TARGET ALS

From Barriers to Breakthroughs:

Accelerating the Future of ALS Research for All

Highlights from the
Target ALS 2025 Annual Meeting

TABLE OF CONTENTS

Dear Friend of Target ALS,

It gives me great pride to share highlights from the Target ALS 2025 Annual Meeting. Since our founding in 2013, Target ALS has become the central hub for ALS research, uniting the individuals and organizations driving progress in the field. It was a remarkable gathering in Boston in early May, reflecting our collective strength and unique approach to solving ALS.

Together, these individuals represent the Target ALS ecosystem and its ability to have an exponential impact to accelerate toward our vision: Everyone with ALS Lives.

It is only by working together that we will succeed in our mission. As our ecosystem continues to gain momentum, I want to share with you the holistic approach we are taking to accelerate the best ideas in ALS research from anyone, anywhere in the world through our three approaches—Research We Fund, Research We Enable, and Research We Conduct:

Research We FUND

We support the best ideas on ALS research from around the world while insisting that scientists with complementary expertise work collaboratively on the same idea. Broadly, the focus of these projects includes understanding the fundamental biology of the disease, translation of ideas from the lab toward the clinic, and discovery of biomarkers.

Research We ENABLE

We provide scientists worldwide access to a broad suite of scientific tools and resources from our Research Cores. These tools, ranging from simple yet critically needed reagents, such as antibodies to precious human biosamples and multi-omic datasets, are accessible to industry and academia with no reach-through on Intellectual Property (IP). More than 1650 projects have already used these tools, and these numbers continue to grow.

Research We CONDUCT

We intend to address the long-standing, intractable challenges that have faced the ALS research landscape. This new goal transcends the aims of generating intellectual property for the foundation or publishing articles for our science team. Our ongoing Global Natural History Study is creating the most diverse and comprehensive repository of biofluids and multi-omic datasets for the worldwide community. We also have Community-Based Pop-Up Clinics—one-day events designed to bring ALS research and care directly to underserved communities.

Coming out of the Target ALS 2025 Annual Meeting, I'm more convinced than ever that we're on the right track with these approaches.

Over three days, we saw **more than 80 speakers** take the stage to present progress made by Target ALS-supported projects focused on understanding the fundamental biology of the disease, drug discovery, and biomarkers. The staggering range of cutting-edge work covered new frontiers, including the following:

- Making progress in drug discovery programs for sporadic and C9orf72 forms of ALS
- Fostering advances in biofluid-based biomarkers spanning cryptic peptides, TDP-43, cell-free blood-based DNA methods, and T cell related biomarkers
- Unveiling of a link between cryptic peptides and the immune system in ALS
- Developing a deeper understanding of the biology of the immune system in ALS, including a role for T cells, microglia, immune pathways within neurons, and transposable elements such as retroviruses and Line1 RNAs

What struck me most was that many of these projects were funded within the past year. That speed, from idea to funding to real, visible progress, is emblematic of the urgency in the Target ALS approach. It is not just a slogan; it is at the core of who we are. While funding agencies can take seven to nine months to move funding support after project proposals are submitted, we commit to doing it in just eight weeks. That pace is intentional. We've designed our review process to be both rigorous and fast because people with ALS and their families cannot afford to wait.

ALS 101

Cryptic Peptides are small protein fragments generated from normally non-coding regions of the genome, often due to abnormal splicing events.

TDP-43 is a protein involved in RNA processing that mislocalizes and aggregates in most ALS cases. Its abnormal accumulation is a hallmark of ALS pathology and is being studied as both a disease mechanism and a biomarker.

Cell-Free DNA (cfDNA) Methods are techniques that analyze DNA fragments circulating freely in the blood, not contained within cells. These methods can be used to detect signs of neurodegeneration or immune activation in ALS.

C9orf72 is a gene where repeat expansions are the most common known genetic cause of ALS and frontotemporal dementia.

T cells are immune cells that play a central role in adaptive immunity. In ALS, T cells may contribute to neuroinflammation and motor neuron damage or protection, depending on their subtype and activation.

Microglia are the resident immune cells of the central nervous system (CNS). They respond to neuronal damage and are involved in the inflammatory landscape of ALS.

Transposable Elements (e.g., Retroviruses and LINE-1 RNAs) are mobile genetic elements that can "jump" within the genome. In ALS, reactivation of these elements may contribute to genomic instability and inflammation.

This isn't a new mindset for us. Even in the early days when Target ALS was first formed, our approach was driven by urgency. We wanted to move quickly but deliberately, funding the best ideas on ALS without becoming the bottleneck. Our grant review process gives reviewers six weeks to evaluate proposals, space for structured discussion, and even a window to revisit and revise their opinions. That intellectual freedom is rare, and many of our reviewers have said how much they value it.

The meeting is always a powerful reminder of why this matters. From the early-stage clinician talks on precision medicine and T cell responses, to the Springboard Fellows presenting on transposable elements and metabolic dysfunction, to the closing sessions on neuroinflammation and TDP-43 drug discovery—every moment underscored the need to keep pushing forward. The energy in the room was palpable. These scientists aren't just presenting ideas; they're laying the groundwork for the future of ALS research. And our mission is to make sure they have the support they need to move fast and think big.

In these challenging times for scientific research, we must continue to take educated risks, move nimbly, and always remain focused on our mission to break down barriers to find effective treatments for ALS.

At Target ALS, we're not just funding science, we have built the roadmap to holistically support the best ideas to accelerate toward breakthroughs. That's what this meeting reflected. That's what we'll continue to do.

Key Takeaway

Look out for this symbol throughout the report to find key takeaways from each research project.

I want to thank our board of directors and members of the Independent Review Committee (IRC), who are a source of wisdom for us, and I want to acknowledge the relentless dedication of my colleagues on the Target ALS team. It is a privilege to work with them.

I want to close this letter by extending my deepest gratitude to people with ALS and their caregivers and families, the scientists who are championing ALS research, and our supporters who make this work possible. Thank you.

