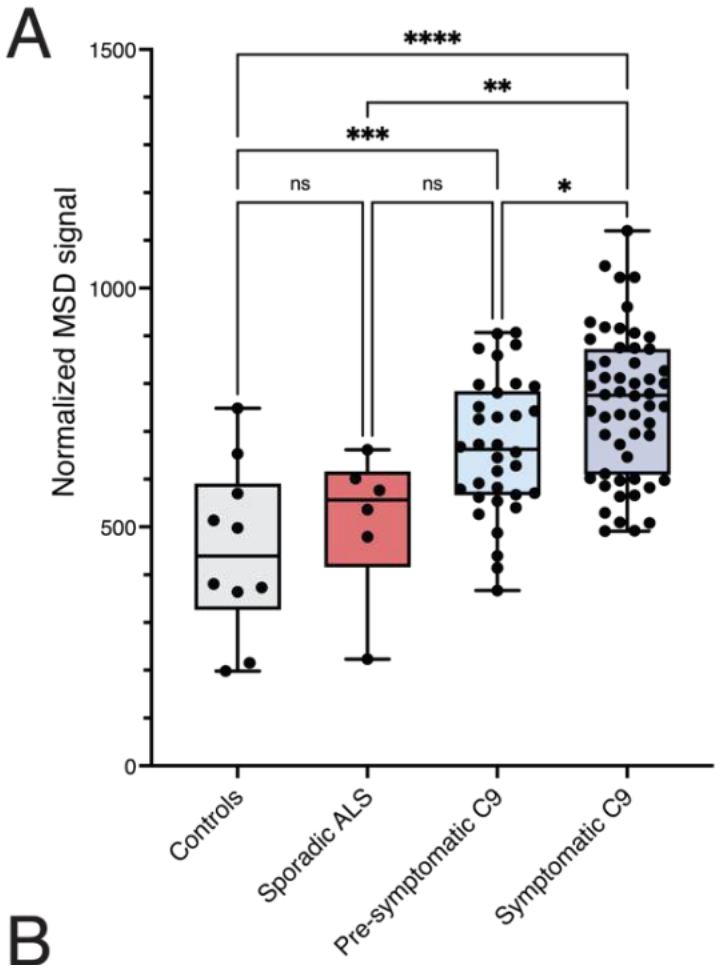
Klim et al, Nat. Neuro2019

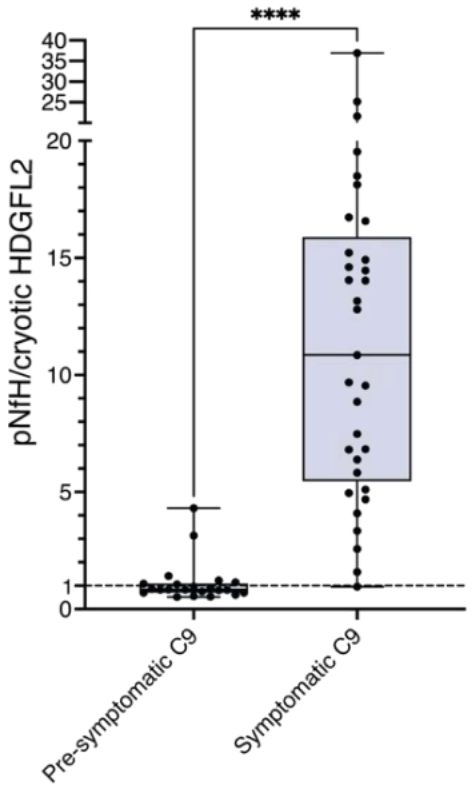
TDP-43 loss of function generated cryptic peptide detected in sALS and C9 ALS CSF

