ALS Research Update

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Disclosures

Research Support: NIH, CDC, Target ALS Foundation, ALS Association, Johns Hopkins University, LKSOM at Temple University.

Chair, Programmatic Panel, Department of Defense (CDMRP) ALS Research Program

Board of Directors, ALS Hope Foundation

Scientific Advisory Board, Everything ALS Foundation

Research in neurological diseases: lost in translation?

John W Griffin

FEBRUARY 2006 VOL 2 NO 2
NATURE CLINICAL PRACTICE NEUROLOGY

JW Griffin is the Editor-in-Chief of Nature Clinical Practice Neurology, and Director of the Department of Neurology and Neurologist-in-Chief at Johns Hopkins University School of Medicine, Baltimore, MD, USA.

The brain sciences are on a roll. Young scientists are choosing the neurosciences for their careers, basic discoveries are accruing at a breathtaking rate, and the relevance of these discoveries to neurological disease is increasing. Accordingly, the governmental funding base for brain research has substantially expanded in the US and other countries in the past decade.

Nevertheless, there is palpable restlessness among disease advocacy groups, philanthropists and neurological investigators. For investigators, the problems are heightened by relative reductions in government funding, notably at the NIH. Among advocacy groups, the mood is one of impatience and frustration; effective treatments for the most prevalent diseases are not emerging at the rate that might have been predicted from the level of investment.

Many investigators and advocacy groups acknowledge deep structural problems in translational research. Government research agencies are viewed as slow in turnaround, bureaucratic, lacking the will to support innovation, and more comfortable supporting incremental research.

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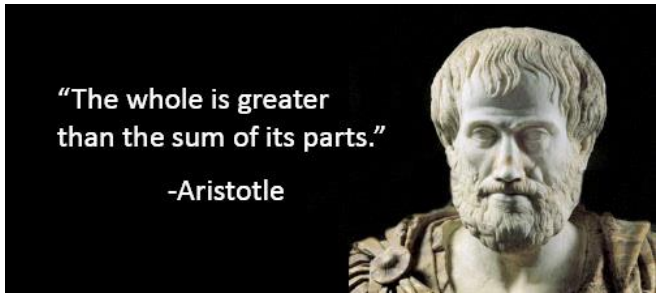
Dr. Griffin's brief essay concluded with a list of recommended strategies that non-governmental funding sources could strive to adopt. These included:

- "**focusing on speed** in answering the 'next questions' by *setting aside flexible funds that can be directed promptly*...
- requiring unfettered exchange of ideas and data...
- and developing new intellectual-property approaches that do not delay progress."

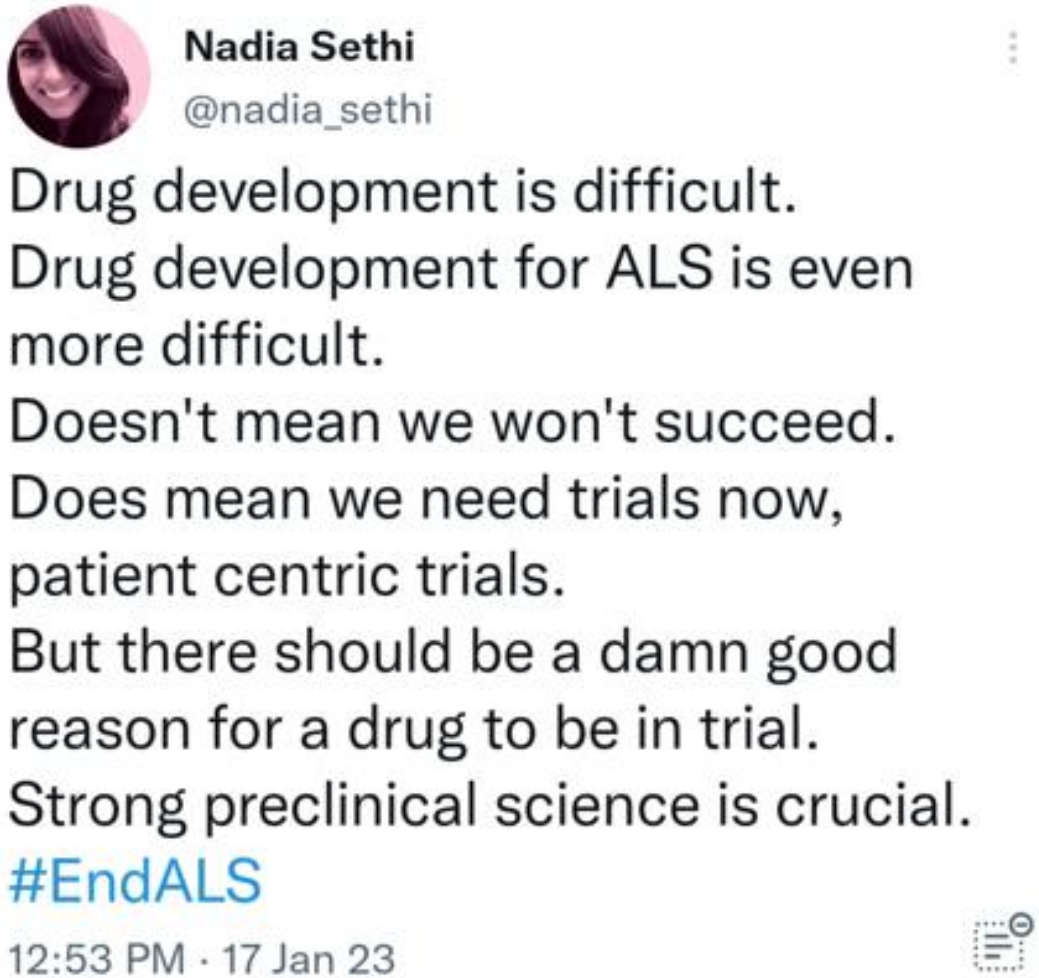
While written over a decade ago, today these ideas still feel forward-thinking, or even downright futuristic, as finding practical ways to implement these principles is not easy.



Jeremy Shefner, MD, PhD

What makes a successful trial?

- A drug with good preclinical science
- Adequate pharmacokinetic information
- The appropriate dose
- An easily measured outcome relevant to disease progression
- An effective design
- Sample size and power that depend on the trial goals.

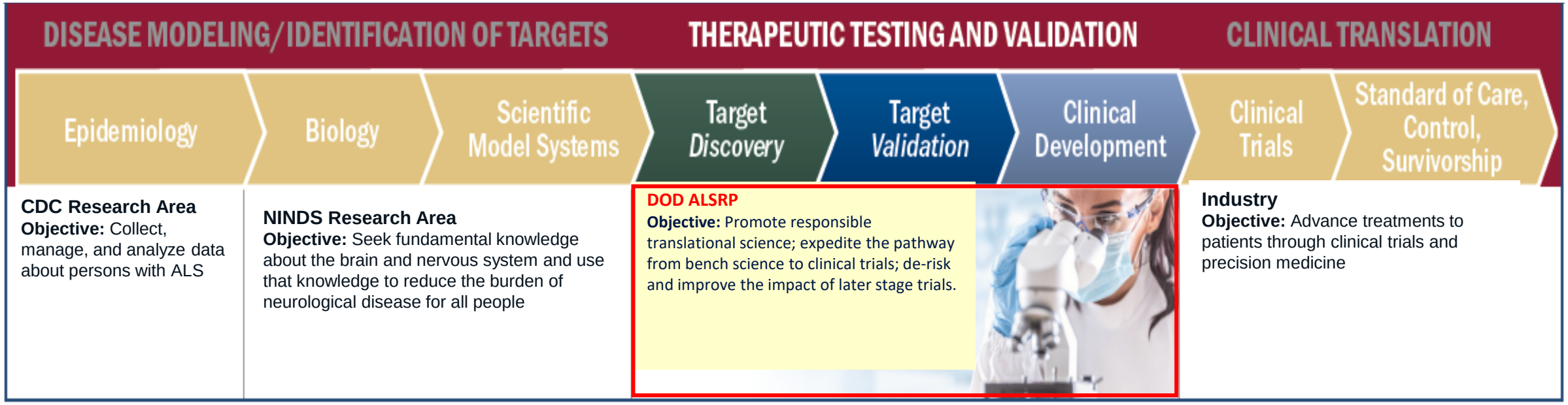


What is a *research pipeline*?

pipeline (n.)

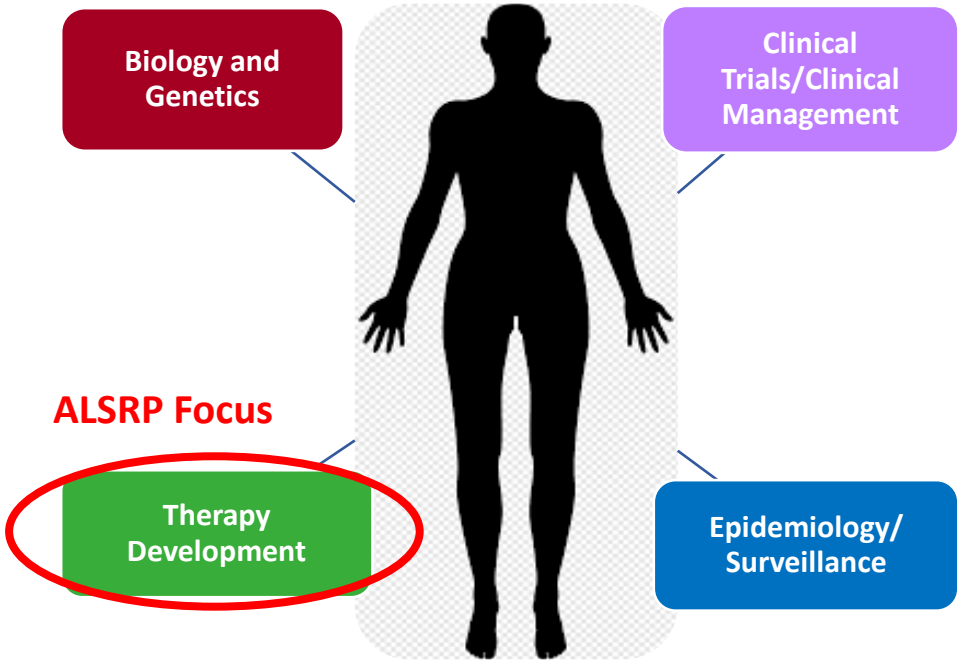
1859, "continuous conduit of pipes chiefly laid underground," from **pipe** (n.1) + **line** (n.). Figurative sense of "channel of communication" is from 1921; surfer slang meaning "hollow part of a large wave" is attested by 1963.

ALS Research Landscape?



A pathway through which discoveries in the laboratory lead to <u>therapeutic development</u> and clinical trials:

- ❑ Proof-of-concept drug discovery
- ❑ Investigational New Drug (IND)-enabling studies
- ❑ Maximization of ALS repositories to link ALS patient biosamples to rigorous molecular data and to <u>validate clinical biomarkers</u>
- ❑ Early phase intervention trials, <u>with compelling biomarker data</u>, to inform and de-risk more advanced trials for the treatment or management of ALS
- ❑ Improve aspects of current ALS clinical care

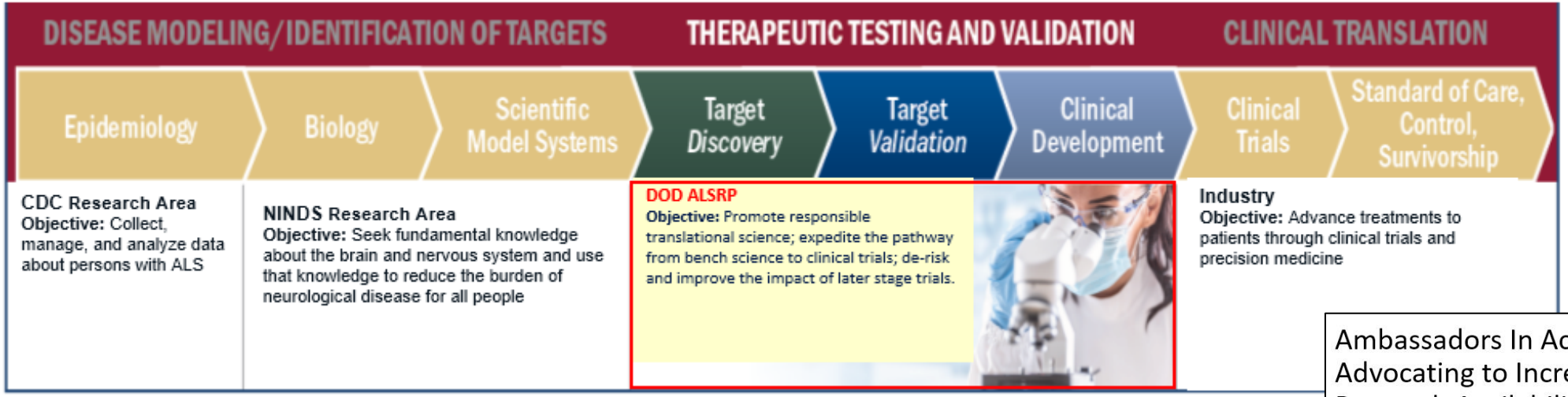


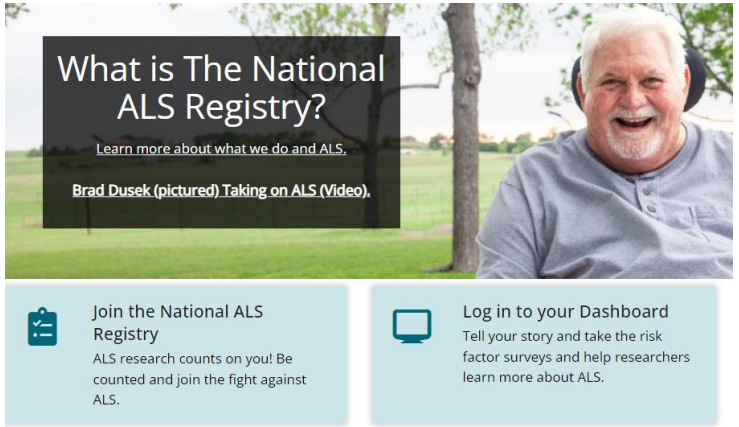
“When did I decide to become a cowboy? I thought we were doctors.”

“wearing many hats”

- Refers to the hats of different uniforms.
- The **Grand Poobah** from Gilbert and Sullivan’s *The Mikado* (1885) – basically held every office in the town of Titipu. First Lord of the Treasury, Lord Chief Justice, Comander-in-Chief, Lord High Armiral, Archbishop, Lord Mayor, Lord High Everything Else.”
- “I wear two hats. Are you asking me this question as president of the Bartenders’ Union or as chairman of the ABC?” (*from an interview published in a 1972 issue of The Village Voice*).

*This is actually Sam Slagheap, the **Exalted Grand Poobah** of the Loyal Order of Water Buffaloes*





Join the National ALS Registry
ALS research counts on you! Be counted and join the fight against ALS.

Log in to your Dashboard
Tell your story and take the risk factor surveys and help researchers learn more about ALS.

Ambassadors In Action- Fundraising to Increase Availability

- Played key roles in raising hundreds of millions for research
- Ex. the Ch

Amyotrophic Later

Ambassadors In Action- Advocating to Increase Research Availability

- Thousands of interactions with members of Congress
  - Helped obtain and maintain funding for National ALS Registry
  - Helped obtain and grow funding for DOD's ALSRP
  - Facilitated Act For ALS in 2021
    - $500 million in new funds for ALS Research and Expanded Access!

Results from the Registry Engagement Session & Future Priorities

Danielle Boyce, DPA, MPH
Stephen Finger and Cathy Collet
Engagement Sessions Team

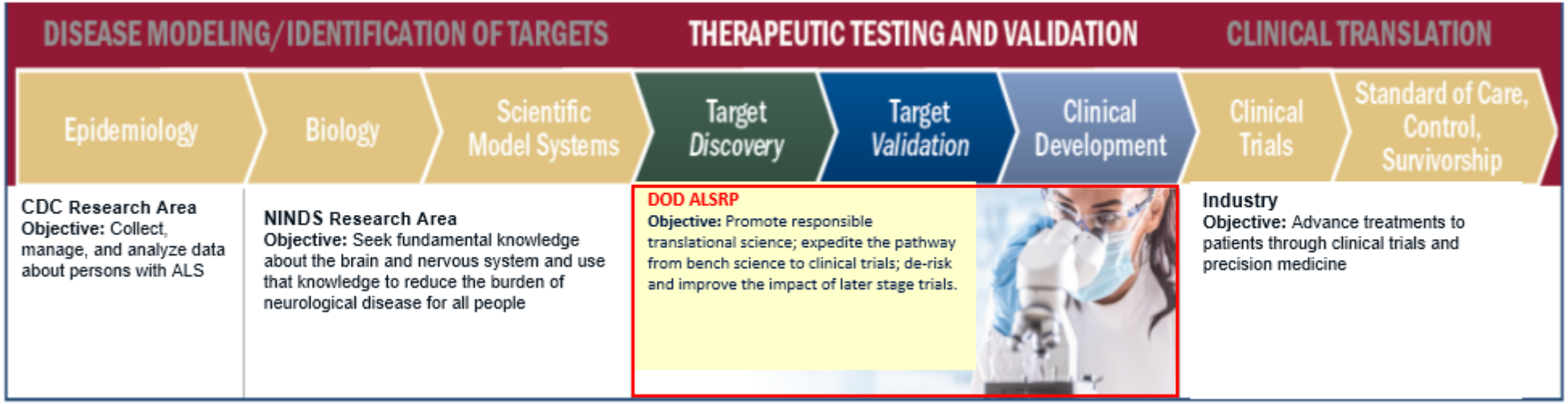
Regarding public engagement, listening sessions were launched in Summer 2022 with patients and caregivers. Led by Dr. Danielle Boyce, the purpose of these sessions was to provide input about where the Registry could make improvements. The 4 sessions allowed for open dialogue between the Registry and stakeholders. More sessions are planned for Fall 2022 to continue these dialogues.