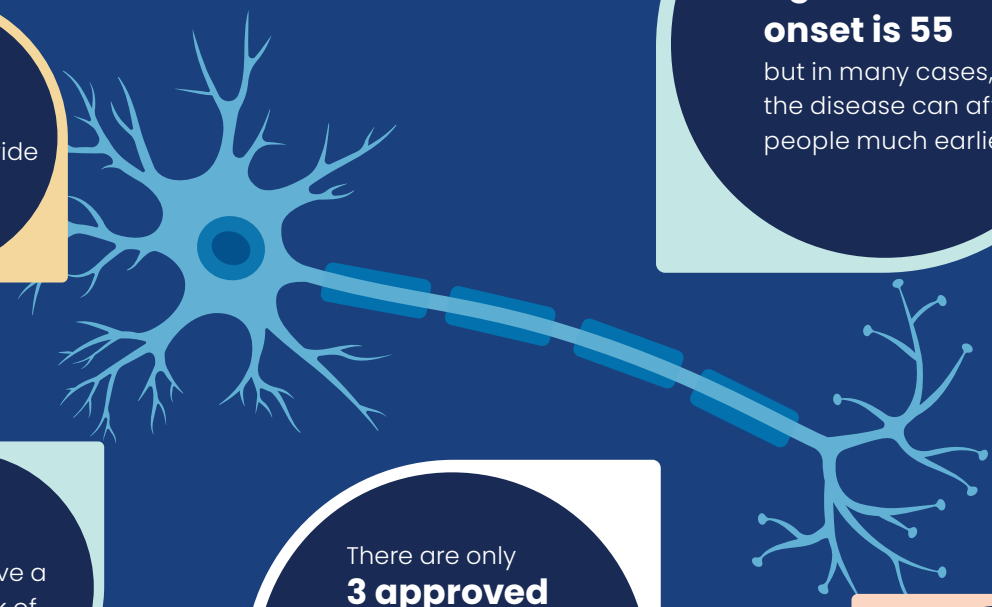
Manish Raisinghani, M.B.B.S., Ph.D.
Chief Executive Officer,
Target ALS

Target ALS By the Numbers

The Disease

About **400,000** people worldwide have ALS

The average age of disease onset is 55 but in many cases, the disease can affect people much earlier



1 in 400 people have a lifetime risk of developing ALS

There are only **3 approved therapies** with limited effectiveness and limited access around the world

2 to 5 yrs is the average life expectancy once diagnosed

Our Impact

$25M

Invested directly into our three core areas of research we fund, enable, and conduct in 2025

10 Clinical trials emerged from Target ALS-funded work

6 Biotech companies launched from Target ALS-funded work

2025 Annual Meeting

32+

Countries
represented by people with ALS, their loved ones, academic institutions, and pharma, biotech, and VC firms

960+

Attendees

143

Academic Institutions

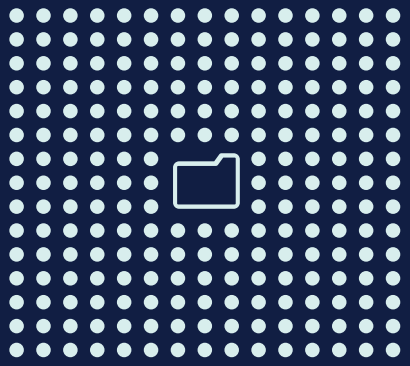
47

Nonprofit Organizations

152

Pharma/Biotech and VC companies engaged with Target ALS research

Of our funded consortia have led to drug discovery programs



350+ Users accessing the Target ALS Data Engine

Breaking Down Barriers in ALS Research

The Target ALS 2025 Annual Meeting showcased a powerful mix of bold new ideas and highly evolved, collaborative projects.

As we were reminded in many sessions, ALS remains a devastating disease. That's why Target ALS remains focused on breaking down the scientific barriers that hold back progress: gaining a deeper understanding of disease biology, driving rapid drug discovery, and developing accessible, non-invasive biomarkers for diagnosis and trial design.

We're proud that our funded portfolio spans all three areas, with growing investments in the biology of TDP-43, C9orf72, SOD1, and FUS and in the emerging areas of biology, including the role of the immune system in motor neuron degeneration. From our Postmortem Tissue Core and Biofluid Repository to the Global Natural History Study and open-access Data Engine, we continue to provide the research community with state-of-the-art techniques and no-strings-attached tools to accelerate discovery.

And the momentum is building. Over 350 researchers are already using our data, and collaborative consortia of preeminent scientists are tackling the science. This is a community that is actively dismantling silos and advancing science to improve care and treatment for all people with ALS.

Two themes I want to highlight are diversity and data that bring us closer to treatment. Our Global Natural History Study continues to grow in geographic and ancestral representation, strengthening the foundation for more inclusive and globally relevant ALS research. I also want to spotlight the ALSFRS-R data showing the benefit of Tofersen in individuals with SOD1 mutations. This is a powerful signal that treating ALS is possible. The data emerging from SOD1 carriers on Tofersen offer critical insights into biomarkers that help us understand the difference between true disease benefit and ongoing progression. These learnings will inform the broader ALS research community and support smarter, more targeted therapeutic development.

Thank you to every scientist and clinician, as well as people with ALS and their caregivers, and communities who contributed to this extraordinary meeting. Together, we are not just imagining a different future—we are building it.

— Amy Easton, Ph.D.
Target ALS

Scan the QR Code to watch the full opening session of the Target ALS 2025 Annual Meeting.

Target ALS Annual Meeting:
Updates from Our Innovation Ecosystem

Core Day 2025: Advancing the Foundation of ALS Research

Target ALS Research Cores are a collection of scientific tools and resources available to researchers worldwide that break down barriers to ALS research. The Target ALS Core Day offers investigators and coordinators involved in our Global Natural History Study and Postmortem Tissue Core a valuable opportunity to connect in person, review study progress, and engage in meaningful discussions on data collection, data generation, and ways to continuously evolve the Cores to advance the ALS research landscape.

Highlights from the Core Day:

Tissue & Genetics:
Expanding Access and Equity

We're working to increase diversity in our postmortem tissue collection and ensure fair access to rare, mutation-positive samples. We're also scaling advanced technologies like long-read sequencing, single-cell RNA, and spatial mapping to better understand ALS at the cellular level.

Biofluids

The Global Natural History Study (GNHS) has enrolled 229 participants across 14 sites, with plans to reach 1,000. The study has already resulted in collection of over 23,000 samples of cerebrospinal fluid, blood, and urine over the course of disease. Expansion of the study to new international sites, including India and South Korea, is helping us reach even more diverse communities.

What's Next

- New tools like fibroblast biobanks are being explored to support disease modeling.
- Updated questionnaires and digital tools will improve patient participation.
- All data is shared freely through the Target ALS Data Engine, already supporting over 350 researchers to date worldwide.

Key Takeway

The Core Day reminded us that progress in ALS doesn't just come from ideas; it also comes from infrastructure. By sharing samples, data, and insights openly, we're accelerating the science that will one day change lives.