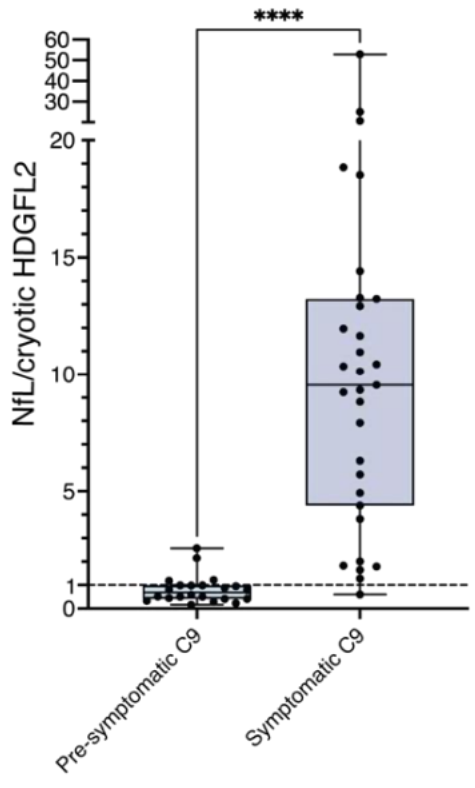




cryptic HDGFL2 Ab

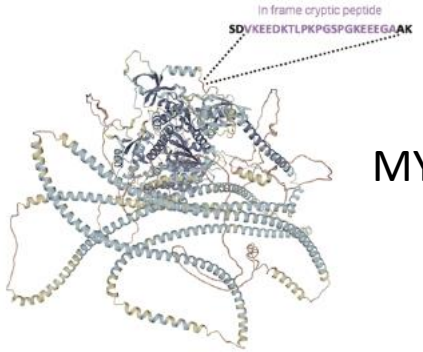






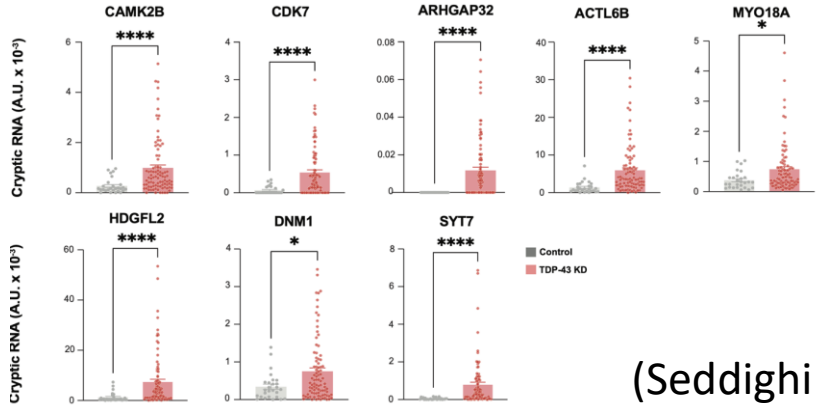
Irwin et al, BioRxiv, 2023

Identification of multiple TDP-43 dependent cryptic peptides in ALS CSF