ALS Strategic Planning Workshop

October 26, 2022 | 10:00 - October 27, 2022 | 5:00

The National Institute of Neurological Disorders and Stroke (NINDS) has initiated a strategic planning process to identify the highest priorities for research that will lead to the discovery of effective interventions for the diagnosis, treatment, management, prevention, or cure of ALS. A steering committee and topic-based working groups comprised of scientists, clinicians, advocates, people living with ALS, and their caregivers used information from a Request for Information (pdf, 180 KB), along with their own knowledge of the research landscape, to develop research priorities for:

- Accelerating research on the biology behind ALS
- Translating fundamental research into potential ALS therapies
- Optimizing ALS clinical research
- Optimizing the quality of life for persons living with ALS and their caregivers
- Identifying opportunities for collaborations and partnerships



Ambassadors In Action-Accelerating Regulatory Pathway

- Participated (with many others) in creating ALS FDA Drug Development Guidance
- Participated (with many others) in recent meetings with FDA, congress related to regulatory aspects of drug development
- Testified at recent FDA hearings on AMX0035
  - Approved in September 2022

BLOG POST from the ALS ASSOCIATION

Case of AMX0035 Proves Advocacy from ALS Community Can Impact Drug Development

Ambassadors In Action-Improving Study Designs

- Interacting with ALS researchers to design more attractive, patient-friendly studies
  - Reviewers for TREAT ALS, DOD ALSRP grant submissions
  - Connecting with funded investigators (ex. Anne Marie Willis, Rick Bedlack)
  - Connecting with Sponsors

PATIENT ADVISORY BOARDS

- MT Pharma
- Biogen
- Cytokinetics
- Avexis
- Patients Like Me
- ALS Untangled
- CReATe Consortium
- HEALEY ALS Platform Trial
- ALS Association
- Patients Like Me
- Corcept Therapeutics
- OSU Medical Center
- AI Therapeutics
- AI Therapeutics
- Alector
- Cytokinetics
- Clinwiki
- (Picnic Health)
- NURO Corp
- (Annexon)
- (Medicinova)

Morris ALS/MND Principles Certificate

Thank you for upholding the Morris ALS/MND Principles!

CDMRP ALSRP

You act with urgency and put those living with ALS and their loved ones first.

Nothing about us without us.

THE MORRIS ALS PRINCIPLES

People living with and impacted by ALS,

Sandy Morris

Sandy Morris,
Person living with ALS

Shelly Hoover

Shelly Hoover,
Person living with ALS

https://morrisalsprinciples.org

FIRST OPINION

The Morris ALS Principles: A model for empowering all disease communities

By Irene Shapiro July 27, 2022

CDMRP ALSRP – Tuesday, June 7, 2022

The CDMRP ALS Research Program (ALSRP) included people living with ALS (PLWALS) on all scientific advisory bodies related to ALS research. Since its inception, the CDMRP ALSRP has included people with lived experience of ALS (PLEx) as consumer reviewers of research grant awards. The scores and input of consumer reviewers carry equal weight as that of the scientific reviewers — a seat and voice at the award ranking table.

DoD (CDMRP) ALS Research Program

https://cdmrp.army.mil/alsrp

Home / Research Programs / Amyotrophic Lateral Sclerosis

News & Highlights

- USC Stem Cell-led studies point the way to broadly effective treatments for ALS (external link)
- FY23 ALSRP Funding Opportunities
- A Combined Cell and Gene Therapy Approach for Preserving Motor Neuron Function in ALS
- FY22 ALSRP Recommended for Funding List
- ALSRP Program Summary Sheet
- Research Resources
- More...

Vision

Improve treatments and find cures for people with ALS

Mission

Fund impactful research to develop ALS treatments

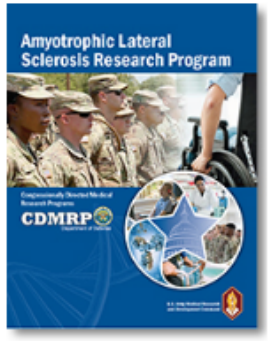
Feedback

Amyotrophic Lateral Sclerosis

Vision *– Improve treatments and find cures for people with ALS*

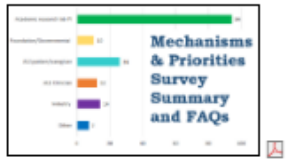
Amyotrophic Lateral Sclerosis (ALS), also known as "Lou Gehrig's disease," is a degenerative neurological disorder without a cure. For reasons that are not well understood, the nerve cells in the brain and spinal cord that control voluntary muscle movement gradually deteriorate. ALS can be difficult to diagnose because the initial symptoms are both subtle and vague and can be attributed to a number of other conditions. Average life expectancy after diagnosis ranges between 3 to 5 years from the onset of symptoms. It is estimated that 5-10% of all ALS cases are inherited (familial disease) while the remaining 90-95% are sporadic, with unknown etiology and risk factors. There is currently no known cure or therapy to effectively halt the progression of ALS. Evidence from scientific research suggests a mutually inclusive relationship between ALS and military service, with a higher rate of incidence in the Veteran population, without any known reason(s) for this incidence.

The ALSRP is guided by a vision to improve treatments and find cures for people with ALS. Through its award mechanisms and funding recommendations, the ALSRP specifically supports impactful research to develop ALS treatments.



» Click on Image to View Program Booklet

» Click on Image to View Strategic Plan



» Click on Image to View Survey Summary and FAQs

ALSRP Supported Initiatives

- Research Resources

Congressional Appropriations

Funding Summary

Programmatic Panels

Peer Review Participants

CDMRP Brief History

- In the early 1990s, grassroots efforts heightened political awareness of breast cancer.
- Congress appropriated $210M to the Fiscal Year 1993 (FY93) DoD budget for a new Breast Cancer Research Program (BCRP) and USAMRDC was directed to administer the program
- The Army sought the advice of the National Academy of Medicine (NAM), which resulted in:
  - A **two-tier review process** – scientific and programmatic reviews
  - A new research model – **fully integrating consumers** into program policy, investment strategy, and research focus
- Congress has added additional research programs and topics to be administered by CDMRP since FY96, including a treatment-focused ALS Research Program beginning in FY07
- Today, CDMRP's are each annually directed, single-year appropriations in the Department of Defense Appropriations Act by sponsoring Members of the House and Senate and at the request of advocates

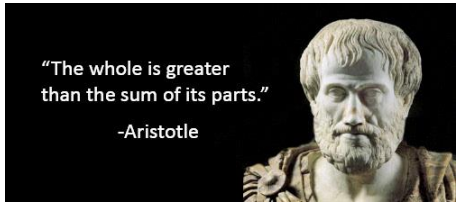
CDMRP Hallmark – involvement of pALS and cALS

Grassroots consumer efforts led to targeted research funding and the creation of the CDMRP. The voices and experiences of consumers plays a pivotal role in the growth of CDMRP research programs

Over 2,100 consumers representing over 1,000 organizations have served on CDMRP Peer Review and Programmatic Review panels

How do we find and develop therapies?

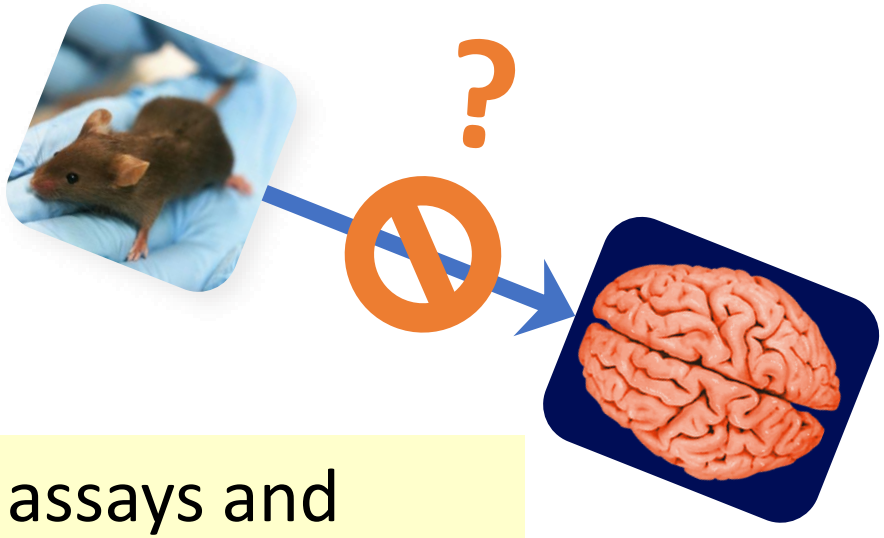
- How is research funded?
- What is ALS?
- How do we search for "***targets***" in the lab?
- What does "***validate***" mean and how can we do a better job of it?
- Why are some things in clinical trials and not other things that also sound exciting?
- Why have so many clinical trials failed?
  - How can we ***de-risk*** industry investments?



- What does "***biomarker***" actually mean?
  - What are the different kinds of biomarkers?
  - Which are most needed?
  - What does it mean to make a biomarker ready for clinical trials?
- ***"Why can't ALS we develop drugs like they do in cancer?" "In HIV?"***
- Can we harness our increasingly connected world to foster real-time collaboration and accelerate innovative drug discovery?

Amyotrophic Lateral Sclerosis

A fatal disorder with variable presentations, rates of progression, and biological “causes.”



- Despite promising preclinical data in laboratory assays and animal models, countless drug candidates have ***failed to translate*** into successful clinical trials.
  - *Are the animal models and cell cultures created by genetic manipulation a good model for what happens in people with ALS (pALS)?*
  - *Are we testing the right treatments in the right pALS, and at the right times?*
  - *Can we do a better job of **validating** new laboratory results with relevant **patient-derived laboratory tools**?*

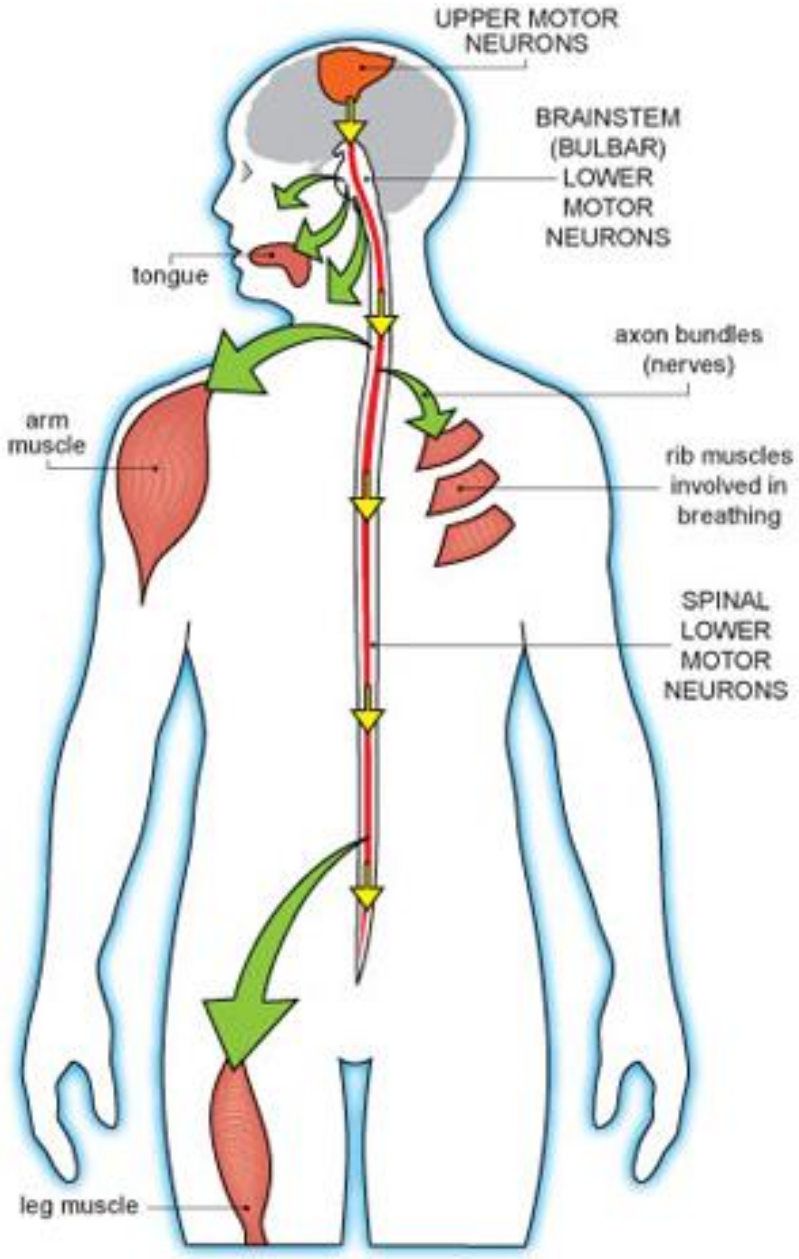
What is ALS?

A disease of progressive weakness

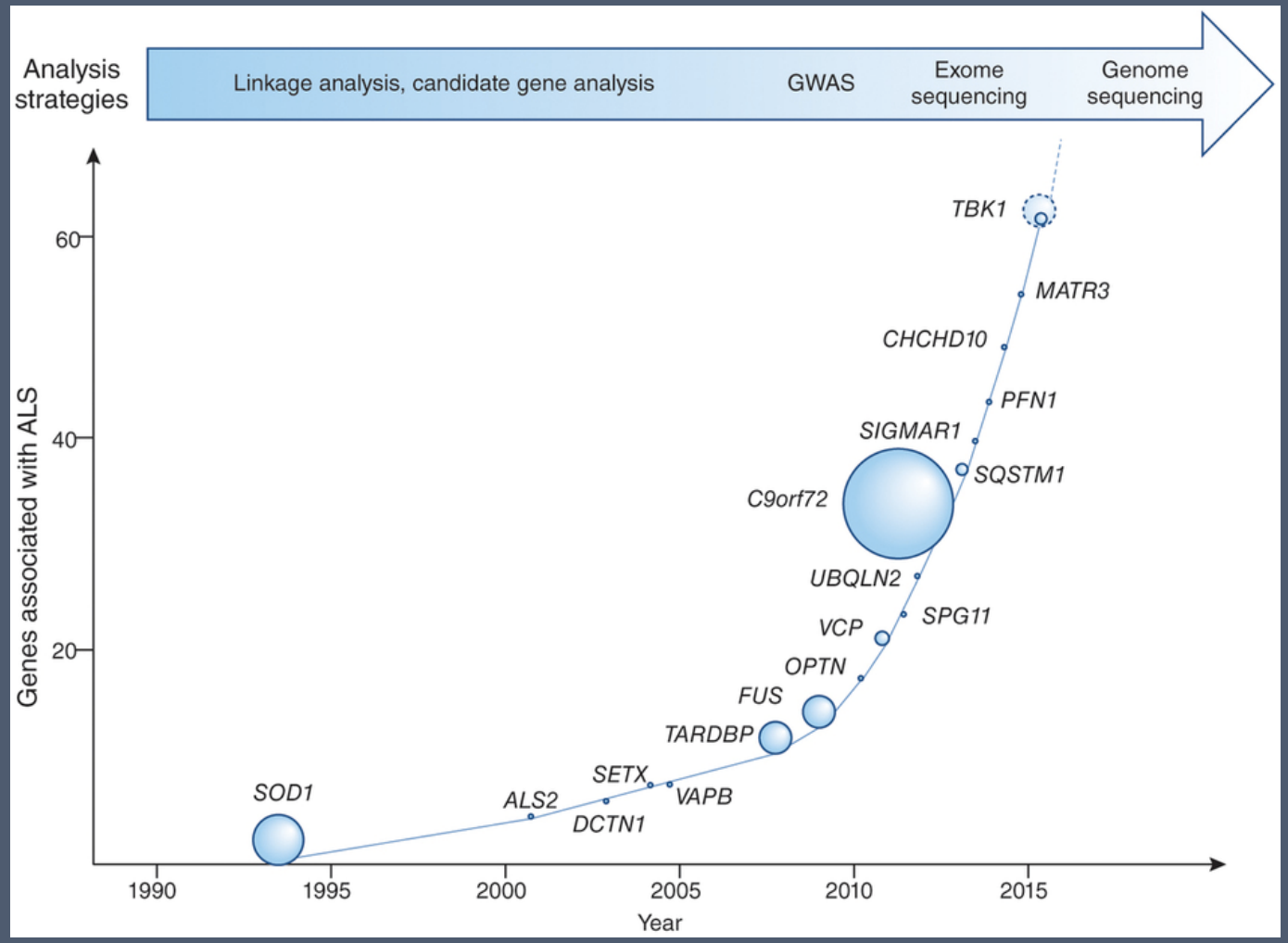
- Normally begins with mild symptoms in one or more muscle groups.
- Gradually “spreads” to affect skeletal muscles in any area of the body.
- Generally spares the muscles that control eye movements, and voluntary control of bowel and bladder.
- Some patients with ALS also develop frontotemporal dementia (FTD), and this is more common with certain genetic mutations (e.g. C9orf72).