Drug Discovery and Development

Expanding the Drug Discovery Pipeline to Increase Effective Therapies for ALS

Most ALS cases (90%) are "sporadic," meaning they have no clear cause. Despite years of research, most treatments target the effects of the disease, not what starts it. A new wave of therapies is aiming to act earlier in the disease process. Target ALS is helping lead this shift by funding cutting-edge research through its Industry-Led Collaborative Consortia, with many programs now moving into clinical trials.

QurAlis: Advancing Targeted Therapies for ALS Through Ion Channel Modulation

QRL-101 is a precision therapy designed to treat neuronal hyperexcitability, a common and often overlooked feature of ALS that may drive disease progression. In early clinical trials, the drug successfully hit its target, showed encouraging biological effects linked to survival, and was well tolerated with mostly mild side effects. QurAlis is now preparing to test an extended-release version in people living with ALS.

Key Takeaway

QRL-101 is a promising, well-tolerated treatment candidate that could address hyperexcitability in a broad population of people with ALS. Early biomarker data confirm that the drug is doing what it's supposed to, laying the groundwork for potential disease-modifying effects.

"QRL-101 is well-positioned to be a potential best-in-class therapeutic with high selectivity, lack of off-target engagement, and multiple formulations for daily or twice-daily dosing to enable application in neurodegenerative and neurological diseases, including ALS and epilepsy."

— Emma Bowden, Ph.D.
QurAlis

Manuela Polydoro, Ph.D., Muna Therapeutics and Target ALS IRC Member, **Yossi Dagon, Ph.D.**, QurAlis, and **Evangelos Kiskinis, Ph.D.**, Northwestern University Feinberg School of Medicine, discuss KCNQ2 Biomarker for Precision Medicine in ALS.

KCNQ2 Mis-Splicing: A Precision Biomarker for ALS

Led by QurAlis, with partners at Northwestern, USC, and Emory, this team is developing a blood test to detect mis-splicing of the KCNQ2 gene, which is linked to hyperexcitability in ALS. By analyzing tiny particles in the blood called extracellular vesicles (EVs), they hope to identify individuals with this gene disruption and explore how it could help with diagnosing, tailoring treatments, and tracking how well therapies work.

Key Takeaway

By tracking KCNQ2 mis-splicing in EVs, this project is building a non-invasive tool to connect TDP-43 pathology to functional deficits, offering a promising biomarker and therapeutic target in ALS.

ALS 101

Mis-splicing refers to errors in how the genetic instructions from a gene are pieced together to make a functional protein. These errors can lead to a faulty or missing potassium channel protein, which may cause nerve cells to become overactive, seen in many people with ALS.

Hyperexcitability is when nerve cells (neurons) become too easily activated or "triggered," firing more often or more intensely than they should. This abnormal activity can disrupt normal brain and nerve function and is linked to conditions such as ALS, epilepsy, and chronic pain.

Extracellular vesicles (EVs) are tiny bubble-like particles released by cells into bodily fluids such as blood and spinal fluid. They carry bits of the cell's internal material, such as proteins, RNA, and lipids, and act like messengers, helping cells communicate with one another. In diseases like ALS, EVs can contain specific disease-related signals, making them a valuable tool for tracking what's happening inside the nervous system through simple, non-invasive tests.

Denali Therapeutics: Learning from the DNL343 Trial in ALS

Denali Therapeutics tested DNL343, a drug aimed at calming the cell's stress response and preventing toxic buildup linked to ALS. While early signs were promising, showing the drug reached its target and affected key biomarkers, the larger trial did not slow disease progression. Still, the results offer valuable lessons for improving future ALS therapies. It is also important to acknowledge Denali's openness to presenting negative results, a testament to a conscientious approach toward research.

ALS 101

Biomarkers are measurable indicators of what's happening inside the body. They can show if a disease is present, how it's progressing, or how well a treatment is working. In ALS, for example, scientists are looking for proteins in the blood or spinal fluid to act as biomarkers.

Key Takeaway

This was a tough outcome, but one that reinforces why Target ALS and the research community invest so heavily in the early stages of drug development. Every trial adds to our understanding so that future therapies entering clinical testing have a greater chance of success.

"Most of you probably know the primary and secondary endpoints were not met in this trial. This was very disappointing for everyone in the ALS research community, but particularly for those people and their families living with ALS. I want to thank the organizers for giving me the opportunity to share these results, with the hope that we can leverage the learnings from this study to further advance therapies for ALS in the future."

— Danna Jennings, M.D.
Denali Therapeutics

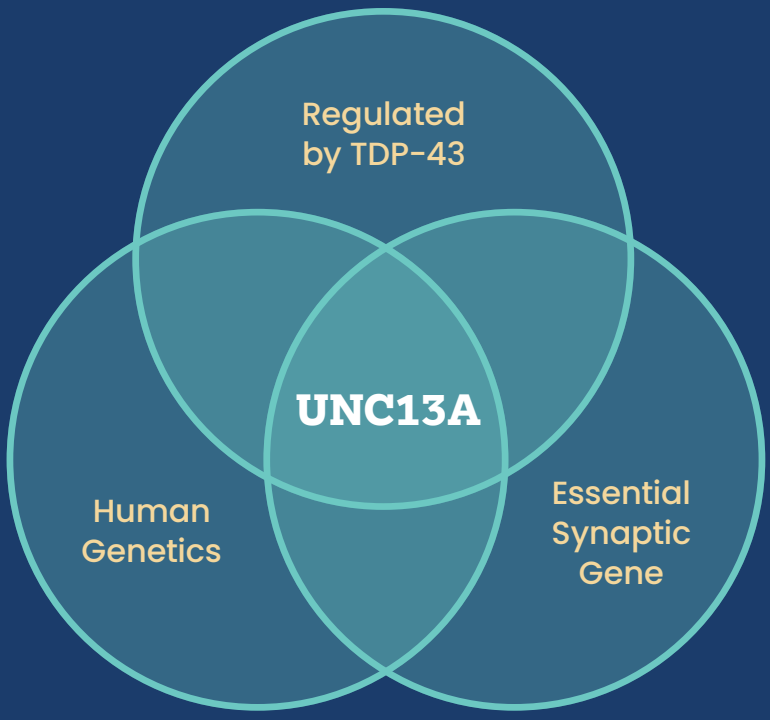
Splice Correction of UNC13A: A New Frontier in ALS Treatment

A multi-institutional team from Trace Therapeutics, Stanford, the University of Michigan, and FMP Berlin is developing a promising and exciting new therapy that corrects RNA splicing errors in the UNC13A gene, seen in most ALS cases and linked to faster disease progression. By using precision molecules called antisense oligonucleotides (ASOs), researchers have successfully restored normal UNC13A function in lab-grown neurons and genetically engineered mice. These corrections improved nerve cell communication, brain circuitry, and key survival markers. The team is now testing this approach in a mouse model that closely mimics human disease, laying the foundation for future clinical trials.