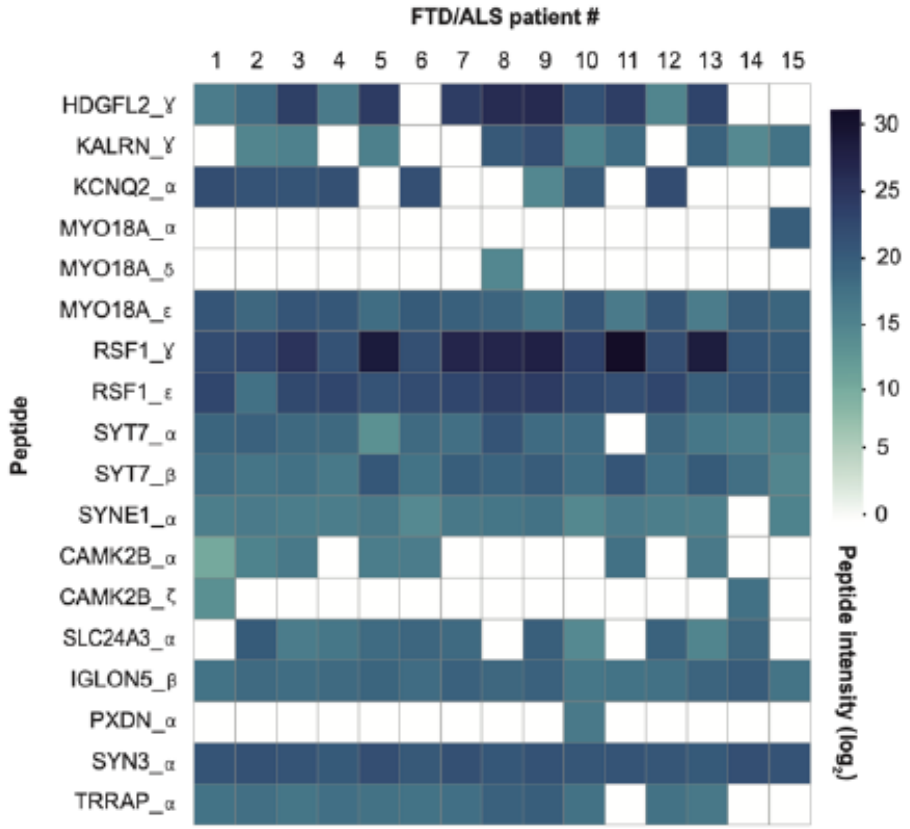
MYO18 cryptic peptide

Detection of cryptic peptides RNA in ALS patients



(Seddighi et al, BioRxiv, 2023)

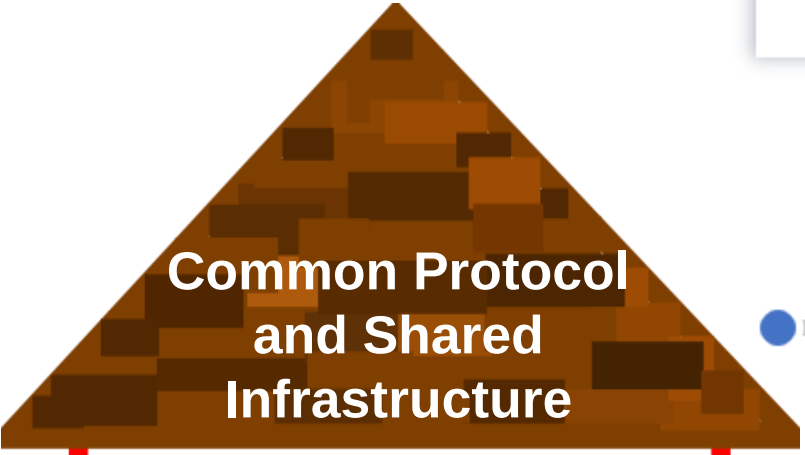
Detection of cryptic peptides in ALS CSF (Mass spect)