ALS is a clinical diagnosis.

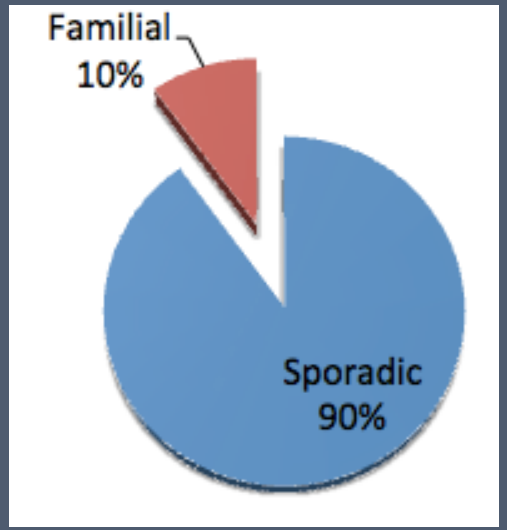
Except for the small percentage of cases due to known genetic mutations, there is no “test” to confirm a diagnosis of ALS other than autopsy.



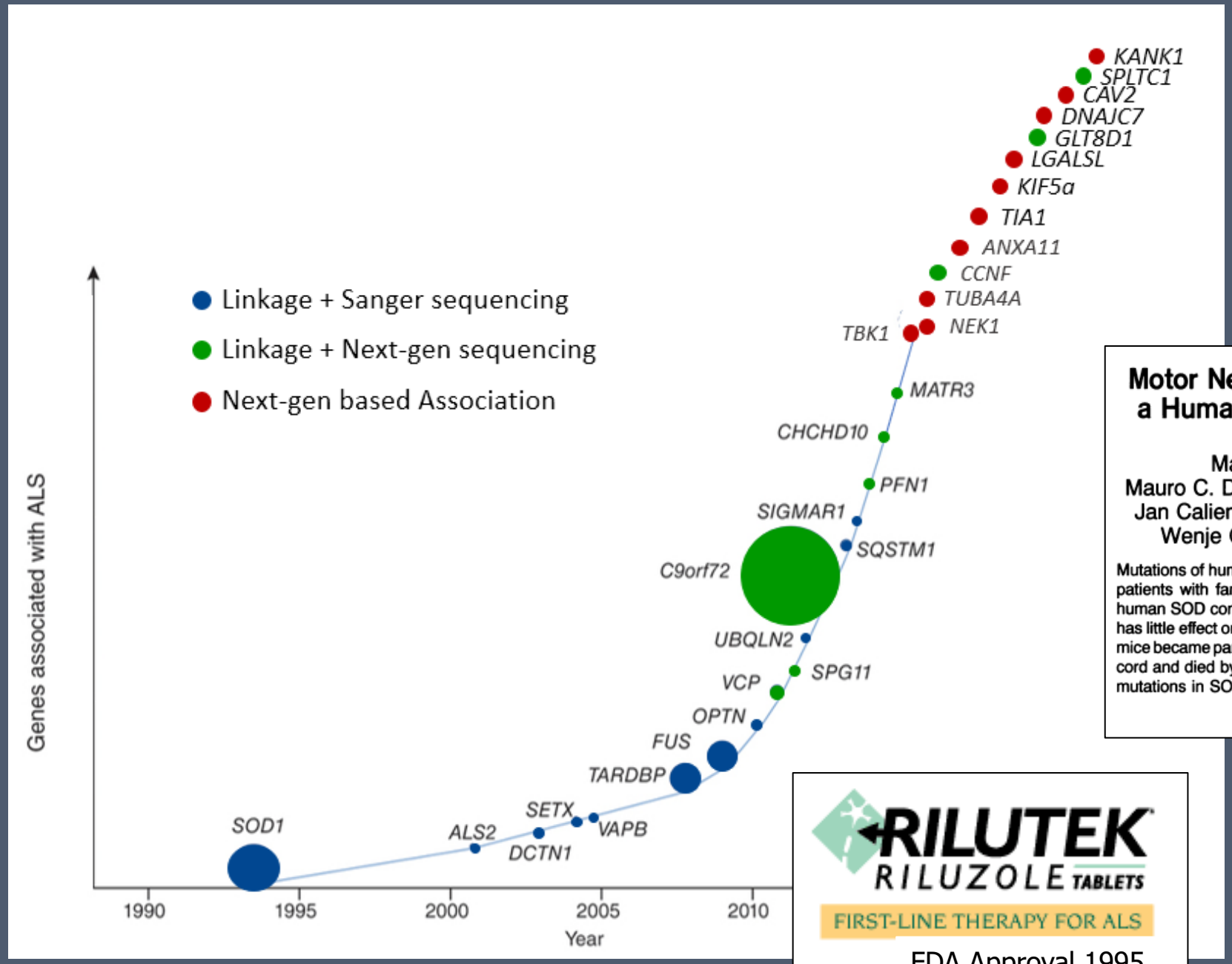
The cause(s) of most cases of ALS remain unknown

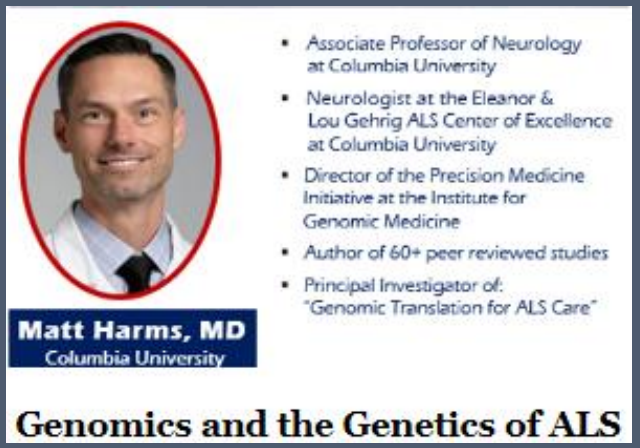


Bettencourt, C., Houlden, H. *Nat Neurosci* **18,** 611–613 (2015)



- Sporadic ALS (SALS)
  - Cause unknown
  - ~90% of cases
- Familial ALS (FALS)
  - Genetically linked
  - ~10% of cases





Motor Neuron Degeneration in Mice That Express a Human Cu,Zn Superoxide Dismutase Mutation

Mark E. Gurney,* Haifeng Pu, Arlene Y. Chiu, Mauro C. Dal Canto, Cynthia Y. Polchow, Denise D. Alexander, Jan Caliendo, Afif Hentati, Young W. Kwon, Han-Xiang Deng, Wenje Chen, Ping Zhai, Robert L. Sufit, Teepu Siddique

Mutations of human Cu,Zn superoxide dismutase (SOD) are found in about 20 percent of patients with familial amyotrophic lateral sclerosis (ALS). Expression of high levels of human SOD containing a substitution of glycine to alanine at position 93—a change that has little effect on enzyme activity—caused motor neuron disease in transgenic mice. The mice became paralyzed in one or more limbs as a result of motor neuron loss from the spinal cord and died by 5 to 6 months of age. The results show that dominant, gain-of-function mutations in SOD contribute to the pathogenesis of familial ALS.

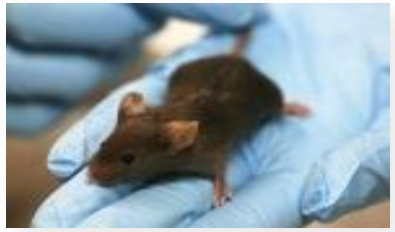
SCIENCE • VOL. 264 • 17 JUNE 1994

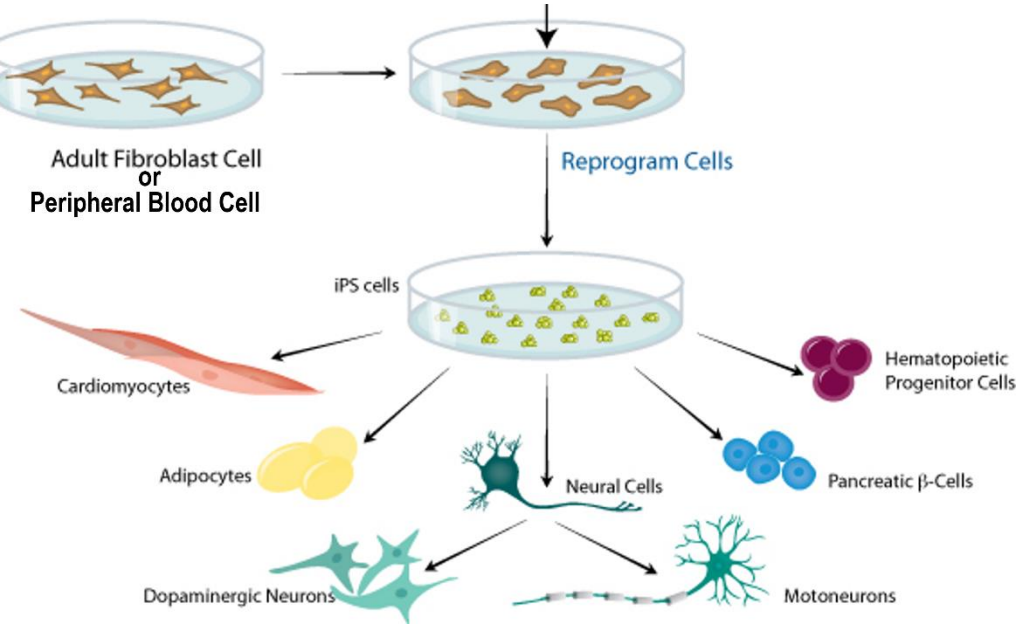
RILUTEK
RILUZOLE TABLETS
FIRST-LINE THERAPY FOR ALS

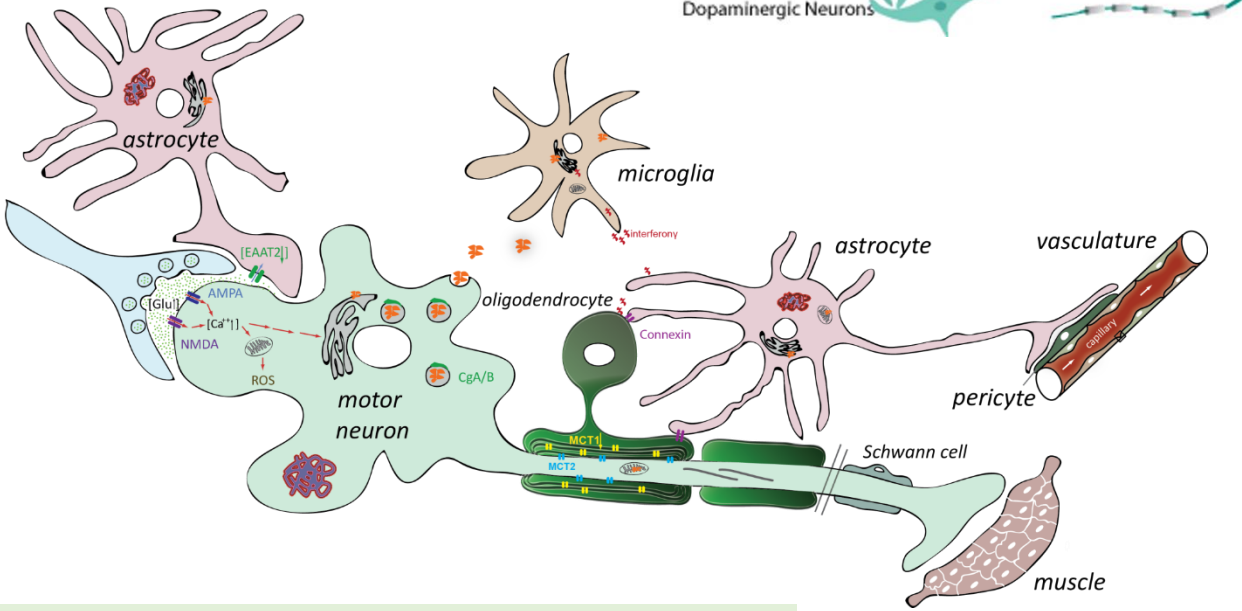
FDA Approval 1995

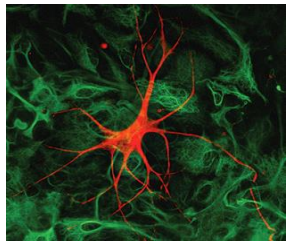
A few examples of "pathogenic" mechanisms implicated in ALS

- Glutamate induced excitotoxicity
- Reactive gliosis and other astrocyte dysfunction
- Oxidative stress
- protein aggregation / misfolded proteins
- ER stress
- Mitochondrial dysfunction
- Activation of neuro-inflammation
- Impaired axonal transport
- Oligodendrocyte dysfunction
- Axonal degeneration
- Dysfunctional RNA processing
- Endogenous Retroviruses
- Abnormal Nucleocytoplasmic Transport
- TDP-43 mis-localization and loss of function
- Microglial activation
- Abnormal calcium homeostasis
- Dysfunctional protein quality control
- Autophagy
- Cortical hyperexcitability
- Environmental exposures



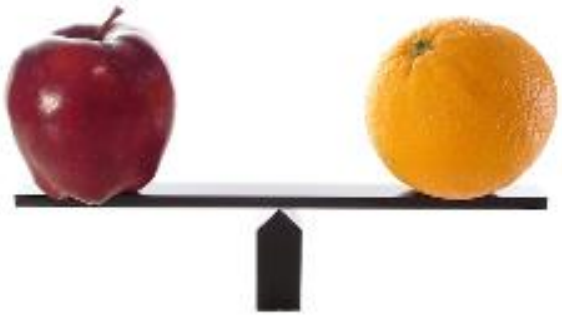


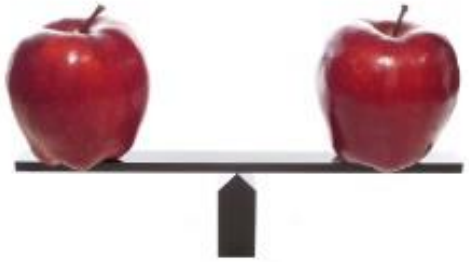


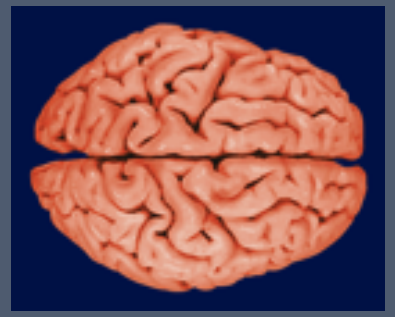


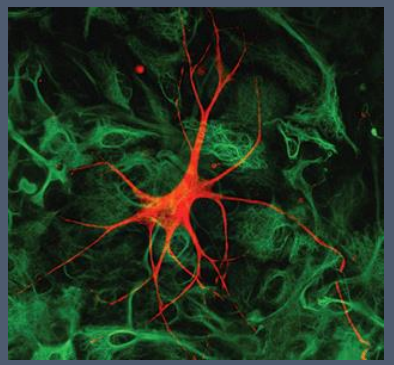
There are many cells and pathways that likely contribute to neurodegeneration in ALS

How do we look for therapeutic targets?

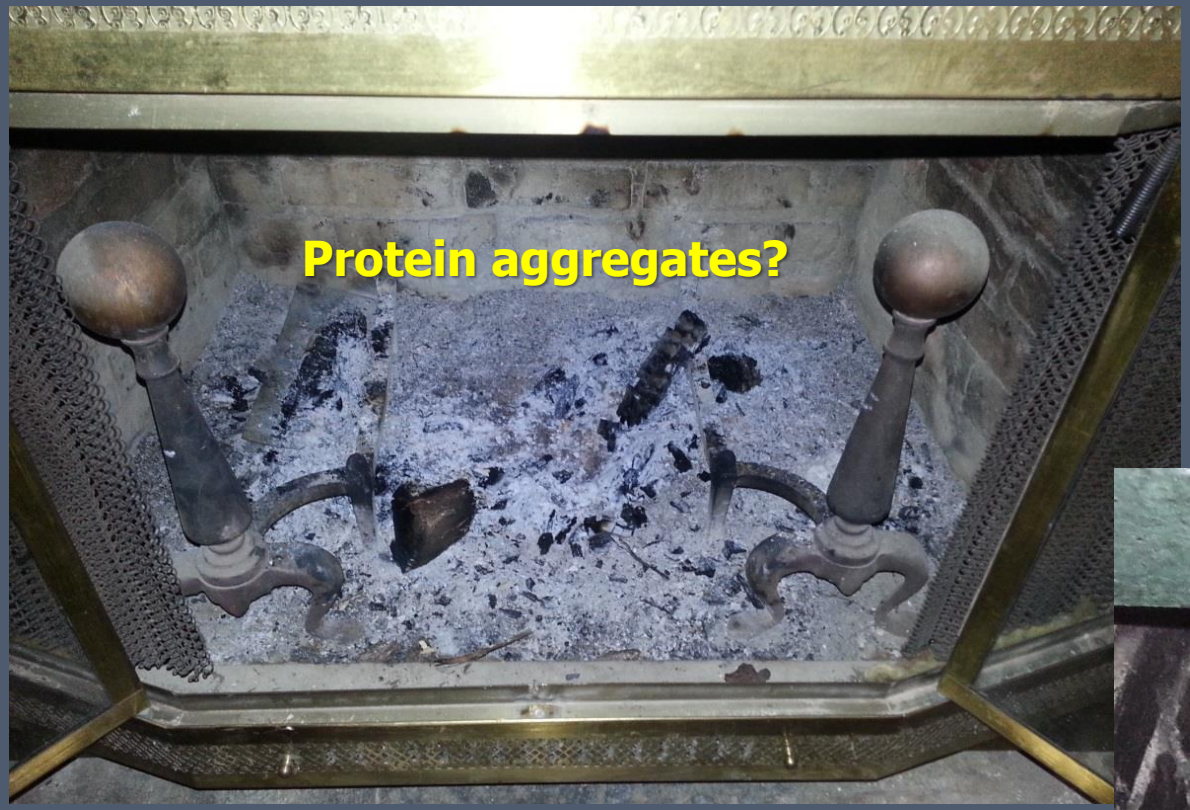


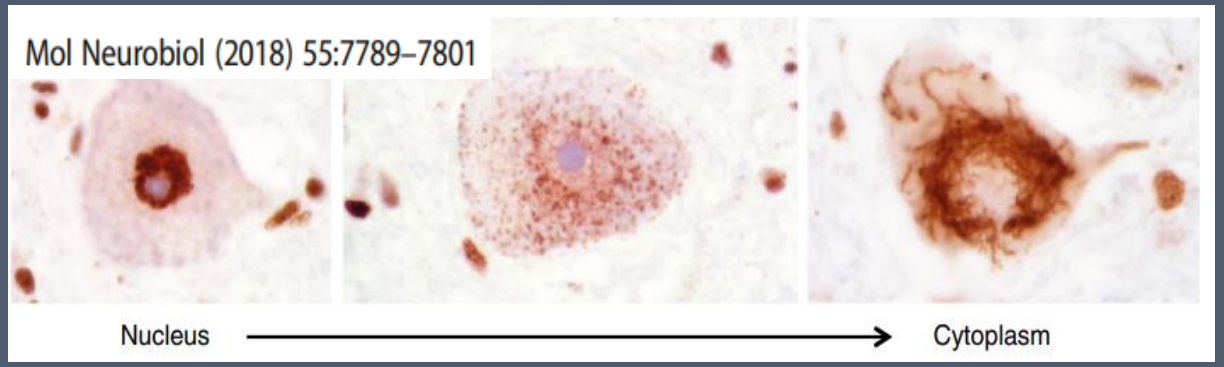







Saline
vs
rhMG53





TDP-43 is translocated to cytoplasm.