Key Takeaway

Correcting UNC13A mis-splicing could offer a broadly applicable therapy for most people with ALS. With early data showing restoration of neuron function and synaptic health, this work is a promising example of how understanding the genetic and mechanistic underpinnings of ALS can unlock transformative new treatments.

The intersection of **human genetics** evidence, a **mechanistic link to TDP-43**, and the **essentiality of UNC13A** distinguish it from other potential drug targets for ALS



◀ **Ryan Morrie, Ph.D.**
Trace Therapeutics

▼ **Shila Mekhoubad, Ph.D.**
Trace Therapeutics

ALS 101

Antisense oligonucleotides (ASOs) are small, lab-made pieces of genetic material designed to bind to RNA in cells. By attaching to specific RNA sequences, ASOs can block or change how certain genes are used, either by reducing harmful proteins or helping the body make more of a helpful one. In ALS research, ASOs are being explored as a way to target the root causes of the disease at the genetic level.

Key survival markers are biological signs that help predict how a disease like ALS will progress or how long a person might live with it. These markers can include specific proteins in the blood or spinal fluid, levels of gene activity, or changes in nerve cell health. In ALS research, improved survival markers often signal that a treatment is having a protective effect on the nervous system, even before major physical changes are seen.

Unlocking RNA Granules: A Promising Therapeutic Pathway in ALS

Denali Therapeutics and UCSD researchers are targeting a protein called OTUD4, which plays a role in the harmful effects of TDP-43. By using ASOs to reduce OTUD4, they've restored levels of a critical nerve-repair protein (STMN2) and reduced cell damage in a stem cell model and avoided side effects in mice. To make this therapy more accessible, they've also developed a new delivery system that can carry ASOs across the blood-brain barrier through a simple IV, rather than spinal injections. Three strong drug candidates are now moving into advanced testing.

Key Takeaway

By intervening upstream in the TDP-43 pathway through OTUD4, this consortium is pioneering a novel therapeutic angle for ALS. With a promising delivery system, potent lead candidates, and efficacy data on the horizon, this approach is advancing quickly and may represent a new class of disease-modifying treatments for ALS.

▲ **Eugene Yeo, Ph.D.**
University of California, San Diego

Joe Lewcock, Ph.D.
Denali Therapeutics

ALS 101

TDP-43 is a protein that normally helps regulate how cells process RNA, which is essential for making proteins and keeping cells healthy. In ALS and some other neurodegenerative diseases, TDP-43 becomes mislocated, leaving the cell nucleus and clumping in the wrong part of the cell. This disrupts vital gene functions and is considered a key driver of nerve cell damage in ALS.

The blood-brain barrier is a protective layer of tightly packed cells that lines the blood vessels in the brain and spinal cord. It acts like a security gate, allowing essential nutrients through while blocking harmful substances, such as toxins or germs. While it protects the brain, it also makes it harder for many medications to reach the brain, which is a major challenge in treating diseases like ALS.

John Andersson, Ph.D.
Karolinska Institutet,
CarryGenes Therapeutics AB

T Cells and ALS: Clues from the Immune System

Two cutting-edge projects have spotlighted the immune system's evolving role in ALS, particularly the behavior of T cells, the body's immune orchestrators.

Dr. John Andersson (Karolinska Institutet and CarryGenes Therapeutics AB) explored how T cells shift and adapt during ALS progression. His team's research reveals striking heterogeneity in T cell activity among patients, with different profiles emerging in blood versus cerebrospinal fluid. Interestingly, some T cell types may contribute to neurodegeneration, while others may be protective. This highlights the immune system's dual-edged nature in ALS.

Meanwhile, Dr. Jenna Gregory (University of Aberdeen) shared promising findings about a molecule called sCTLA-4, usually studied in cancer. Her research shows that it behaves differently in people with ALS and could help both identify specific types of inflammation in the disease and guide more personalized treatment approaches.

"Both of our grants from Target ALS were for ideas we couldn't get funded anywhere else. They weren't pedestrian. But Target ALS saw the value. That support allowed us—and the lab—to work on something truly transformative. The Annual Meeting is a place where high-risk, high-reward ideas are welcomed, where novel thinking is encouraged, and where you get to connect with a global community that wants to push this field forward."

— Jenna Gregory, MB BChir, Ph.D.
University of Aberdeen

Discover how Dr. Jenna Gregory is bringing oncology-style precision to ALS—using T cells not just to treat but to predict the disease. Scan the QR code to **read the full story** of her bold, theragnostic vision.

Key Takeaway

Immune responses in ALS are far from one-size-fits-all. T cell profiles vary significantly between individuals and disease stages. Together, these studies point to a future where immune-based biomarkers and personalized therapies could help tailor treatments for subtypes of ALS, mirroring precision strategies used in oncology.

Beyond "Junk" DNA: Targeting Transposable Elements in ALS

Long considered genomic leftovers, transposable elements such as LINE1 and HERV-K are gaining recognition as active players in neurodegenerative disease. Two groundbreaking projects supported by Target ALS are now exploring how these ancient genetic elements may both drive ALS pathology and offer new routes to precision diagnostics and therapies.

ALS 101

Transposable elements, sometimes called "jumping genes," are pieces of DNA that can move to different places in our genetic code. In healthy cells, they're usually kept quiet, but in ALS, certain types, such as LINE1 and HERV-K, can switch on when they shouldn't. This can cause problems in nerve cells, such as stress, damage, or inflammation, and researchers are exploring how this might drive the disease and open the door to new treatments.

Dr. Yini Li: Epigenetic Control of LINE1 in C9orf72 ALS

Dr. Yini Li, a Target ALS Springboard Fellow who recently launched her own lab at Purdue University, is studying how a genetic element called LINE1 builds up in the most common form of genetic ALS linked to the C9orf72 gene. Her team found that quieting LINE1 activity with targeted RNA therapies can help nerve cells better withstand stress. This research highlights a promising new approach to ALS treatment by targeting a previously overlooked RNA-related mechanism.

Yini Li, Ph.D.
Purdue University

Scan the QR code to **read the full blog** on how Dr. Li is rethinking the role of "junk" DNA and charting a bold path toward RNA-targeted therapies.

Erez Eitan, Ph.D.
NeuroDex

Transposable Elements in Extracellular Vesicles: A Biomarker-Driven Consortium

A collaborative team led by NeuroDex is using tiny particles from brain cells, called extracellular vesicles (EVs), to detect transposable elements such as HERV-K and LINE1 in the blood, potential biomarkers linked to ALS. By combining this non-invasive testing with a promising therapy called EN1, which may quiet LINE1 activity and protect neurons, the team hopes to better match patients to treatments and track their responses.