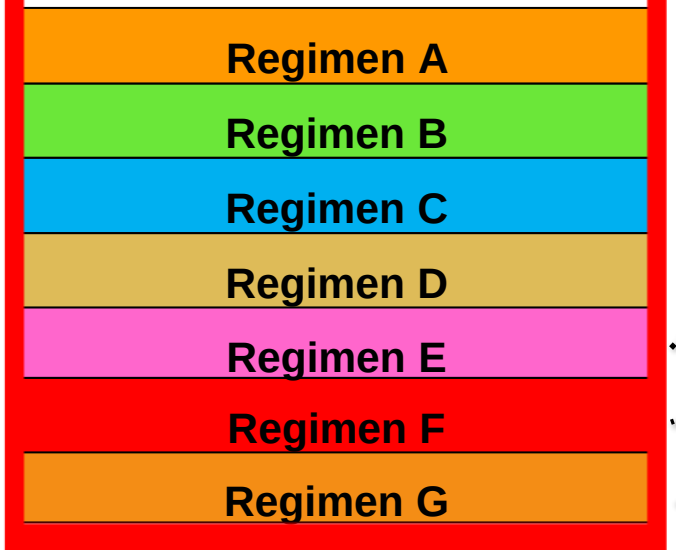


Functional Biomarkers for sALS: TDP-43

- Multiple TDP-43 readouts coming:
  - cryptic peptides (e.g. ELISA), RNA analytics
- Needed studies
  - The first two identified- more are likely to come
  - Need data on reliability, reproducibility, sensitivity
    - Banked CSF may be used
  - Correlation with disease parameters
    - rate of progression, clinical subtypes, age, sex, etc
  - Response to drugs ??
  - Correlation with existing biomarkers: NFL?, inflammation, etc

HEALEY ALS Platform Trial:



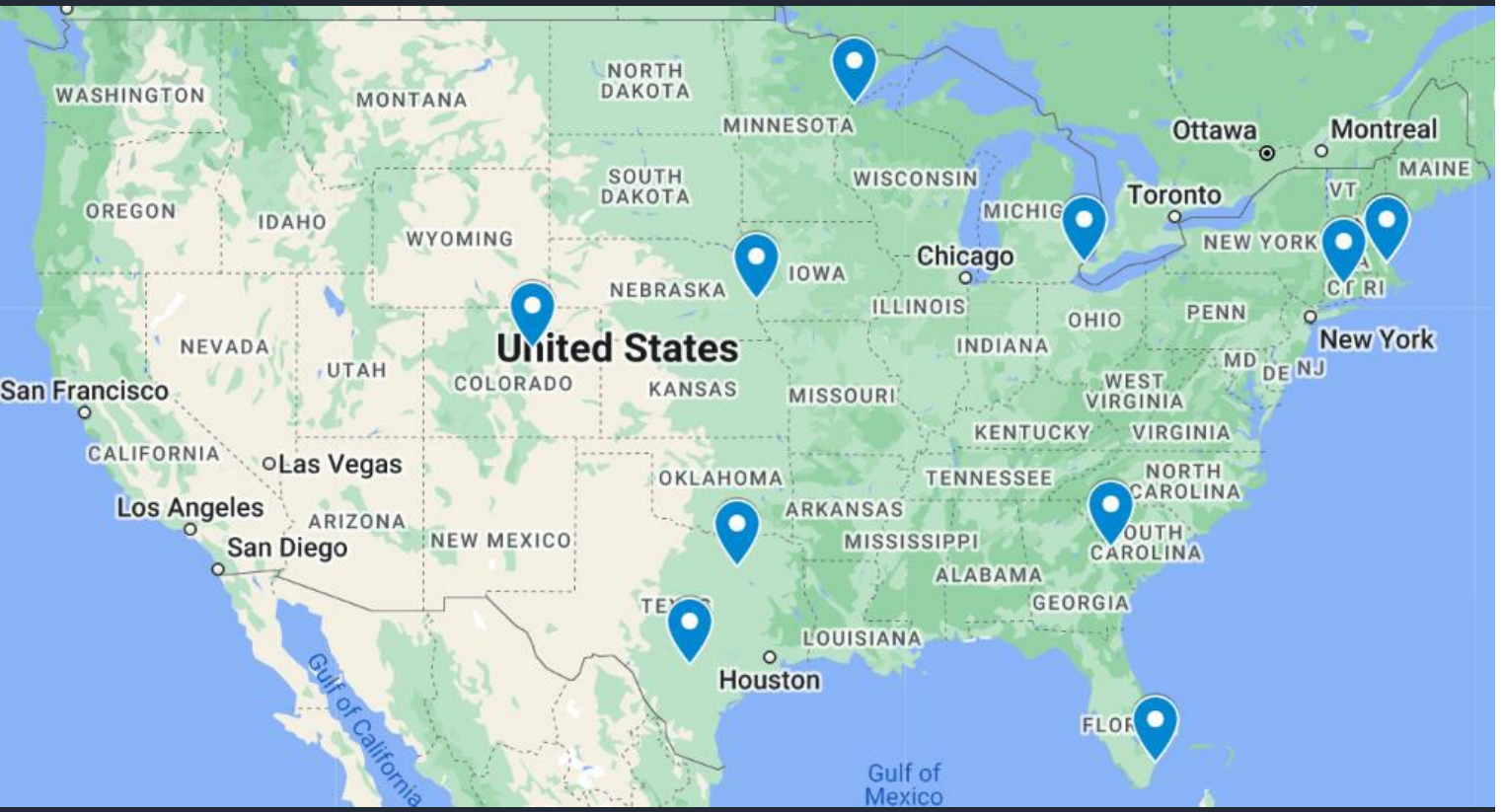


SEELOS THERAPEUTICS | ENROLLMENT COMPLETE

Calico | IN START-UP

DENALI THERAPEUTICS | IN START-UP

11 Sites Currently Active for Regimen F



(as of 3/16/23)

- Nova Southeastern University
- Essentia Health
- Texas Neurology
- Mass General Hospital
- University of Nebraska
- Hospital for Special Care
- Henry Ford Hospital
- Augusta University
- Beth Israel Deaconess
- University of Texas HSC
- University of Colorado

Site Map & Contacts:

https://bit.ly/3g2NZr5

Regimen F Resources on MGH Website

Regimen F: ABBV-CLS-7262, by Calico and AbbVie- Now Recruiting

ABBV-CLS-7262 is an investigational drug developed by Calico Life Sciences LLC in collaboration with AbbVie Inc. ABBV-CLS-7262 aims to restore function in cells affected by ALS by normalizing protein synthesis and preventing further sequestration and aggregation of TDP-43, thereby protecting neurons, and possibly slowing ALS progression.

The integrated stress response (ISR) is a fundamental transient process that regulates cell function during various stressful conditions. Tissue studies suggest that the ISR is chronically induced in people with ALS. It is proposed that TDP-43 aggregates, a hallmark feature in the motor neurons of people with ALS, could be formed by a chronically induced ISR. ABBV-CLS-7262 activates the protein complex eIF2B, which is a key regulator of the ISR. Binding of ABBV-CLS-7262 desensitizes eIF2B to stress and decreases the ISR. Reduction of the ISR restores normal protein synthesis, reduces TDP-43 sequestration in stress granules, and may decrease TDP-43 aggregation.

A prior first-in-human study of ABBV-CLS-7262 showed that this drug was well-tolerated by participants, demonstrated target engagement by increasing eIF2B enzymatic activity, and suppressed the ISR in blood cells. ABBV-CLS-7262 crossed the blood brain barrier at concentrations predicted to be efficacious in ALS. ABBV-CLS-7262 is currently being investigated in a Phase 1b study in people with ALS (NCT04948645), and will be studied further as part of the HEALEY ALS Platform Trial.

Watch this video for more information on the mechanism of action behind ABBV-CLS-7262.

Download brochure

Healey Center
Sean M. Healey & AMG Center for ALS at Mass General

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

HEALEY ALS Platform Trial

Regimen F

ABBV-CLS-7262

Developed by Calico Life Sciences LLC in collaboration with AbbVie Inc.

Investigational products included in the HEALEY ALS Platform Trial are selected by a team of experts after careful review of the study drug and the science supporting its treatment potential in Amyotrophic Lateral Sclerosis (ALS). Regimen F is testing an experimental medication called ABBV-CLS-7262, and the trial will involve in-person study visits every 4 to 8 weeks (about 6 visits total over the course of 24 weeks).

Please discuss the possible benefits and risks of this investigational product with your study team.