- Loss of nuclear function
- Gain of toxic cytoplasmic function

Pathological TDP-43 inclusions are found in over 90% of ALS and 50% of FTD cases.

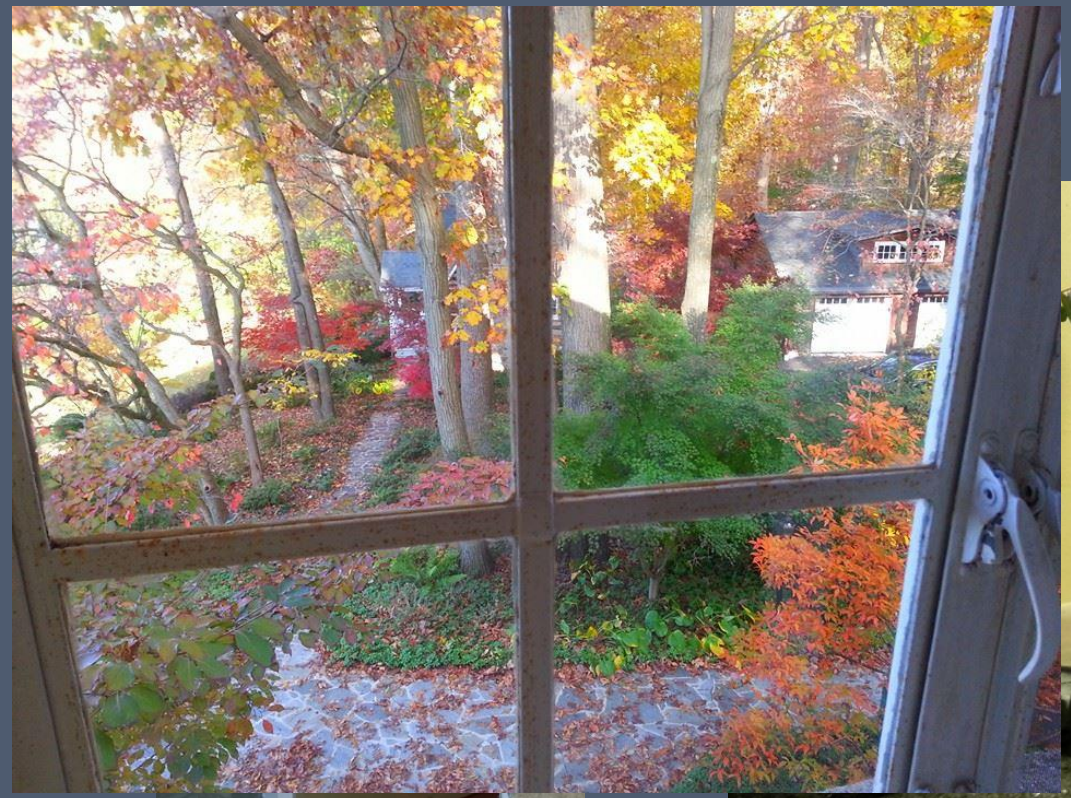
Mitochondrial dysfunction?
Oxidative stress?
Dysfunctional energy transport?

By adjusting inter-related pathways, we try to compensate for the abnormality

- ALS is a clinical diagnosis.
- There likely are many distinct “causes” of ALS.
- In most cases, the disease may be the product of multiple inter-related factors.
- Many efforts are focused on identifying **distinct patient subsets**, such as with various integrated –omics approaches.

Ideally, we would like to address the underlying causative abnormality, such as a specific genetic mutation.

We still don’t understand how so many general cellular mechanisms and diverse mutations can all cause the very specific clinical picture seen in ALS.



The genetic mutation!

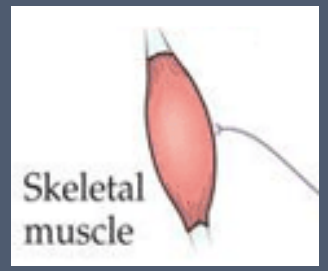

LEGO
SUPER HEROES

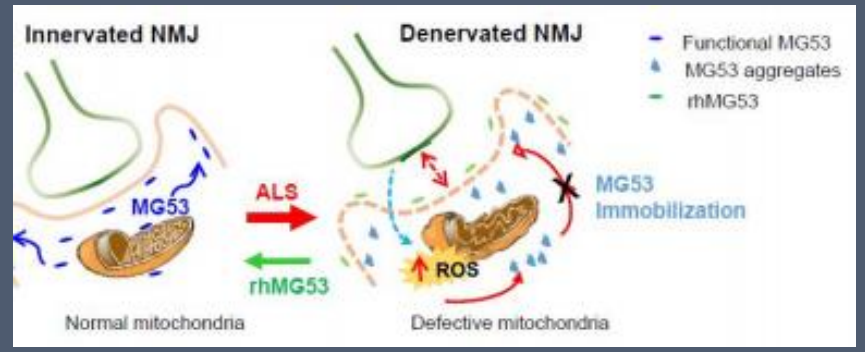
Antioxidants **2021**, *10*, 1522. https://doi.org/10.3390/antiox10101522

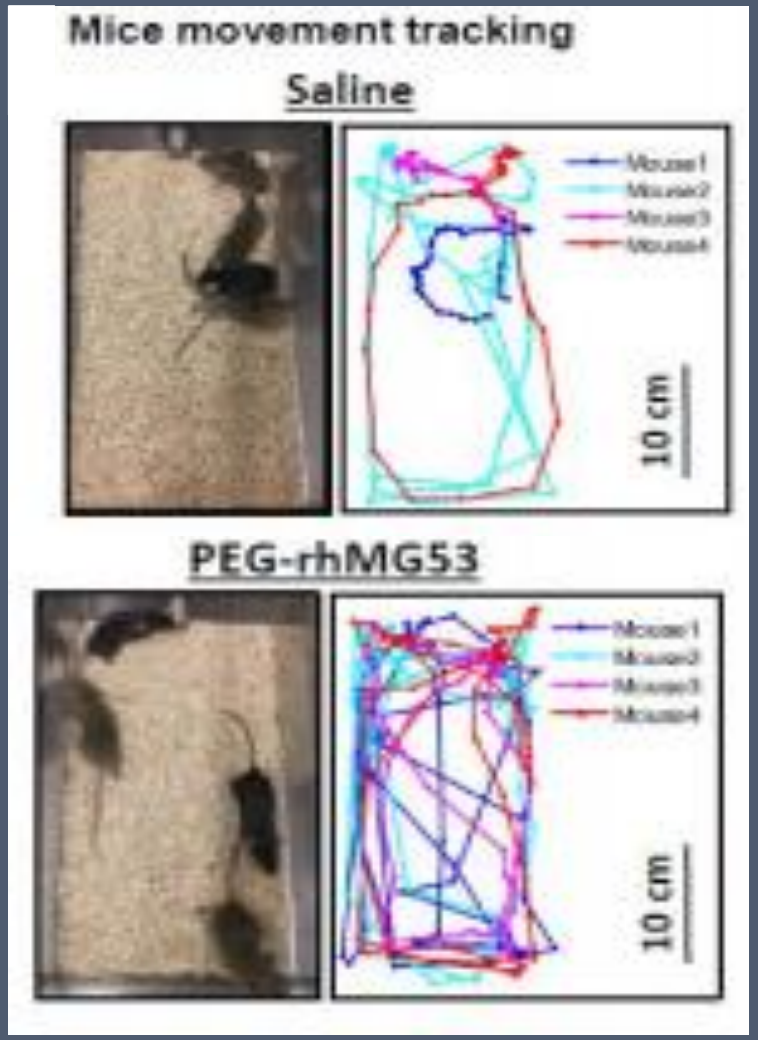
Article

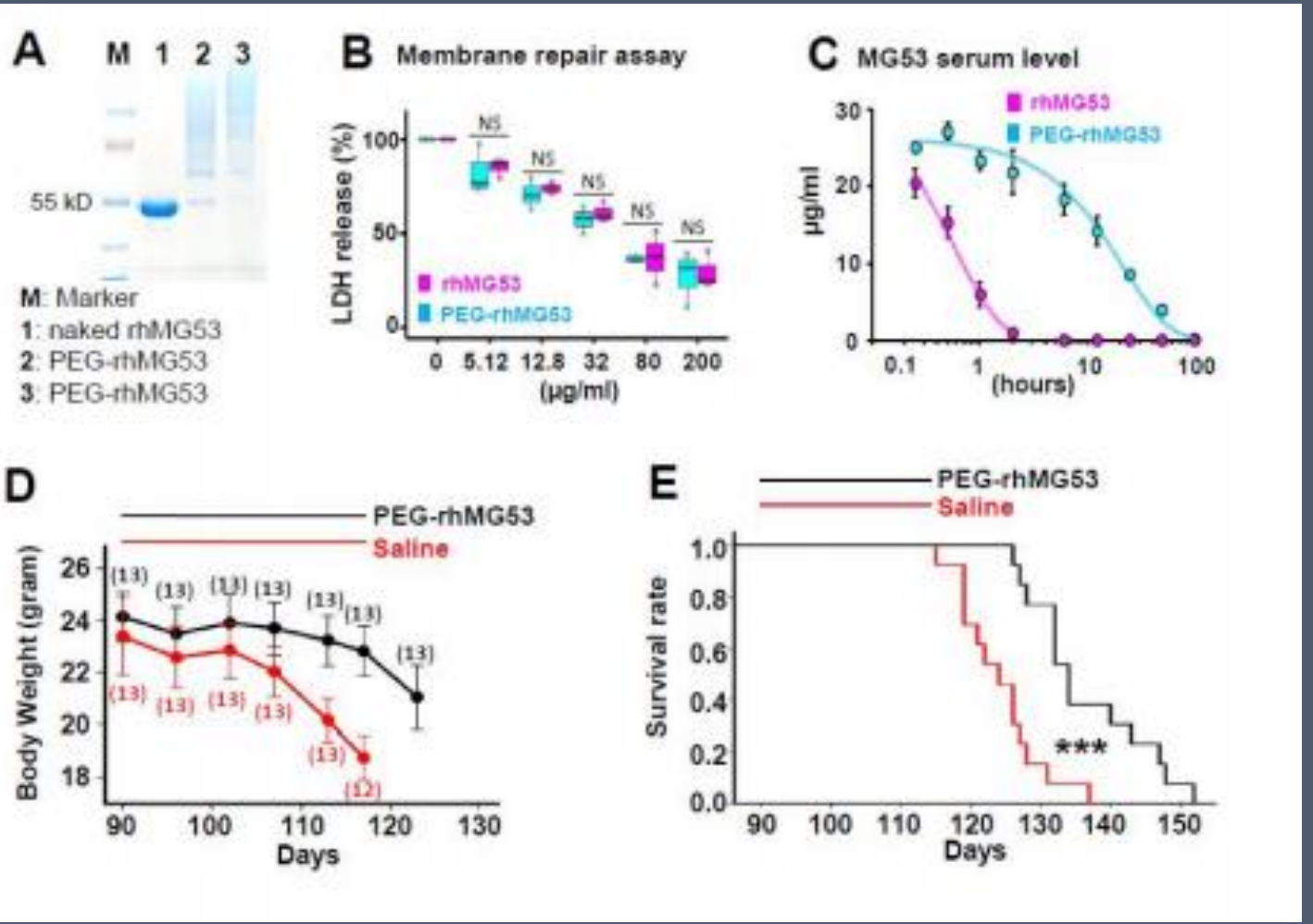
MG53 Preserves Neuromuscular Junction Integrity and Alleviates ALS Disease Progression

Jianxun Yi [1,2], Ang Li [1,2], Xuejun Li [1,2], Kiho Park [3], Xinyu Zhou [3], Frank Yi [3], Yajuan Xiao [2], Dosuk Yoon [2], Tao Tan [3], Lyle W. Ostrow [4], Jianjie Ma [3,*] and Jingsong Zhou [1,2,*]









Why do clinical trials fail?

Example: Ceftriaxone

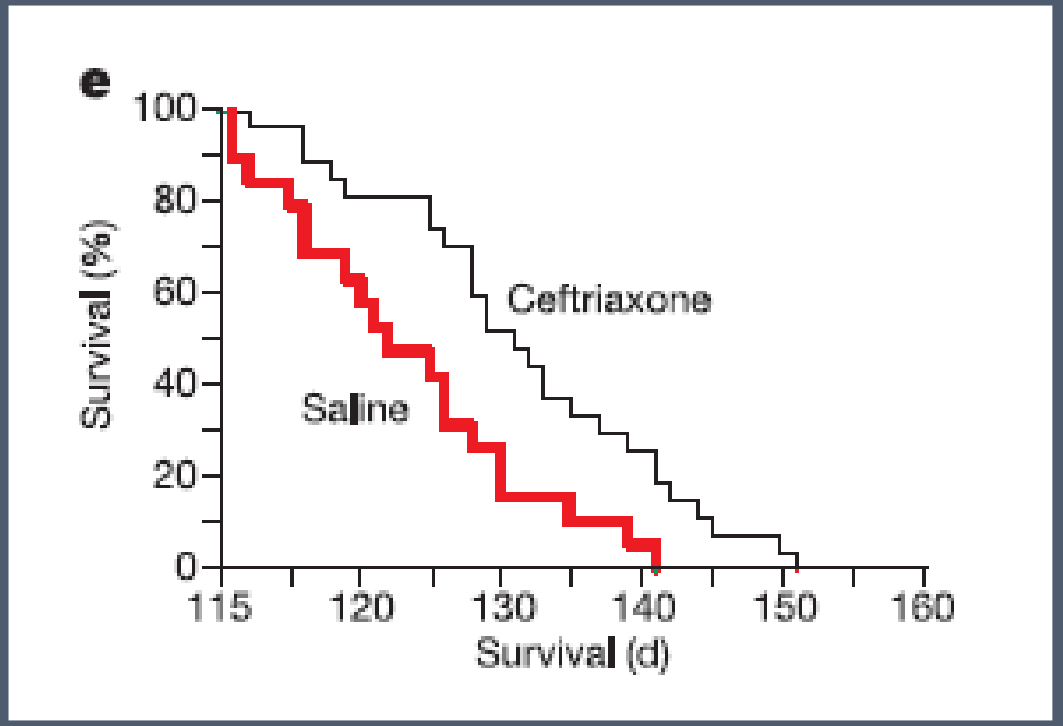
- Screened >1,000 FDA approved drugs and found that Ceftriaxone increased EAT2 glutamate transporter expression on astrocytes, and prolonged survival in the SOD1 ALS Mice.

- When taken to clinical trials in ALS patients, Ceftriaxone showed a significant effect in Phase 2, but failed in Phase 3.

β-Lactam antibiotics offer neuroprotection by increasing glutamate transporter expression

Jeffrey D. Rothstein[1,2], Sarjubhai Patel[1], Melissa R. Regan[1], Christine Haenggeli[1], Yanhua H. Huang[2], Dwight E. Bergles[2], Lin Jin[1], Margaret Dykes Hoberg[1], Svetlana Vidensky[1], Dorothy S. Chung[1], Shuy Vang Toan[1], Lucie I. Bruijn[3], Zao-zhong Su[4], Pankaj Gupta[4] & Paul B. Fisher[4]

NATURE | VOL 433 | 6 JANUARY 2005 | www.nature.com/nature



Did ceftriaxone fail because…

- The glutamate-excitotoxicity hypothesis is just wrong, or perhaps is only true for a subset of pALS?
- The drug didn't cross the blood brain barrier in high enough quantities?
- EAAT2 glutamate transporter up-regulation wasn't sufficient?