Key Takeaway

Together, these projects are redefining how transposable elements are viewed in ALS, not as genetic noise, but as both drivers of pathology and tools for precision medicine, bringing us closer to earlier diagnoses and targeted treatments.

Looking for more detail on these projects? You can access the full *Drug Discovery and Development: Highlights from the Target ALS 2025 Annual Meeting* blog on the Target ALS website.

Nicholas Wood, Ph.D., FRCP, FMedSci, UCL Institute of Neurology and Target ALS IRC Member, **Amanda Guise, Ph.D.**, Biogen, **Alyssa Coyne, Ph.D.**, Johns Hopkins University, and **Jeffrey Rothstein, M.D., Ph.D.**, Johns Hopkins University, discuss Therapeutic Targeting of Antisense C4G2 Repeat RNA in C9orf72 ALS/FTD.

C9orf72 and ALS

The C9orf72 repeat expansion ALS is the most common genetic cause of ALS, accounting for up to 40% of familial ALS and ~7% of sporadic cases. Mutations in the C9orf72 gene have also been linked to frontotemporal dementia (FTD).

Treating individuals with C9orf72 is a focus of our drug portfolio, with about 30% of our advanced drug discovery pipeline dedicated to this population.

Spotlight on C9orf72 Projects Featured at the Annual Meeting:

Targeting C9orf72 Antisense RNA: A Refined Approach to ALS/FTD Treatment

Researchers from Biogen, Ionis, and Johns Hopkins are taking a new approach to treating ALS and FTD caused by a mutation in the C9orf72 gene. After a previous drug targeting one form of toxic RNA showed no benefit, new evidence pointed to a different form, antisense RNA, as the more harmful driver, shifting the team's focus.

Key Takeaway

While the first clinical trial didn't succeed, researchers have made real progress with new therapies that reduce toxic proteins in lab and animal models. They're learning from past challenges to develop more effective treatments for people with C9orf72-linked ALS and FTD.

Rewriting the Rules:
Dr. Claire Clelland's CRISPR Strategy for ALS

Dr. Claire Clelland (UCSF) is leading a groundbreaking effort to create a personalized gene therapy for people with C9orf72-linked ALS and FTD. Her team has shown that custom CRISPR tools can remove the toxic mutation from patient-derived neurons. Now, in partnership with Denali Therapeutics, they're working on a novel way to deliver this therapy safely to the brain using a nonviral, IV-based system.

Key Takeaway

Dr. Clelland is a true trailblazer — developing one of the first personalized CRISPR strategies for ALS that accounts for genetic differences across C9 carriers. With proven success in editing patient-derived motor neurons and a delivery platform in development with Denali, she's building a therapy with real-world potential. With expeditious and holistic support from Target ALS, including critical cell lines and tools, this bold science is now on the path to becoming a transformative treatment.

ALS 101

Sense RNA is the strand that matches the normal genetic code used by cells to make proteins.

Antisense RNA is the opposite strand, which is not normally used to make proteins but can still affect cell function.
In some diseases such as ALS and FTD, a mutation can lead to the production of both sense and antisense RNA. These extra RNA molecules can become toxic, building up in cells, disrupting normal processes, and contributing to nerve cell damage.

CRISPR is a powerful gene-editing tool that allows scientists to make precise changes to DNA, like cutting out or fixing faulty genetic material. It works like molecular scissors, guided by a piece of RNA that tells it exactly where to go. In diseases like ALS, CRISPR offers the potential to correct the mutations at the root of the problem right at the DNA level.

"Every day I think about the patients who are waiting on us. ***There's not a second to waste.****"*

— Claire Clelland, M.D., Ph.D.,
University of California, San Francisco

Scan the QR code to **read the full blog** and learn how Dr. Clelland is pushing the boundaries of what's possible in neurodegenerative gene therapy.

Decoding Microglia: A New Lens on C9orf72-ALS

Dr. Pegah Masrori, an emerging generation awardee of Target ALS funding, is uncovering how the brain's immune cells, called microglia, behave differently in C9orf72-linked ALS compared to other forms of the disease. Her team found that in C9orf72-linked ALS, microglia are less reactive and more stable, likely due to lower expression of the C9orf72 gene itself. This suggests that immune cells, not just neurons, may play a key role in how ALS develops and progresses.

Key Takeaway

By highlighting how microglial behavior differs between C9orf72 and sporadic ALS, this project adds a valuable dimension to the field's understanding of non-neuronal drivers of disease and underscores the importance of developing precision biomarkers and therapies that reflect ALS's cellular complexity.

Looking for more detail on these projects? You can access the full *The C9orf72 Puzzle: Cracking ALS's Most Common Genetic Code* blog on the Target ALS website.

Volkan Granit, M.D., Biohaven Pharmaceuticals and Target ALS IRC Member, and **Pegah Masrori, M.D., Ph.D.,** KU Leuven Center for Brain & Disease Research in Belgium.

Real Research, Real Impact: Dive into the Poster Showcase

As part of the Annual Meeting, several researchers presented posters showcasing their latest work. Much of this work was made possible through Target ALS's biofluids, postmortem tissue, and data core resources. These posters reflect our vision to democratize ideation on ALS research worldwide through an open-access infrastructure, enabling discovery.

If you'd like to explore their research, scan the QR code to **flip through our digital poster book.**

Identifying and Developing Biomarkers

Finding the Key to Successful Clinical Trials Through Biomarkers for ALS

Understanding ALS begins with a challenge: we can't directly observe what's happening in the brain. Instead, scientists must rely on biomarkers, biological signals found in blood, spinal fluid, imaging scans, or physical functions like breathing and speech to track how the disease unfolds. However, developing reliable biomarkers has been especially difficult in ALS.

Tackling TDP-43: A Systems-Level Approach to a Central Driver of ALS

TDP-43 is a key protein that goes awry in nearly all (97%) ALS cases, causing damage by clumping in the wrong part of cells and disrupting vital processes. Because it's complex and varies across patients, it's been hard to target with treatments or use as a reliable marker. That's why Target ALS is dedicating a major portion of its research to tackling TDP-43 from multiple angles, from early discovery to therapy development and non-invasive tools for earlier diagnosis.

Target ALS's coordinated approach is grounded in three areas:

01

Therapeutic Discovery: Advancing diverse strategies to modulate toxic TDP-43 while preserving its critical function.