Visit our website to learn more about what to expect in the trial process:
https://bit.ly/3ExRal8

About Regimen F:

Regimen F is a Phase 2/3 trial enrolling approximately 240 participants to evaluate the safety and efficacy of ABBV-CLS-7262 as a potential treatment for ALS. This regimen involves biomarker analysis and cerebrospinal fluid collection via lumbar punctures to assess the effects of ABBV-CLS-7262.

3:1 Active Drug to Placebo Ratio: Participants who enroll in this trial have a 3 in 4 (75%) chance of being assigned to active study drug and a 1 in 4 (25%) chance of being assigned to placebo during the initial 24-week randomized controlled trial (RCT) period.

Active Treatment Extension (ATE): Participants have the option to enroll in the ATE for ABBV-CLS-7262 upon completion of the 24-week RCT. During ATE, all participants will receive the active study drug.

To see if you may qualify, please review the list of eligibility criteria:
https://bit.ly/30ctynm

For general questions about the HEALEY ALS Platform Trial, **Contact the Patient Navigator:**

healeyalsplatform@mgh.harvard.edu
833-425-8257 (HALT ALS)

https://bit.ly/3SIwH4X

Printable Brochures!

↓

Regimen F Brochure

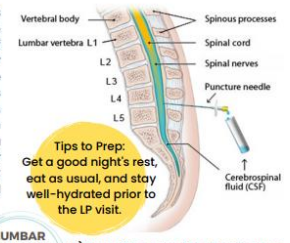
Lumbar Puncture Brochure

General Platform Trial Brochure

Understanding HEALEY ALS Platform Trial Study Procedures

LUMBAR PUNCTURE

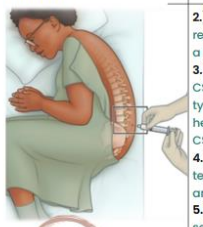
A Lumbar Puncture (LP), or Spinal Tap, is a procedure to remove a small sample (10-15mL or ~1 tablespoon) of cerebrospinal fluid (CSF) from the lower spine. CSF is the fluid that surrounds the brain and spinal cord, and it contains proteins, cells, and other substances that may be important biomarkers in ALS research. During the procedure, a needle is inserted between two lumbar vertebrae (backbones) in the lower back and into the space in the spinal canal that contains CSF.



Tips to Prep: Get a good night's rest, eat as usual, and stay well-hydrated prior to the LP visit.

Sometimes, people feel worried that a lumbar puncture could be risky or painful. In reality, this is a safe and common procedure to collect CSF!

LUMBAR PUNCTURE STEP BY STEP



1.) You will be asked to sit or lie down in a position that helps widen the spaces between the bones of the lower spine.

2.) The doctor will cleanse the skin on your lower back to reduce risk of infection, then use a small needle to inject a local anesthetic (such as lidocaine) to numb the site.

3.) The LP needle is inserted into the space containing CSF. A special atraumatic spinal needle (Sprotte) is typically used to reduce the chance of a post-puncture headache. The doctor may need to readjust the needle if CSF cannot be drawn with the first insertion.

4.) Spinal fluid is collected into specimen tubes for lab testing. The LP needle is removed, your back is cleaned, and a band-aid is placed over the LP site.

5.) For your comfort and safety, it is recommended that someone drive you to and from the LP study visit.

QUESTIONS? Prior to enrolling in a clinical trial, your study team will discuss the LP procedure with you. Please ask your study team for clarification if you have any questions while reviewing the informed consent form.

Patient Navigation
Central resource for people living with ALS

Catherine Small

Allison Bulat

Phone: 833-425-8257 (HALT ALS)

E-mail:healeyalsplatform@mgh.harvard.edu

Weekly webinar registration:

https://bit.ly/3r6Nd2L

ALS Link sign-up:

https://bit.ly/3o2Ds3m

Upcoming (Spring!) Webinars:

March 23- Biomarker Discussion with **Jeffrey Rothstein, MD PhD** (Johns Hopkins)

March 27- Regimen F Drug Science Q&A with Calico

March 30- Weekly Q&A