- If we had a way to track EAAT2 levels in the brains of our patients, maybe we could have answered that question.

ALS ASSOCIATION
ALS Awareness Month

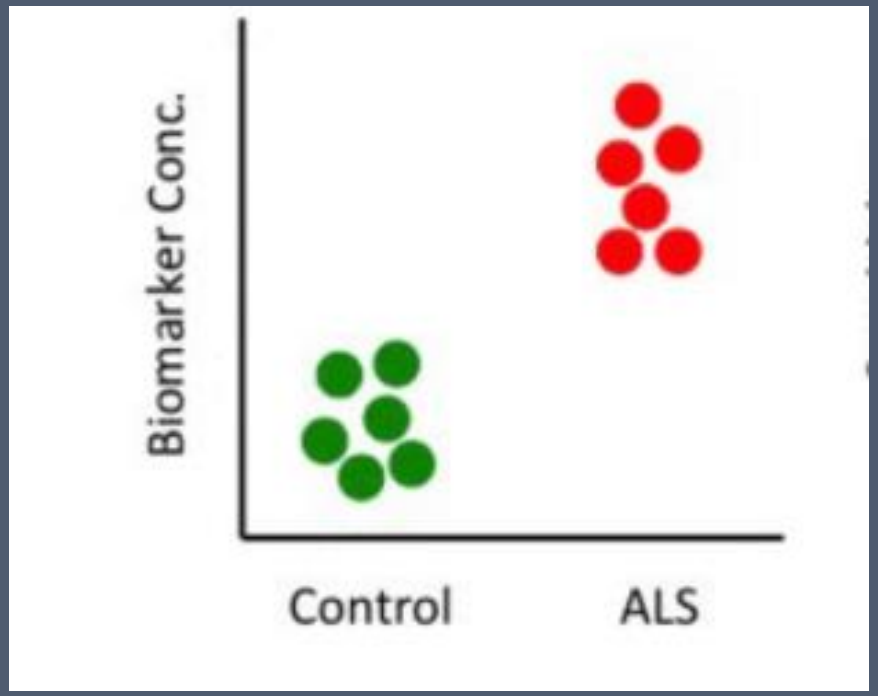
FOR IMMEDIATE RELEASE

Academic and Pharmaceutical Leaders Meet in Boston to Discuss Biomarkers in ALS

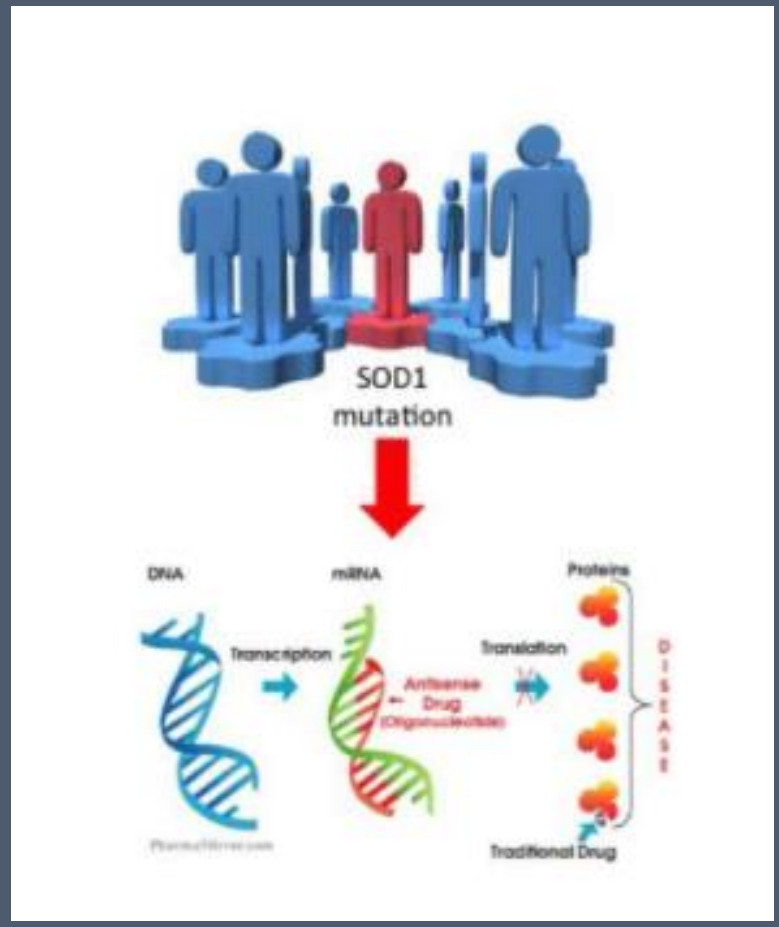
Washington, D.C. (May 19, 2014) — Leaders from academic institutions, non-profit organizations, and pharmaceutical companies will meet in Cambridge, Mass., on Monday, May 19, to discuss biomarkers in amyotrophic lateral sclerosis (ALS).

- "A biomarker is any measurement such as a blood test or imaging result, that tracks the disease process and the effects of treatment…
- The existence of a reliable progression biomarker can influence a pharmaceutical company's decision whether to invest the millions of dollars needed to support a large clinical trial…
- Most importantly, biomarkers would expedite clinical trials and determine whether a treatment effect is beneficial or not and **whether the drug has reached its target**."

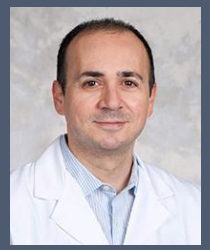
IMPORTANTLY, there are actually several different kinds of biomarkers!



Diagnostic biomarker

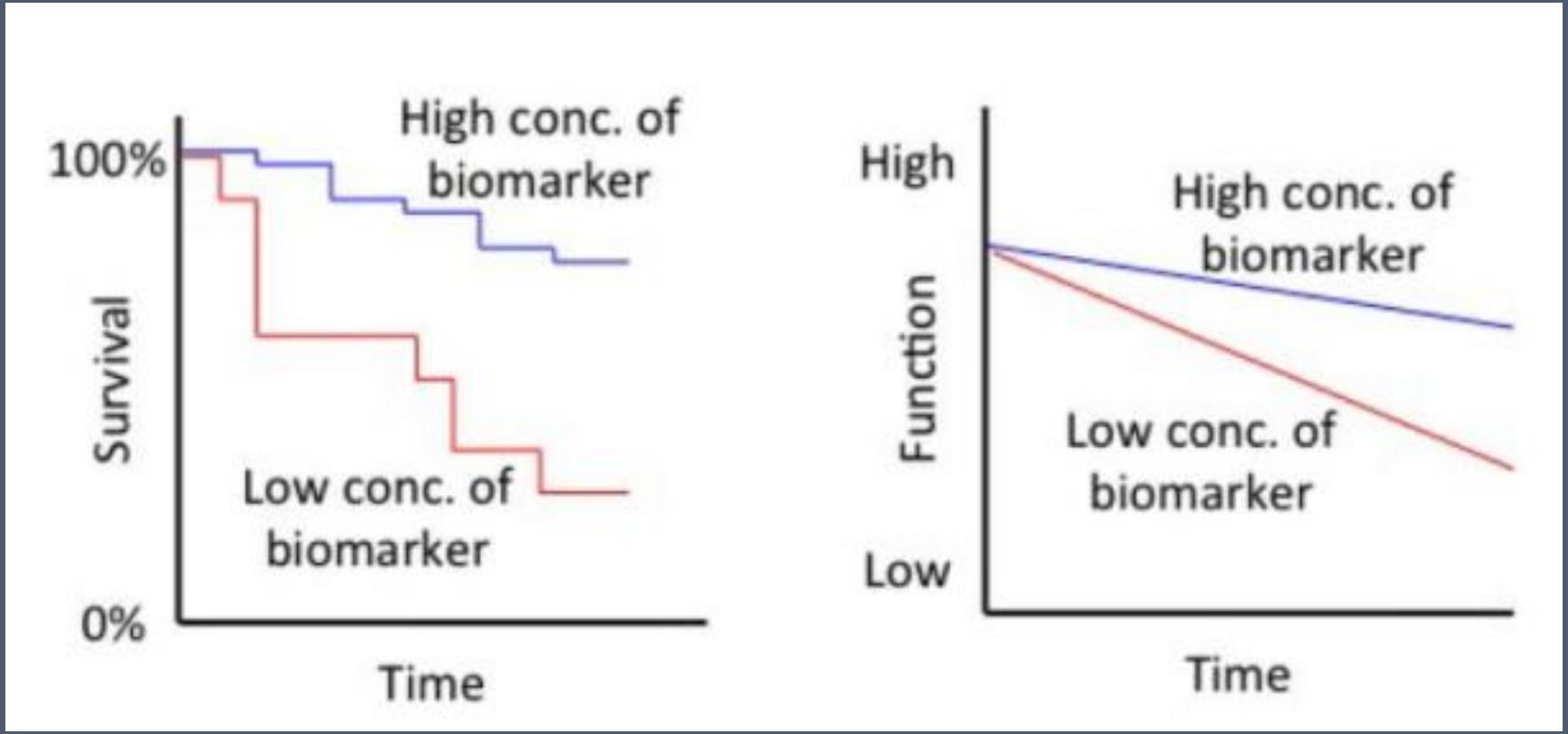


Predictive biomarker



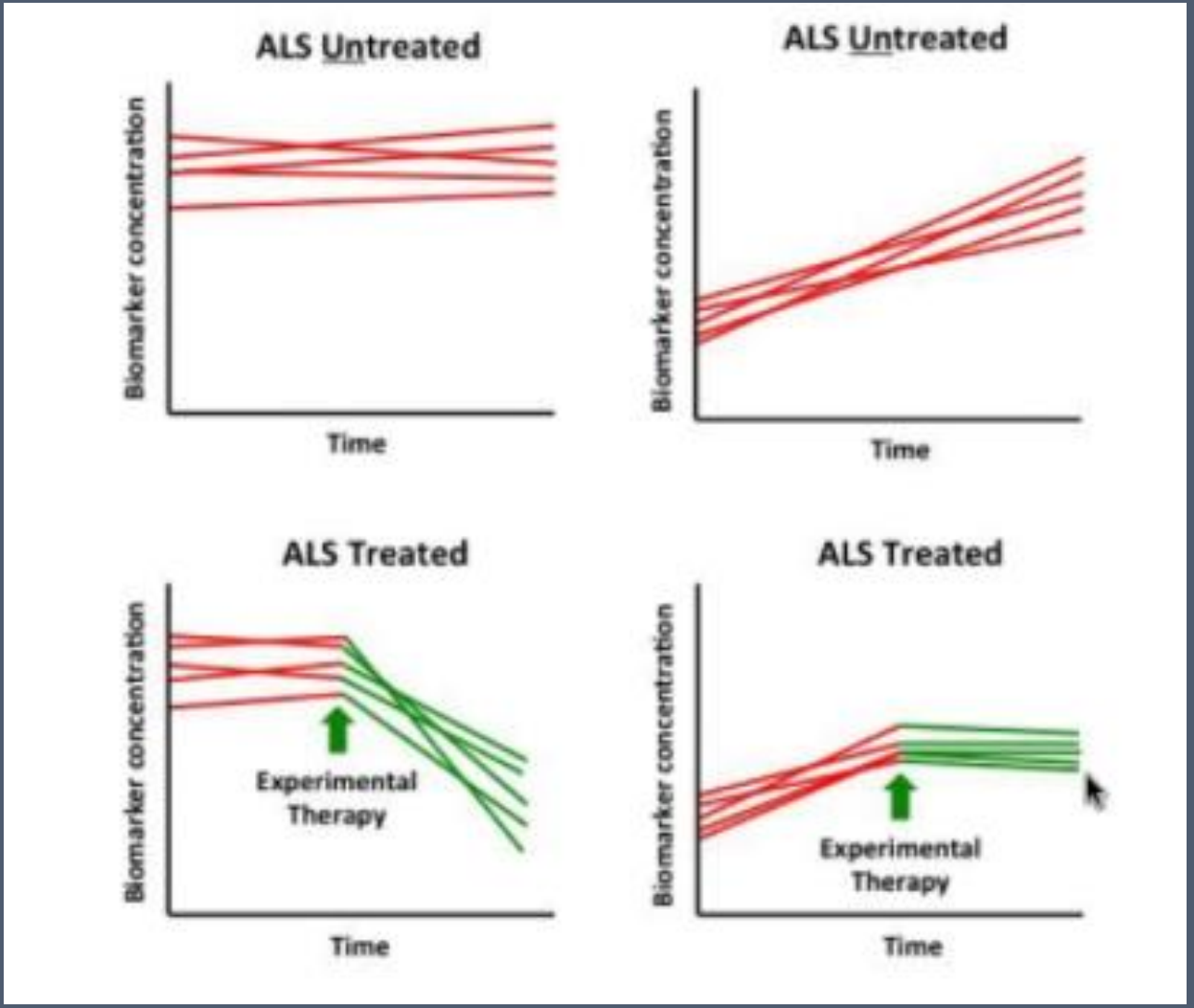
(Thanks to Dr. Michael Benatar for these biomarker figures!)

What would you call a biomarker like this?



Prognostic biomarker

How about these?

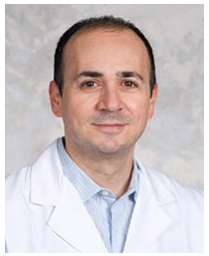


Pharmacodynamic biomarker

We actually have several promising biomarker "candidates" in ALS

- Measurements in blood, CSF, urine
- Brain imaging techniques
- Lots of papers analyzing individual sets of samples.
- Different centers collecting samples.
- Different labs doing the tests.

What do we need to do to make them truly "*clinical trial ready*"?



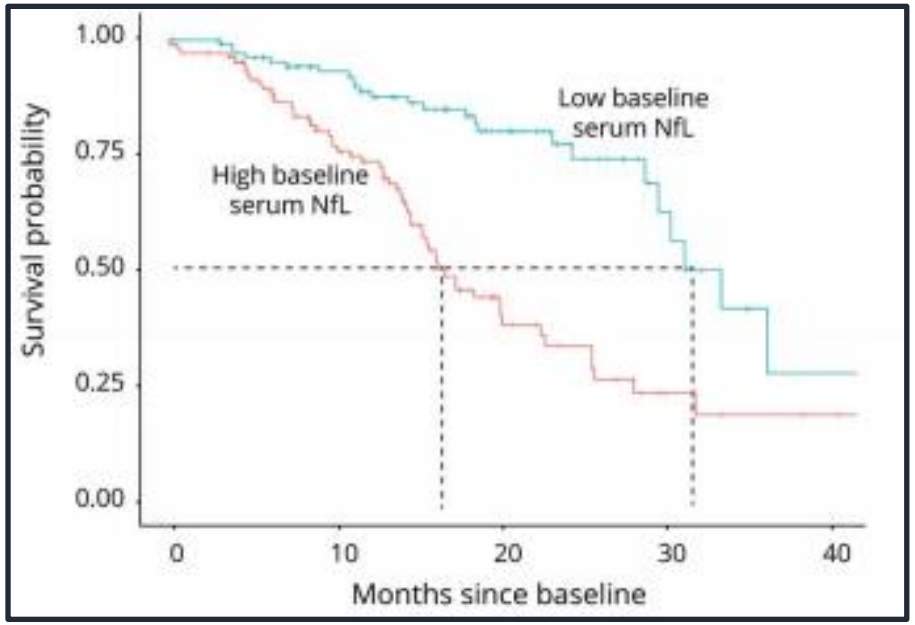
Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS

Michael Benatar, MD, PhD, Lanyu Zhang, MS, Lily Wang, PhD, Volkan Granit, MD, Jeffrey Statland, MD, Richard Barohn, MD, Andrea Swenson, MD, John Ravits, MD, Carlayne Jackson, MD, Ted M. Burns, MD, Jaya Trivedi, MD, Erik P. Pioro, MD, PhD, James Caress, MD, Jonathan Katz, MD, Jacob L. McCauley, PhD, Rosa Rademakers, PhD, Andrea Malaspina, MD, PhD, Lyle W. Ostrow, MD, PhD, and Joanne Wuu, ScM, on behalf of the CReATe Consortium

Neurology® 2020;95:e59-e69. doi:10.1212/WNL.0000000000009559

Table 2 Analytic characteristics of neurofilament light and phosphorylated neurofilament heavy

	Neurofilament light		Phosphorylated neurofilament heavy					
	Simoa		Simoa		Iron horse		Euroimmun	
	Serum	CSF	Serum	CSF	Serum	CSF	Serum	CSF
Total samples	614	78	614	78	614	78	614	78
Samples with values below LLD, n								
In both replicates	0	0	0	1	26	0	64	0
In only 1 replicate	4	1	15	2	36	0	73	0
Difference (in pg/mL) between replicates, mean (95% CI)[a]	−0.05 (−4.0 to 3.9)	−0.03 (−11.8 to 11.7)	−0.4 (−26 to 25)	1.0 (−7 to 9)	−0.8 (−16 to 14)	−4.9 (−90 to 80)	−0.02 (−38 to 38)	67.9 (−163 to 298)
CV,[b] mean	3.2	2.9	4.7	2.1	4.0	2.7	5.3	3.0
Samples with CV >10, n (%)	12 (2.0)	1 (1.3)	51 (8.3)	0 (0.0)	63 (10.3)	0 (0.0)	88 (14.3)	0 (0.0)



EVERYTHING ALS
CARE TO CURE

JOIN THE

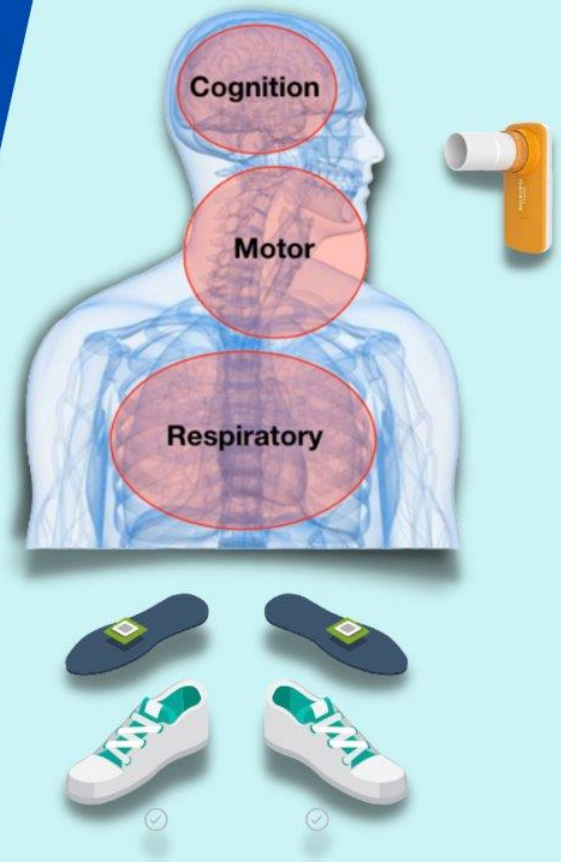
Multi-disciplinary RADCLIFF STUDY

Looking for individuals who are in the early stages of ALS diagnosis.