02

Biomarker Development: Enabling earlier detection and patient stratification through investment in TDP-43-targeted biomarkers.

03

Shared Research Infrastructure: Providing open-access tools, such as postmortem tissue, biofluids, preclinical models, and reagents, to accelerate and validate progress across the field.

Key Takeaway

Only a few drugs that have entered clinical trials have targeted TDP-43 pathology, believed to be an early event leading to motor neuron degeneration in ~97% of ALS cases. Target ALS-funded projects are taking bold, mechanistically driven approaches to tackle TDP-43 pathology at its roots. These projects represent a new wave of TDP-43–directed therapies that aim to intervene early in the ALS disease cascade and may even be used to prevent onset of clinical symptoms.

Protein-Targeting Strategies

Disrupting Toxic Protein Partnerships: TDP-43 and Tankyrase

Dr. Leeanne McGurk, an emerging generation awardee of Target ALS funding, from University of Dundee, has discovered that an enzyme called Tankyrase binds to and stabilizes TDP-43 in the wrong part of the cell, making it more toxic. Her team pinpointed exactly where this binding happens and showed that blocking it reduces damage in lab models. Since related drugs already exist for cancer, this opens up a fast-track path to potential ALS treatments.

Key Takeaway

By targeting the Tankyrase-TDP-43 interaction, Dr. McGurk is opening a new therapeutic avenue, one that could restore TDP-43's function and slow neurodegeneration in ALS.

Leeanne McGurk, Ph.D.
University of Dundee

Consortium: Structure-Based Discovery of TDP-43 Blockers

The SISMIC-TDP43 Consortium, led by Dr. Morwena Latouche at the Paris Brain Institute and top research institutes—including International Centre for Genetic Engineering & Biotechnology (Dr. Emanuele Buratti), Institut Pasteur (Dr. Olivier Sperandio), and CEA Paris-Saclay (Dr. Jean-Christophe Cintrat) — is using AI and advanced imaging to find drugs that block TDP-43 from clumping. With support from Target ALS, they've already identified four promising compounds that break down these toxic clumps in lab tests and are now testing them in cells.

Scan the QR code to **read our full blog** about Dr. Latouche's innovative approach to targeting ALS at the molecular level.

Key Takeaway

This project is combining artificial intelligence, structural biology, and biochemistry to identify small molecules that could stop or reverse TDP-43 aggregation—a hallmark of ALS and FTD—paving the way for novel, precision-targeted therapeutics.

Scan the QR code to **read the full blog** on Dr. McGurk's innovative approach to targeting ALS at the molecular level.

Spotlight on Biomarkers to Detect TDP-43, Featured at the Annual Meeting

Sarah Smith, M.D., Ph.D.
Brigham and Women's Hospital, Harvard

TDP-43 Seed Amplification: A Diagnostic Breakthrough in Progress

Dr. Sarah Smith (Brigham and Women's Hospital, Harvard) is developing a cutting-edge test that can detect tiny, disease-related clumps of the TDP-43 protein. Her approach, called a seed amplification assay (SAA), has already distinguished affected brain samples from healthy ones and is now being tested on spinal fluid for early, non-invasive diagnosis. In 2025, Dr. Smith will be utilizing CSF from the Target ALS longitudinal biofluid repository for further tests.

Key Takeaway

TDP-43 SAAs are emerging as a powerful tool to detect disease-specific protein aggregates in biofluids, offering real potential for early, accurate diagnosis of ALS as well as FTD. Target ALS supports researchers such as Dr. Smith as part of our effort to bolster an emerging generation of clinicians.

ALS 101

A seed amplification assay (SAA) is a lab test used to detect tiny amounts of misfolded proteins, called "seeds", that can trigger the clumping of normal proteins. In diseases like ALS, SAA can identify these early protein aggregates (such as misfolded TDP-43) in samples, such as spinal fluid, potentially allowing for earlier and more accurate diagnosis. It's similar in concept to how a small spark can start a fire—the assay amplifies the signal to detect even very small amounts of disease-related protein.

Frontotemporal Dementia (FTD) is a neurodegenerative disease that affects the brain's frontal and temporal lobes, leading to changes in behavior, personality, and language. FTD is closely related to ALS as both conditions can share the same underlying genetic causes, such as the C9orf72 gene mutation, and both involve the buildup of abnormal TDP-43 protein in brain cells. Some people may develop symptoms of both diseases, which is known as ALS-FTD, showing the strong connection between movement and cognitive decline in these disorders.

Unlocking TDP-43 Structures for ALS Diagnostics

Dr. Javier Oroz (CSIC Madrid) is developing tools to detect misfolded TDP-43 protein in biofluids by studying how its structure changes in ALS compared to healthy individuals. Using advanced protein design, his team is creating probes that can recognize and amplify disease-specific forms of TDP-43, aiming to improve early and accurate diagnosis. Dr. Oroz is also utilizing CSF from the Target ALS longitudinal biofluid repository.

Javier Oroz, Ph.D.
CSIC Madrid

Key Takeaway

By decoding the structural diversity of TDP-43 aggregates, Dr. Oroz is building the foundation for highly specific diagnostic tools, turning the complexity of protein misfolding into a roadmap for earlier and more accurate ALS detection.

ALS 101

HDGFL2-CE is a cryptic peptide, meaning it's a short protein fragment that is not normally produced in healthy cells. It is generated when **TDP-43**, a key RNA-binding protein, becomes mislocalized or dysfunctional.

Cracking the Code: Biomarkers to Detect and Monitor TDP-43 Pathology in ALS and FTD

A powerhouse team from the NIH (Dr. Michael Ward), the Mayo Clinic (Dr. Leonard Petrucelli and Dr. Mercedes Prudencio) and University College London (Dr. Pietro Fratta, Project Leader) is developing next-generation biomarkers that directly reflect TDP-43 dysfunction. They've zeroed in on cryptic peptides such as HDGFL2-CE, which only appear in neurons affected by the disease, and created ultrasensitive tests to detect them. Early results show these peptides may track disease severity and even trigger immune responses, opening new doors for diagnosis, monitoring, and treatment. These researchers are utilizing longitudinal CSF samples from Target ALS to do their final assay validation.

Key Takeaway

By tracing the unique molecular fingerprints of TDP-43 dysfunction, this consortium is laying the groundwork for a first-in-class biomarker strategy that could transform how ALS and FTD are diagnosed, monitored, and treated. These efforts offer a direct readout of disease activity and could even reveal new immune-based therapeutic opportunities.

Read more about their research here.