This **IRB-approved study** is completely remote- all assessments will be completed in your home. This study will focus on walking, breathing function, and speech analysis to make progress towards a digital biomarker.

The collected data will enable development of novel machine learning/AI based tools to improve current assessment & treatment of individuals diagnosed with ALS using physiological signals and objective measurements.

LEARN MORE



www.everythingals.org/research

How can we measure changes in speech?

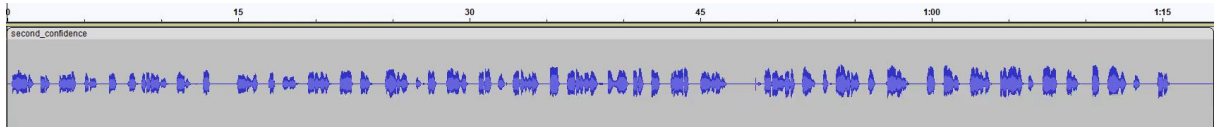
Current approach: ALSFRS-R

How is your speech?	Score
Normal speech processes	4
Detectable speech disturbance	3
Intelligible with repeating	2
Speech combined with nonvocal communication	1

Challenges

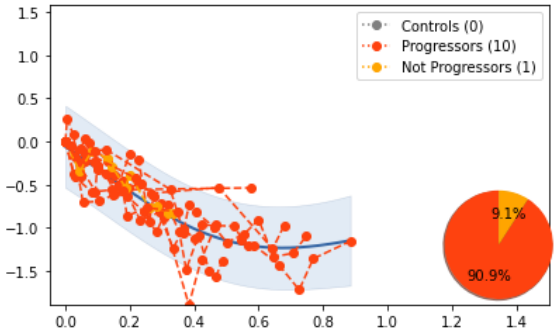
- Small dynamic range
- Scoring is subjective

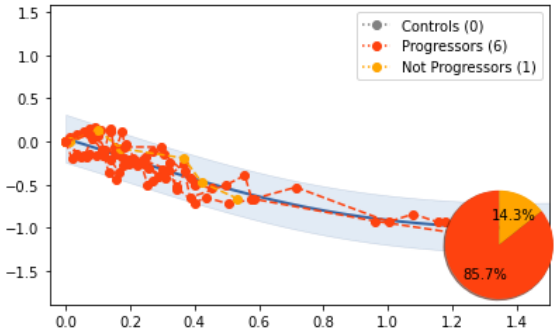
The patient below was scored as normal:

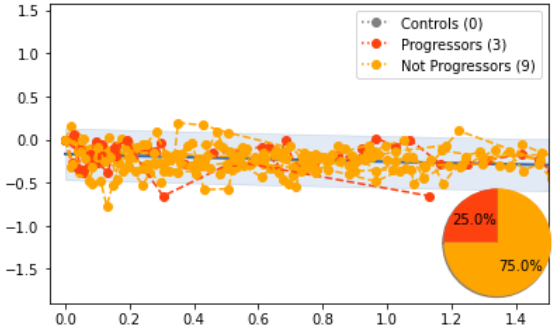


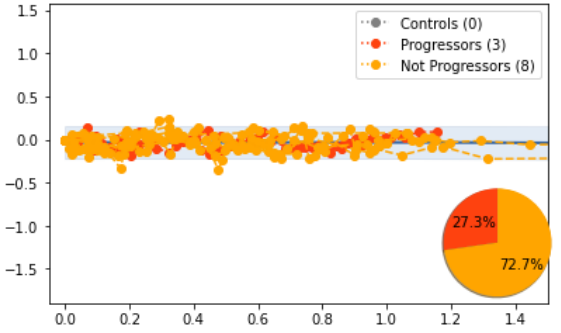
AI/ML IDENTIFIES PATTERNS OF PROGRESSION WITH MORE SENSITIVITY

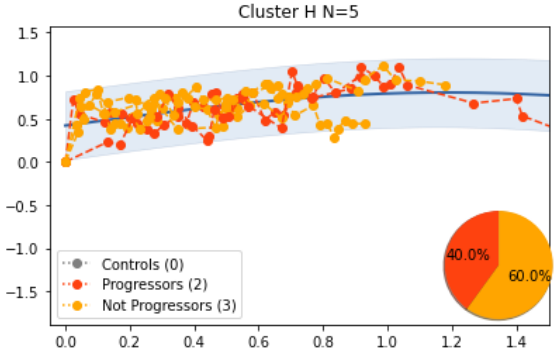
EVERYTHINGALS
CARE TO CURE

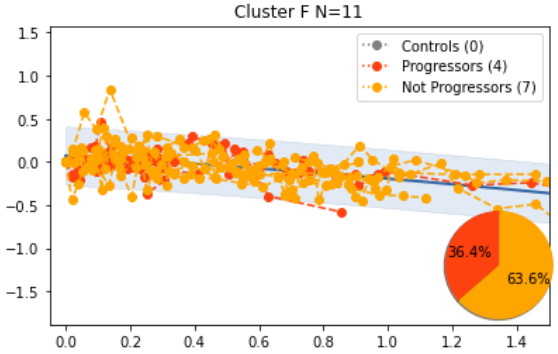


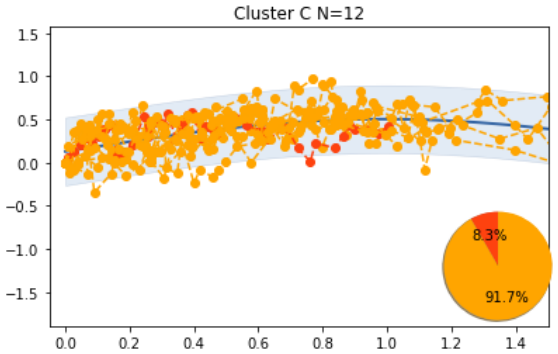


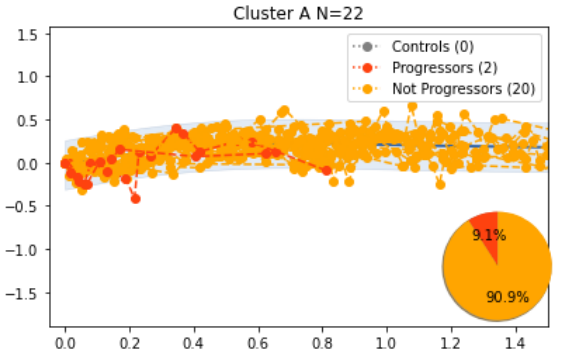












Identifying progression when patients report no progression in ALSFRS-R

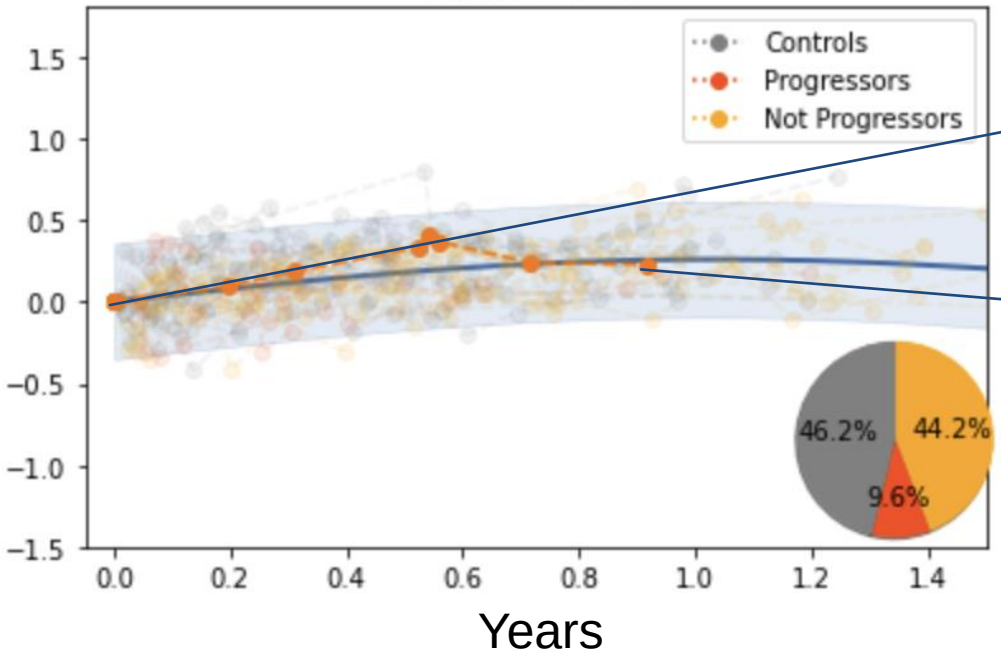
ALSFRS-R does not report progression

ALSFRS-R reports progression

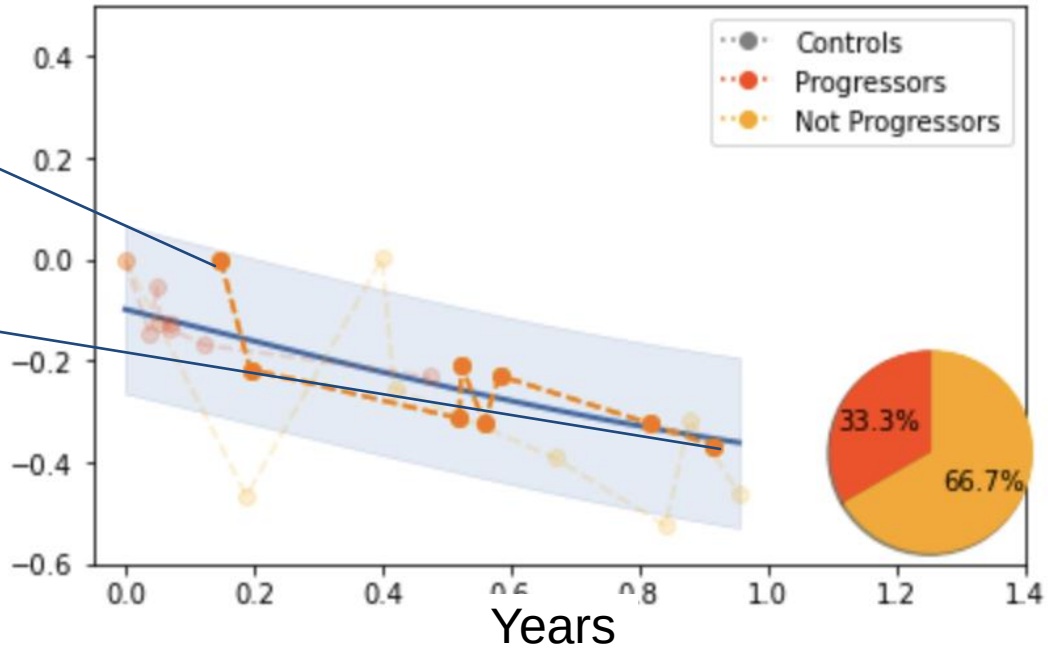
SOME PATIENTS MAINTAIN THEIR SPEAKING RATE BUT BECOME HARD TO UNDERSTAND

SR: 1.8 Syl per sec
Confidence: 0.84
Bulbar: 12
Speech: 4

Speaking Rate Trajectory



Transcription Confidence Trajectory



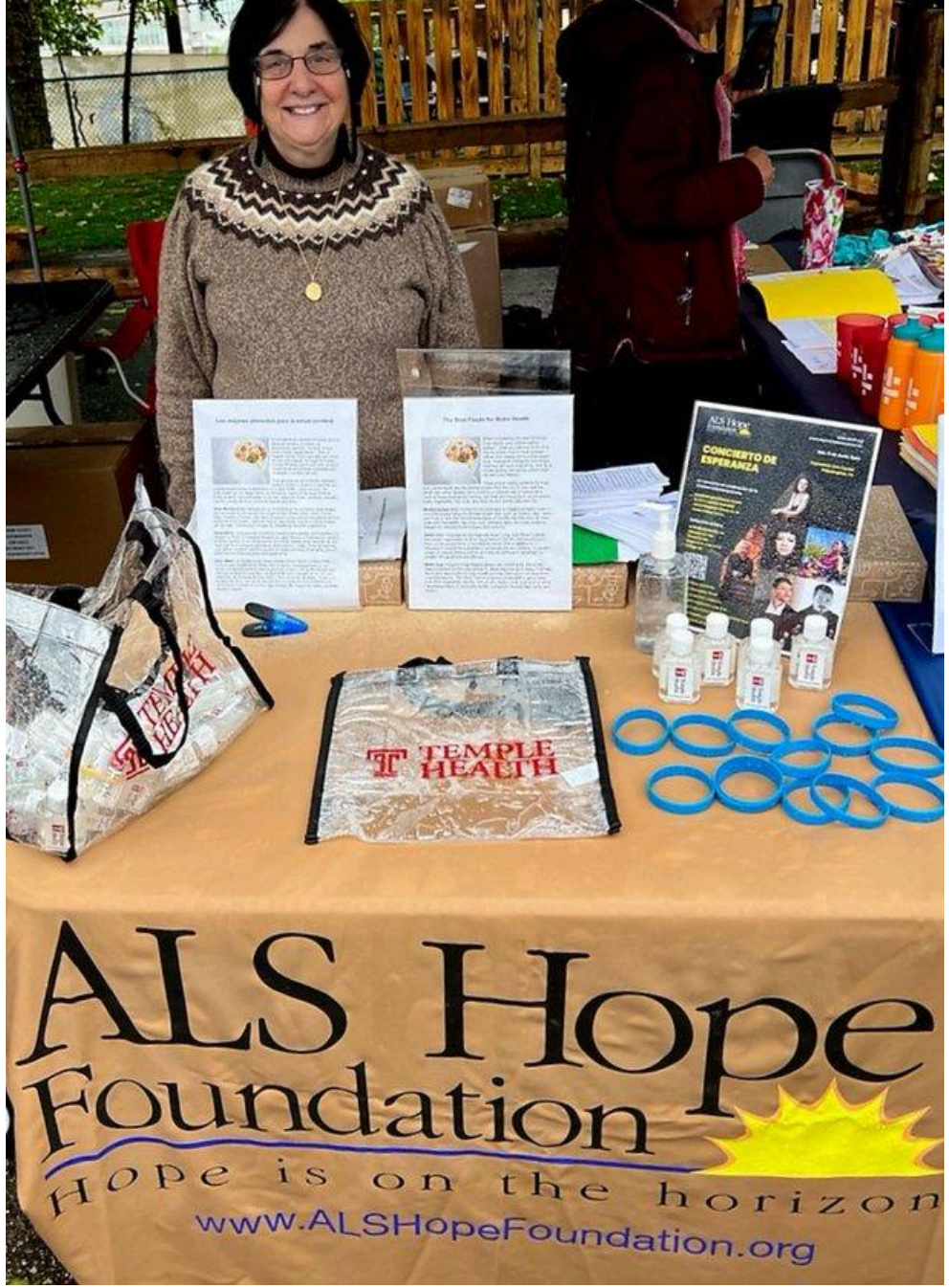
SR: 1.8 Syl per sec
Confidence: 0.48
Bulbar: 12
Speech: 4

EVERYTHINGALS
CARE TO CURE

END THE LEGACY
GENETIC ALS & FTD

The genetic ALS & FTD community is large and growing.

ALS & FTD are terminal conditions, and being at a heightened risk for them can have profound impacts on people and families. We organized Genetic ALS & FTD: End the Legacy to provide educational and support resources to, encourage and promote research about, and advocate for the Genetic ALS & FTD community.