Brad Friedman, Ph.D., Genentech, Inc. and Target ALS IRC Member, **Michael Ward, M.D., Ph.D.,** NINDS, **Leonard Petrucelli, Ph.D.,** Mayo Clinic, and **Pietro Fratta, Ph.D.,** University College London, discuss novel biomarkers to detect and monitor TDP-43 pathology in ALS/FTD.

Next-Generation Fluid Biomarkers: Tracking TDP-43 Pathology via Extracellular Vesicles

A global team led by Novartis, along with researchers from DZNE, Oxford, and KU Leuven, is developing a new way to track ALS and FTD by studying extracellular vesicles (EVs), which are tiny particles released by cells that carry disease-related proteins and RNA. Using samples from the Target ALS biobank, they've found that EVs from people with ALS and some FTD cases contain clear signs of TDP-43 dysfunction, including cryptic RNA and phospho-TDP-43. This approach could allow for simple, non-invasive tests to detect and monitor disease through blood or spinal fluid.

Read more about how Target ALS is tackling TDP-43 here.

"Target ALS is really fostering this collaboration with the access to longitudinal human biofluids and patient omics datasets. I think this is a valuable resource that is going to impact the success of our consortium."

— Arti Patel, Ph.D.
Novartis Institutes for BioMedical Research (NIBR)

Key Takeaway

This consortium is transforming our ability to measure TDP-43 dysfunction in people living with ALS. By decoding molecular signals within extracellular vesicles, they are building non-invasive, scalable biomarkers to track ALS and FTD progression, bringing us one step closer to precision diagnostics and earlier intervention.

ALS 101

Cryptic RNA refers to faulty or "hidden" RNA messages that aren't normally produced in healthy cells. These appear when proteins such as TDP-43 stop functioning properly and allow incorrect sections of RNA, called cryptic exons, to be included. These flawed messages can lead to the production of abnormal or harmful proteins, and they're a sign of TDP-43 dysfunction in diseases like ALS and FTD.

Phospho-TDP-43 is a modified form of the TDP-43 protein that has been chemically tagged with phosphate groups. This change is linked to the protein misbehaving, clumping in the wrong part of the cell and contributing to nerve cell damage. It's considered a hallmark of ALS and FTD and is often used as a marker of disease activity.

Using Neural Networks to Predict ALS Progression

Dr. Robert McFarlane (Trinity College Dublin), an emerging generation awardee of Target ALS funding, is building neural network models that predict changes in ALSFRS-R scores, which is a key clinical measure used in trials, based on massive, population-level datasets. His model captures both linear and nonlinear disease trajectories, offering personalized, short-term forecasts that could help flag trial failures early, reduce reliance on placebo arms, and better stratify patients.

Key Takeaway

Dr. McFarlane's dynamic model turns real-world ALS data into a powerful forecasting tool, paving the way for smarter clinical trial design and more responsive patient care.

Scan the QR code to **read the full blog** on how Dr. McFarlane is using digital twins to reimagine ALS trials.

Robert McFarlane, M.B.B.S., Ph.D. candidate
Trinity College Dublin

Looking for more detail on these projects? You can access the full *Identifying and Developing Biomarkers: Highlights from the Target ALS 2025 Meeting* blog on the Target ALS website.

Identifying Novel Drug Targets: Basic Biology

Understanding Environmental and Biological Causes of ALS

The search for ALS treatments starts with understanding the biology behind the disease. Target ALS is broadening this view by supporting research beyond motor neurons, exploring the immune system, metabolism, and other overlooked areas.

At the 2025 Annual Meeting, research teams shared breakthrough findings using advanced tools, such as proteomics and single-cell analysis, work that's helping uncover the root causes of ALS and paving the way for new therapies.

Profiling the Immune System in ALS with Genomic Precision

Dr. David Gate (Northwestern University) is using cutting-edge tools to study how the immune system behaves in different forms of ALS. His team has found unique immune cell patterns in both sporadic and C9orf72-linked ALS, along with signs of inflammation in the spinal cord that may play a role in nerve cell damage. These discoveries highlight the immune system as both a marker of disease and a possible driver of progression.

David Gate, Ph.D.
Northwestern University

Uncovering TDP-43 Dysfunction in Glial Cells

A multi-institutional team is uncovering how TDP-43 dysfunction in support cells such as astrocytes and microglia may actively contribute to ALS. Their research shows that when TDP-43 is lost in these cells, it causes DNA damage and instability, potentially setting the stage for nerve cell degeneration. This highlights that glial cells may not just react to ALS, they could be helping drive it.

Rita Sattler, Ph.D.
Barrow Neurological Institute

Key Takeaway

Together, these projects are reshaping our understanding of ALS as a disease of not only neurons but the entire cellular ecosystem. By decoding immune and glial dysfunction at single-cell resolution, they are laying the foundation for biomarkers and interventions tailored to each cellular contributor to ALS progression.

ALS 101

Glial cells are the support cells of the nervous system. Unlike neurons, they don't send electrical signals, but they play crucial roles in keeping the brain and spinal cord healthy. They provide nutrients, remove waste, protect against injury, and help maintain the environment around neurons. The main types include astrocytes, microglia, and oligodendrocytes. In diseases like ALS, glial cells can become dysfunctional and may actively contribute to nerve cell damage.

Astrocytes are star-shaped support cells in the brain and spinal cord. They help keep nerve cells (neurons) healthy by providing nutrients, cleaning up waste, and maintaining the balance of chemicals around them. In diseases like ALS, astrocytes can become overactive or dysfunctional, which may contribute to nerve cell damage.

Microglia are the brain and spinal cord's resident immune cells. They act as the first line of defense, constantly monitoring for damage or infection and cleaning up debris. In diseases like ALS, microglia can become overactive or dysfunctional, leading to inflammation that may worsen nerve cell damage.

Mapping ALS Genetics and Organelle Dysfunction to Find Therapeutic Targets

A leading research team from the University of Sheffield (Dr. Johnathan Cooper-Knock, Project Leader), the University of Pennsylvania (Dr. Ophir Shalem), Stanford University (Dr. Michael Snyder), and the Weizmann Institute of Science (Dr. Eran Hornstein) is using AI, large-scale screening, and cell imaging to understand how genetic changes and misplaced proteins contribute to ALS. They've identified a gene, CCDC146, which normally helps maintain key cell structures, but ALS-associated mutations in this gene disrupt those structures, leading to cellular damage. Encouragingly, targeting CCDC146 in mice has been shown to restore motor function. The team is also mapping how different ALS-related mutations affect the inner workings of cells, helping to group patients by how their cells behave rather than by genetics alone.

Key Takeaway

By linking genetic risk, cellular dysfunction, and therapeutic response, this consortium is charting a new course for ALS precision medicine, transforming big data into tangible drug targets.