Nadia's Analysis

Active or upcoming interventional trials (globally): 108

Proportion of trials enrolling:
Sporadic ALS: 91%
Familial ALS: 10.1%
(some enroll both)

Specific Mutations (# of Trials):
C9orf72 (6), SOD1 (2), Ataxin-2 (1), FUS (1), UNC13a (1)

A Database to Signal Opportunity and Hope

Dr. Nadia Sethi Consumer Story

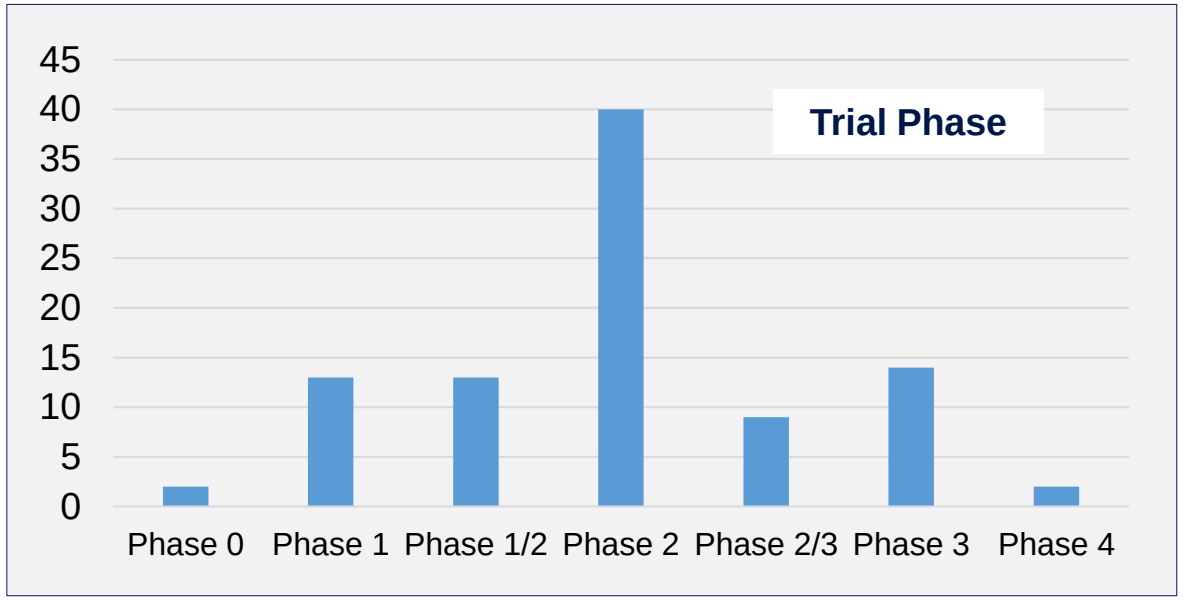
Dr. Nadia Sethi Programmatic Panel Consumer

Dr. Nadia Sethi is a dentist by training and an advocate by experience. As a dental surgeon, Nadia already had a strong healthcare background when she experienced amyotrophic lateral sclerosis (ALS) first-hand as a caregiver for her late husband. Diagnosed with ALS in 2019, Dr. Sundeep Sethi served on the Peer Review Panel for the CDMRP ALS Research Program (ALSRP). His strength, passion, and drive to help the ALS community persevered throughout his personal battle with ALS. "When Sundeep was diagnosed, we felt helpless. Engaging with others in the community and helping to advance the science of ALS became a source of comfort and felt empowering while fighting a disease that takes so much away."

Working with I AM ALS, a patient-centric ALS advocacy and support organization, Nadia led efforts to create ALS Signal, a comprehensive online platform for ALS clinical research information. As a searchable registry of ALS clinical trials around the world, ALS Signal provides a one-stop resource for patients and caregivers looking for clinical trial information. Nadia hopes the dashboard may have an even bigger impact in the future: "One of my hopes from the beginning of organizing this database was to share this information in ways that could impact the science. I do not see how we can achieve new treatments without an understanding of the current scope of ALS clinical research. I also

Biomarker use in trials:

- Only ~50% of trials appear to be incorporating **ANY** biomarkers beyond traditional endpoints (ALSFRS-R, etc), and/or collecting biosamples/imaging/other measures for new biomarker validation/discovery.
- The vast majority of trials for sporadic ALS are recruiting broad patient populations, despite targeting **specific biological pathways** that may only have therapeutic relevance to specific patient subsets.
- **Predictive** and **Pharmacodynamic Biomarkers** are sorely lacking in trials other than gene-targeting strategies for specific familial mutations.



A Challenge Best Tackled Together – Bridging the ALS Therapeutic Gap with Industry Partners

March 29, 2022

Joseph Lewcock, Ph.D., Denali Therapeutics and member of the ALSRP Programmatic Panel

Dr. Joseph Lewcock

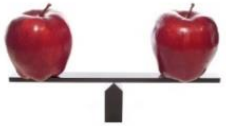
Joseph Lewcock, Ph.D., is Chief Science Officer and Head of Discovery with Denali Therapeutics and a member of the Programmatic Panel for the Amyotrophic Lateral Sclerosis Research Program (ALSRP). Dr. Lewcock provides critically important industry perspectives to ALSRP strategic planning, as the program takes major steps into the clinical trial funding space. We caught up with Dr. Lewcock recently and asked him a few questions.

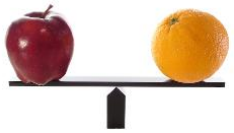
Q: Dr. Lewcock, thank you for taking the time to chat with us. First of all, can you give us a rundown of how the ALS therapeutic development landscape has changed in recent years?
A: What we are seeing in the ALS drug development landscape now is a continuation of the more fundamental changes in the way people have approached ALS drug development over the last 5-10 years, based on advances in our understanding of the genetic contributors to ALS. Interestingly, there is a split in the types of therapeutic approaches being pursued between targeted strategies with genetic rationale and biomarkers to de-risk development, and those based on more general neurodegeneration biology that may apply to ALS. Some of the targeted approaches may have great promise, but are designed for only a genetically defined patient subpopulation of ALS patients with specific genetic mutations. Meanwhile, therapies that target neurodegeneration more broadly represent a more challenging road based on our incomplete understanding of disease mechanisms, and a lack of "predictive" biomarkers to determine which patients are most likely to respond to which therapies.

Q: What ALS therapeutic strategies are currently of greatest interest to industry?
A: One area the drug development industry is focused on is novel biomarkers of all varieties. Biomarkers are essential to determining the patient populations that may respond to a new therapy or to confirm the activity of a drug. Without effective biomarkers, clinical trial participation in ALS tends to be a catchall for all patients where an impact on specific patient subpopulation may be missed. Everyone would love to see more *targeted approaches*, but there is still a lot to learn about the drivers of disease outside of small genetically defined patient populations. More investment in biomarkers that bridge this gap is absolutely critical. At present, a company would have to take more risk to explore a therapeutic strategy that targets sporadic ALS, which represents ~90% of patients. A particularly promising approach is to develop a biomarker alongside a therapeutic effort from early on. Therefore, the ALSRP funding mechanisms are a great opportunity for companies to mitigate this risk.

Why are patient-derived biosamples important?

- Since no laboratory model or assay represents the findings of every person with ALS, it is important to **validate** findings with relevant patient-derived laboratory tools.
  - Postmortem Brain and Spinal Cord
  - Muscle (biopsy or postmortem)
  - iPS Cells
  - Biofluids





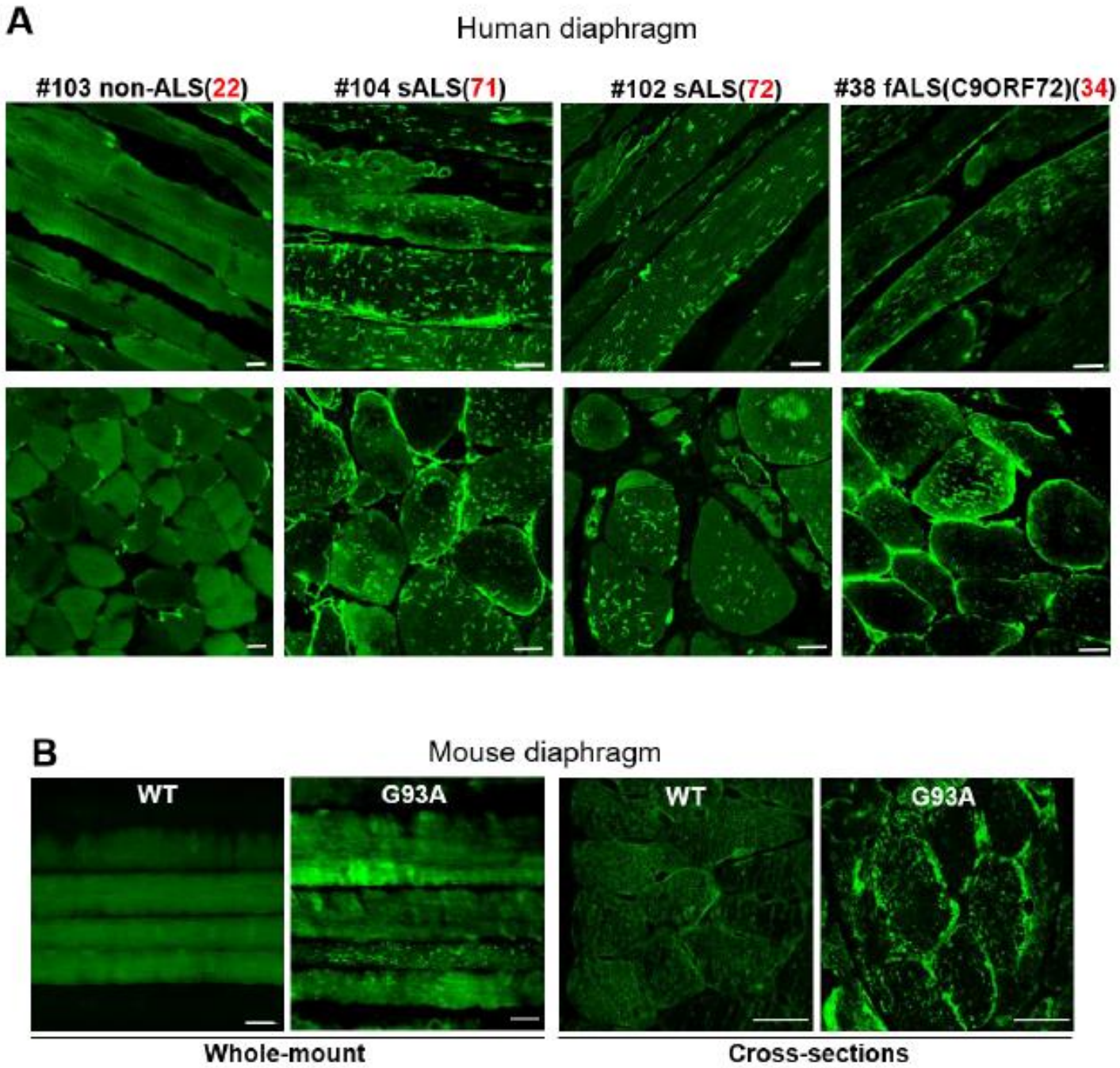
- We also need rigorous and standardized clinical, epidemiological, and pathological data linked to the biosamples.
- There remains a substantial unmet need for high quality matched biosamples (blood, CSF, tissues) and data for ALS research.

Antioxidants **2021**, *10*, 1522. https://doi.org/10.3390/antiox10101522

Article

MG53 Preserves Neuromuscular Junction Integrity and Alleviates ALS Disease Progression

Jianxun Yi [1,2], Ang Li [1,2], Xuejun Li [1,2], Kiho Park [3], Xinyu Zhou [3], Frank Yi [3], Yajuan Xiao [2], Dosuk Yoon [2], Tao Tan [3], Lyle W. Ostrow [4], Jianjie Ma [3,*] and Jingsong Zhou [1,2,*]



How is research funded?

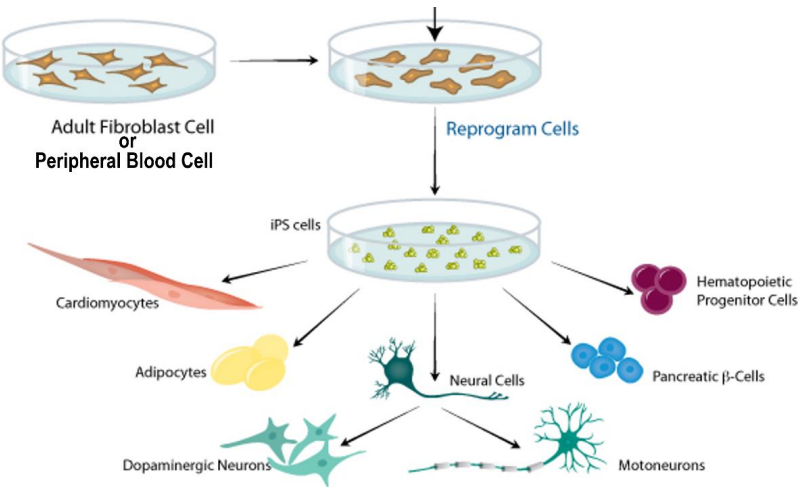
- **The first NIH Study Section met in February 1946**, to debate strategies for finding new treatments for syphilis.
- This was the beginning of formalized ***peer review*** – whereby research proposals are evaluated by scientific experts and stakeholders, rather than an established old-boy network or politicians.
  - Study sections met to review grant proposals, but this was only part of their charge - they were specifically tasked with promoting ***new and emerging investigations that had the potential to lead to the most rapid breakthroughs***.
  - Thus, each original study section meeting included a comprehensive survey of new and exciting methods and discoveries.
- The NIH peer review system was widely praised for helping the U.S. lead the world in medical research.
- Not surprisingly - patient advocacy groups, non-profit foundations, and philanthropies adopted the NIH model for making their own funding decisions.

The way we fund scientific research has remained largely unchanged since the first NIH study section met *over 75 years ago.*

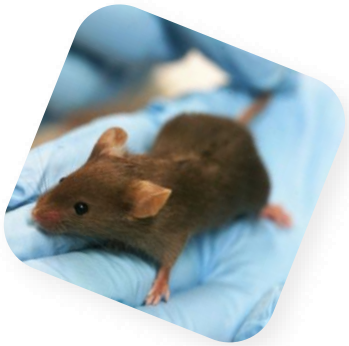
Researchers submit proposals to a "**funding cycle**" review process spread out over several months:

- A funding agency writes a ***Request for Applications*** **(RFA)**, which is released several months before a grant submission deadline.
- Scientists submit proposals conforming to the RFA specifications, often after a preliminary round of review for ***pre-proposals*** or ***letters of intent*** to limit the eventual number of full submissions.
- A committee of **peer reviewers** is established, and each proposal is assigned for critical review by 2 or 3 committee members.
- A **meeting of the entire review committee** is convened, and the proposals are discussed and ranked.
- An **executive council or programmatic panel** may meet at a later date to make final funding recommendations – taking into account the merit-based peer reviews, budget constraints, public priorities, and overall research portfolio considerations.
- Contracts are then executed between the funding agency and the institutions where the research will be performed.

Only a small percentage of proposals can be funded in a given cycle



- Reviewers need to make difficult judgements about
  - The potential impact of the proposed work
  - The experimental design
  - The qualifications of the scientists



- Reviewers consider whether specific ***targets, disease pathways,*** *or* ***laboratory models*** (like mutant mice or cell lines) are more likely to improve our understanding of a disease and translate to new therapies.
  - It can be difficult to judge which models or targets are most relevant, until we succeed in developing truly effective therapies based on these laboratory tools.

The "study" role of past National Institutes of Health study sections

Thoru Pederson
Program in Cell and Developmental Dynamics and Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01605

ABSTRACT **The original National Institutes of Health (NIH) study sections had two missions. The review of grant applications was the enduring one that we all recognize. The second original function, less remembered today, was to stand ready to advise the NIH, and in fact the entire community in a given biomedical field, on the current state of that discipline, as well as to opine on what new vistas were arising and to suggest (or occasionally even launch) appropriate courses of action. The present contribution is intended to remind us of this lesser-known original function of NIH study sections. We might ponder whether today's study sections, although more overworked than Sisyphus, should again take up this second function.**

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Keith G. Kozminski
University of Virginia

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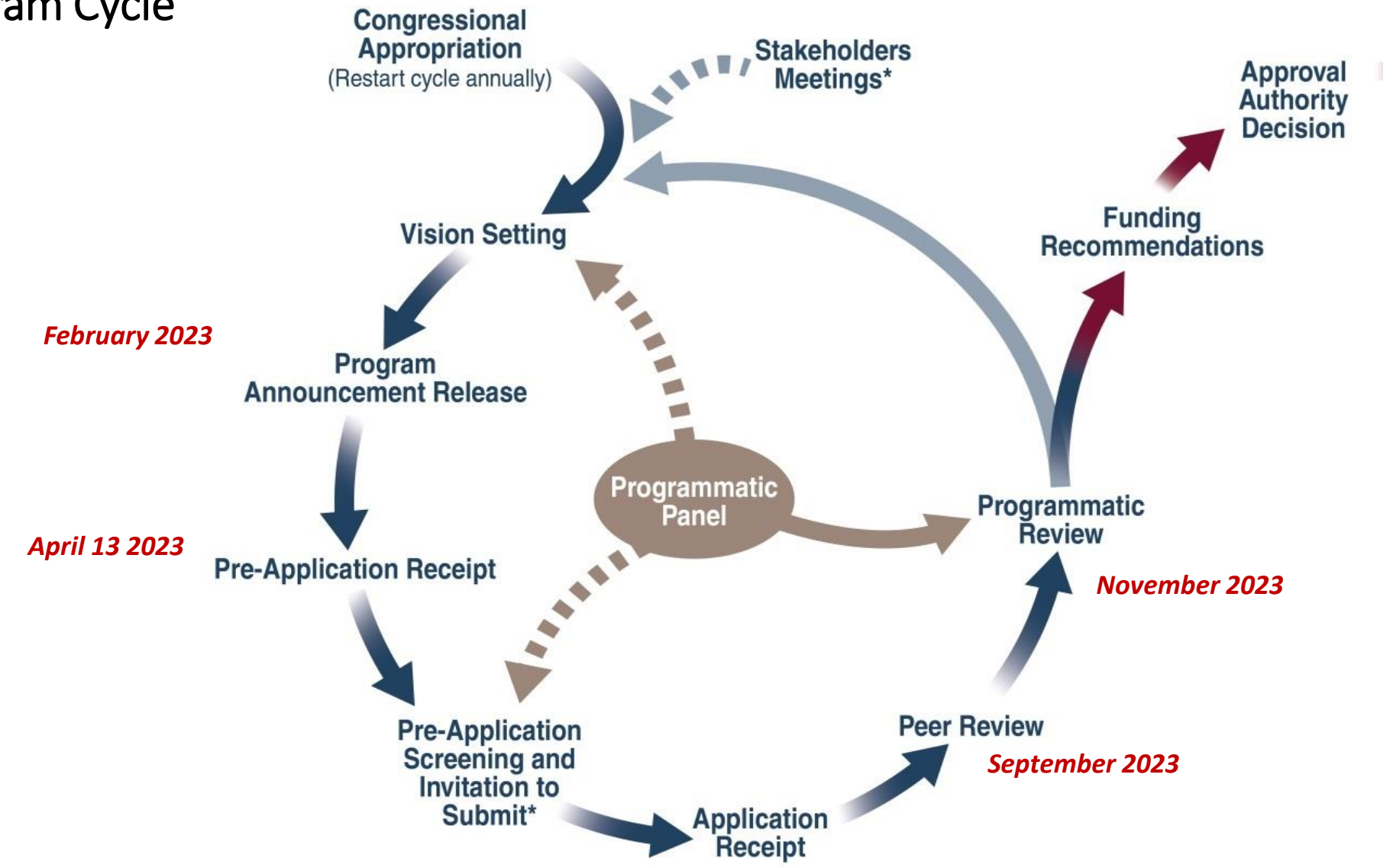
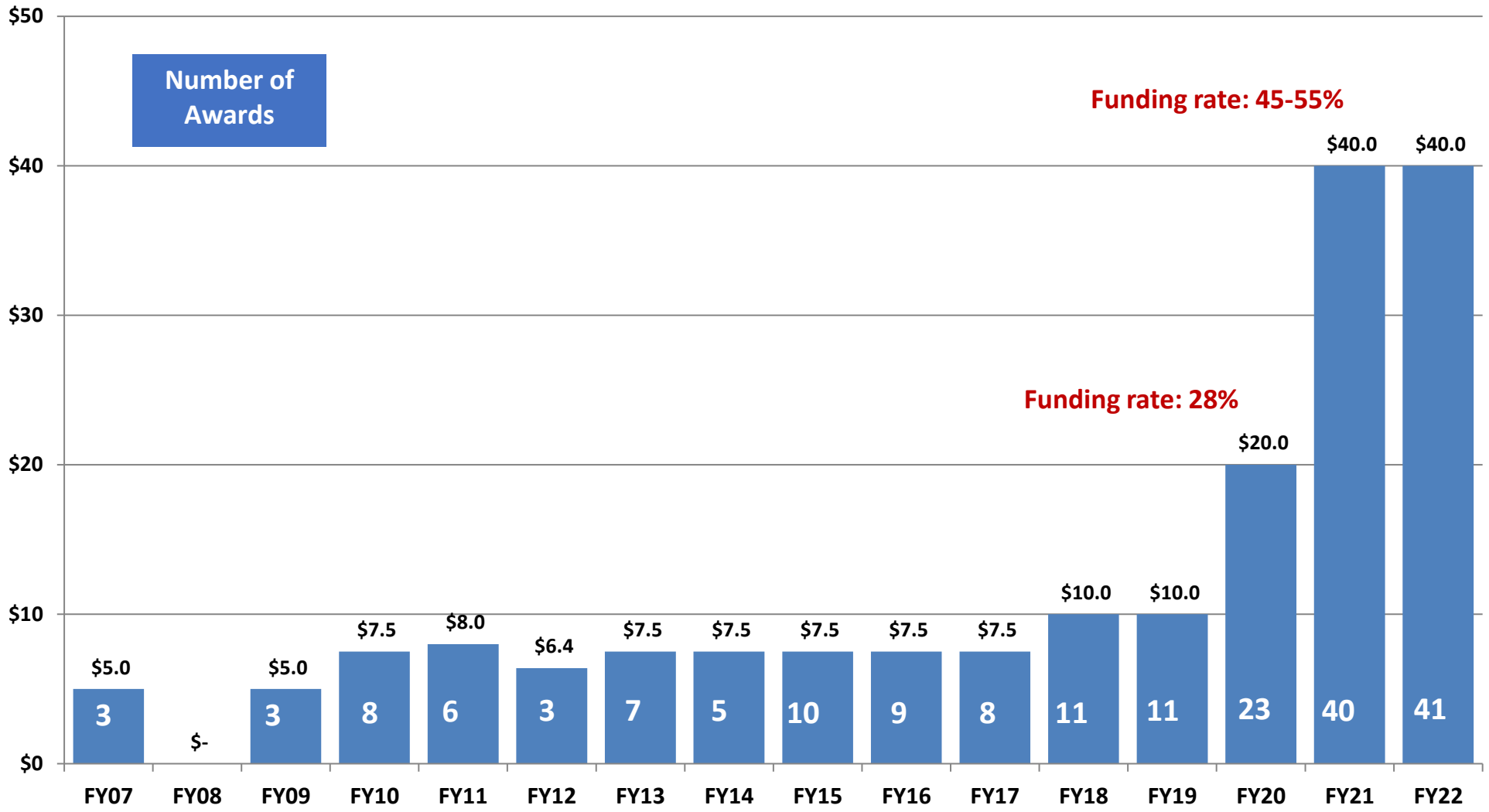
Revised: Jul 9, 2012
Accepted: Jul 13, 2012

FIGURE 1: The NIH Syphilis Study Section—the first study section—photographed at its inaugural meeting in 1946. Reproduced from Mandel (1996).

FY23 ALSRP Program Cycle



ALSRP Congressional Appropriations



ALSRP FY23 Funding Mechanisms

Therapeutic Bench → **Therapeutic Bedside & Clinical Care**

Improving Translation

Therapeutic Idea Award	**Therapeutic Development Award**	**Pilot Clinical Trial Award**	**Pilot Clinical Trial Award – Clinical Care Tier**	**Clinical Biomarker Development Award**
Proof-of-concept **drug discovery**	Investigational New Drug **(IND)-enabling studies**	Early phase **intervention trials, with compelling biomarker data**, to inform and de-risk more advanced trials for the treatment or management of ALS	Improve aspects of **current ALS clinical care**	Develop and **validate clinical biomarkers to enrich clinical trials**

<table>
<tr><th>Therapeutic Idea Award</th><th>Clinical Biomarker Development Award</th><th>Therapeutic Development Award</th><th>Pilot Clinical Trial Award</th></tr>
<tr><td colspan="4">Strong Rationale</td></tr>
<tr><td colspan="4">Potential Impact</td></tr>
<tr><td colspan="2">Data/Resource Sharing</td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td colspan="2"><u>Must</u> Incorporate Use of Biomarkers</td></tr>
<tr><td>Innovation</td><td>Leverage Existing Clinical Resources</td><td>Strong Preliminary Data</td><td>Clinical Trial Readiness</td></tr>
</table>

New requirements for all FY23 Clinical Trial Proposals

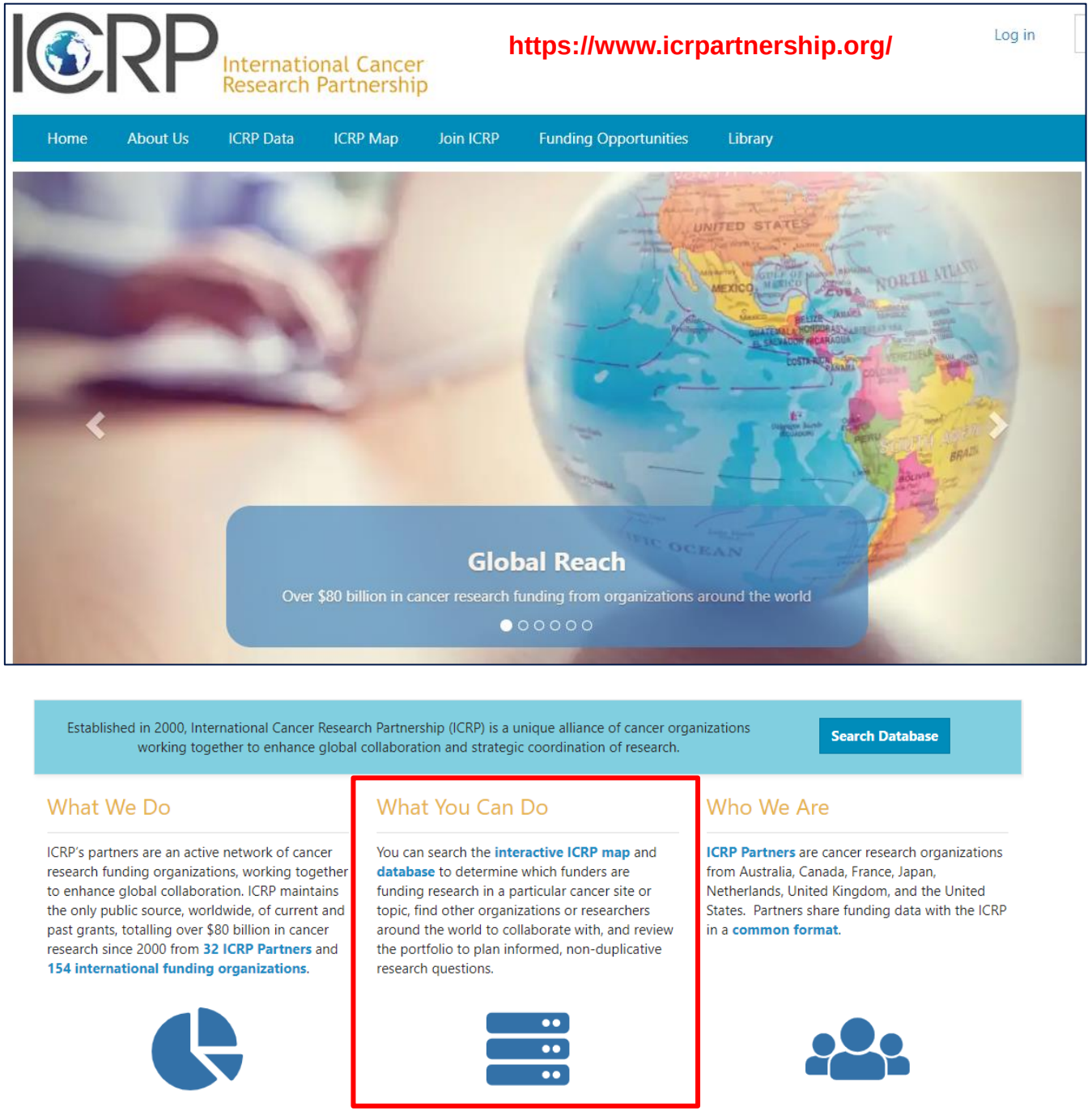
- All clinical trial proposals are required to establish and utilize effective and equitable collaborations and partnerships with community members.
- Recognizing the strengths of each partner, scientific researchers and community members collaborate and contribute equitably on all aspects of the project.
    - Lived Experience Consultation
    - Partnership with a community-based organization
    - Community Advisory Board

Can we help accelerate the overall ALS Research Funding Pipeline?

- The reliance on competitive funding cycles, spread out over several months, can impede new ideas and discoveries from being rapidly explored, validated, and embraced by the research community.
- Many exciting and truly deserving grant proposals end up re-submitted to different RFAs by different organizations over several years before funding is secured.
- Even in the best-case scenario, when a proposal is fully funded after a first submission, the grant may not be awarded until many months after an innovative idea was first formulated, or exciting preliminary data was generated.

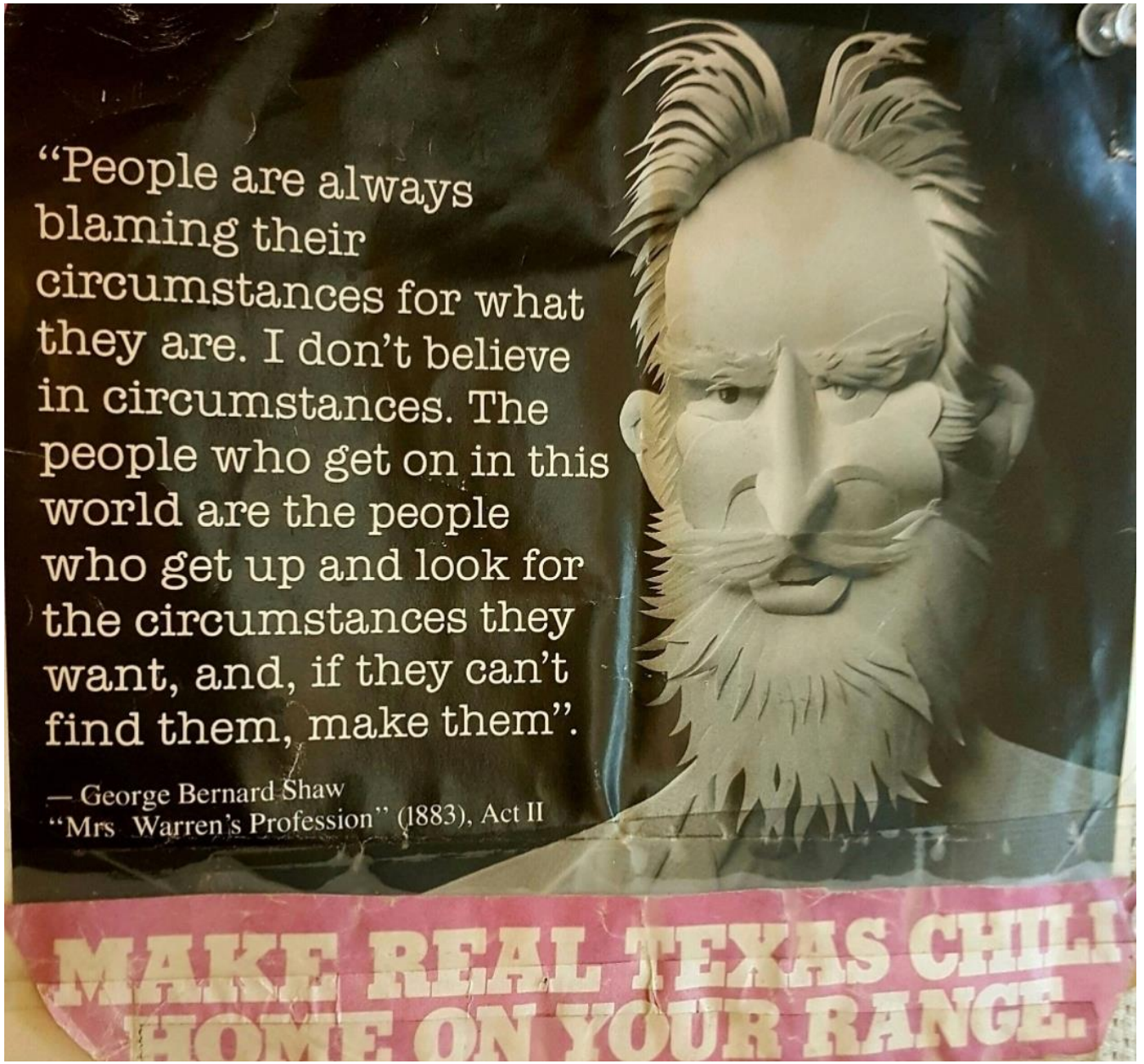
Portfolio Coding

- ICRP example
- Need community buy in – most already coding grants for peer review and other processes
- Need to develop a common coding language
- Need platform to house data *CDMRP does not have infrastructure for support/database management (all congressionally appropriated funding is for R&D)




RESERVED PARKING
WOOSTER
VESEC


MANCHESTER CITY
MANCHESTER CITY FOOTBALL CLUB


"People are always blaming their circumstances for what they are. I don't believe in circumstances. The people who get on in this world are the people who get up and look for the circumstances they want, and, if they can't find them, make them".
— George Bernard Shaw
"Mrs Warren's Profession" (1883), Act II
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APRIL 2023 NEWSLETTER

A REVIEW OF APRIL
WHAT A MONTH!

Gala of Hope

Biogen

Tofersen Approved!

Hear from PALS Mark Stem

Volunteer Month

Occupational Therapy
Brings Possibilities to Life

Occupational Therapy Month

Care Collaboration

Research Updates

Research Luncheon

Run for Hope

Concierto

Collen's Classic

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MAY 2023

MAY REVIEW &
A LOOK AHEAD

Nurses' Week

Better Speech and Hearing Month

Educational Webinars

Maintaining my independence
INTERNATIONAL ALLIANCE OF ADVANCED ASSOCIATIONS

Advocacy

Research Updates

Philly Top Docs

Research Luncheon

Upcoming Events