Elizabeth Buttermore, Ph.D., Boston Children's Hospital and Target ALS IRC Member, **Johnathan Cooper-Knock, BM BCh, Ph.D.,** University of Sheffield, **Eran Hornstein, M.D., Ph.D.,** Weizmann Institute of Science, and **Ophir Shalem, Ph.D.,** Univeristy of Pennsylvania.

Neurons Fight Back: Innate Immunity and Cell Death in ALS

A team led by MGH and Harvard is uncovering how inflammation in ALS may start inside the neurons themselves, not just as a reaction to damage, but as a possible driver of it. Using lab-grown neurons and mouse models, they identified key immune pathways triggered by ALS-related stress. One protein called GSDME was found to cause cell damage, but when it was blocked, nerve cells survived and motor symptoms improved.

Key Takeaway

This work reveals that targeting neuron-specific immune responses, especially GSDME activation, could halt neurodegeneration at its source, offering a promising new direction for ALS therapies that go beyond symptom management.

Looking for more detail on these projects? You can access the full *Identifying Novel Drug Targets: Key Insights from the Target ALS 2025 Annual Meeting* blog on the Target ALS website.

Closing Reflections: Where We Stand and Where We're Headed

The final session of the 2025 Target ALS Annual Meeting, led by Dr. Chris Henderson, Target ALS Board Member, featured an honest discussion on how far ALS research has come and what it will take to realize our vision of a world where **Everyone Lives**.

Panelists Dr. Toby Ferguson (CMO, Voyager Therapeutics, Inc.), Dr. Pietro Fratta (Professor of Cellular and Molecular Neuroscience, University College London, Department of Neuromuscular Diseases) and Dr. Carole Ho (CMO and Head of Development, Denali Therapeutics) highlighted major progress in genetic models, biomarkers, and emerging therapies, alongside growing insights into complex disease drivers such as immune and glial cells. They also acknowledged ongoing challenges, including clinical trial setbacks and the need for better patient targeting, while reaffirming their commitment to bold, collaborative science that keeps people with ALS at the center.

Chris Henderson, Ph.D., Target ALS Board Member, **Toby Ferguson, M.D., Ph.D.,** Voyager Therapeutics, and **Pietro Fratta, Ph.D.,** University College London.

Watch the closing panel discussion on YouTube.

Key Takeaway

ALS is an unforgiving disease, but the field is evolving and Target ALS is helping drive that momentum. With bold science, shared tools, and patient-aligned urgency, we are inching closer to breakthroughs that once felt out of reach.

Everyone Lives.

This has been a difficult year.

At last year's Target ALS Annual Meeting, I fell ill and what began as a cold developed into pneumonia. While I was in the hospital, my pulmonologist recommended that I have a tracheostomy, which my wife, Alisa, and I decided to proceed with immediately. I spent 16 days in the hospital, and since then, I have required 24/7 care. My privacy was lost, and I began relying on a 430-pound wheelchair. Over the course of the year, I've experienced progressive weakening of my voice, legs, arms, and hands.

To continue communicating, including during this year's Annual Meeting, I've been using an AI application called ElevenLabs.

While these physical challenges are the nature of ALS, I remain an optimist and there is nothing that I'm more optimistic about than ALS research and Target ALS.

Over the past three years at Target ALS, we've increased our research budget by four times and significantly expanded our impact. Our guiding values are impatient optimism, deliberate disruption, and radical collaboration, and they shape everything we do. We bring together academics, companies, other ALS organizations, other neurological disease organizations, and the NIH to fuel innovation and accelerate discoveries.

Target ALS supports research through three key strategies:

Research We FUND

As the largest private funder of ALS research in the world, our consortia grants are fueling the future of ALS treatment.

Research We ENABLE

We provide a suite of critical tools and resources that empower scientific innovation, enabling more than 1650 projects to date to explore the unknowns of ALS.

Research We CONDUCT

We are conducting studies that explore the disease in diverse populations that will address longstanding intractable questions for ALS research, including a Global Natural History Study. We will soon have 18 sites across the world.

In the past year, our Independent Review Committee (IRC) has selected 21 projects out of 177 applications submitted by 470 principal investigators from 254 institutions located in 26 countries. In early 2024, we launched our Data Engine, which has already been accessed by over 350 users.

I'm especially proud that this year, Target ALS is funding three new research consortia focused on developing novel modalities, approaches that target ALS at the genetic level. These projects explore advanced tools such as CRISPR gene editing and antisense oligonucleotides (ASOs), technologies designed to precisely turn off or correct the harmful genetic instructions that may drive the disease.

Each consortium brings together top academic researchers and biotech partners working side by side to move these complex therapies from the lab bench toward real world clinical use. We are making progress on basic biology, genetics, biomarkers, AI, and novel therapeutics.

On a personal note, I continue to find joy and strength in my relationships and having a purpose, two things I believe matter most in life. In the past year, my wife and I have had three granddaughters born, bringing our total to five granddaughters born since I was diagnosed. They all live close by, and I see them often. My family and friends have been a constant source of support, and my purpose remains unwavering: to ensure everyone lives with ALS. That is my mission and my purpose.

Every single person present at the Annual Meeting is contributing to the rapid advancement of ALS research. Your support made their attendance possible. Because of you, I am confident we are going to solve this disease for every person with ALS.

Thank you for helping to build a world where everyone lives. I will continue to be involved in Target ALS until I can't do it anymore, which I hope will be for a very long time. I hope you'll continue to join us.

Thank you,

Dan Doctoroff
Founder and Chairman,
Target ALS

Watch Dan's Annual Meeting remarks

THANK YOU.

The progress highlighted throughout the Target ALS 2025 Annual Meeting and the work that makes it possible, would not happen without the generosity of our community.

We are deeply grateful to the many individuals and foundations who support our mission and to our corporate partners, including Biogen, Bristol Myers Squibb, insitro, Mitsubishi Tanabe Pharma America, and Prevail Therapeutics, for their sponsorship of the Annual Meeting.

Your commitment fuels the breakthroughs we pursue every day.

Biogen

Prevail THERAPEUTICS
A Wholly Owned Subsidiary of Eli Lilly and Company

insitro

Bristol Myers Squibb®

Mitsubishi Tanabe Pharma America

Target ALS Foundation

244 Madison Avenue #1025
New York, NY 10016

(332) 333-4140 | targetals.org

BOARD OF DIRECTORS

TARGET ALS

Target ALS Foundation
244 Madison Avenue #1025
New York, NY 10016
(332) 333-4140

targetals.org