A PATH TO A WORLD WHERE

EVERYONE LIVES

Highlights from the 2024 Target ALS Annual Meeting

TARGET ALS

TARGET ALS IMPACT REPORT | SUMMER 2024

TARGET ALS ANNUAL MEETING

Dear Friend of Target ALS,

Each spring, the Target ALS Annual Meeting brings members of our Innovation Ecosystem together over three days to share the latest breakthroughs and forge new collaborations, driving progress toward effective treatments for ALS. This year's meeting had **the largest attendance in history, with over 850 attendees** present from academic institutions, pharmaceutical and biotech companies, venture capital firms and nonprofit organizations - both in-person and virtually - reflecting the growth of both our funded portfolio of scientists and the impact our work has had on expanding ALS research.

Despite the record-breaking attendance, we have continued to **foster close relationships and trust among the scientists present** that has become a hallmark of our conference. This atmosphere is critical for researchers to feel comfortable sharing unpublished data from their ongoing work and engage in rigorous discussions that can lead to new ideas and new partners to accelerate research from the laboratory bench to the patient bedside. Underscoring this sentiment, Dr. Joseph Lewcock, Ph.D., Chief Scientific Officer at Denali Therapeutics said, "I've had the pleasure of being at every Target ALS meeting since the first one. I can see it's been incredibly impactful to be involved, not just through the consortia that we've been a part of, but through the relationships we've built at this meeting."

This year, we heard presentations focused on our three investment areas: identifying novel drug targets by improving our understanding of disease biology, driving development of therapeutics to transform ALS from a terminal disease into a chronic disease, and discovering biomarkers to improve diagnosis, disease monitoring, and clinical trials. The presentations not only showed progress across each of these areas, but expanded our perspective of ALS – featuring new avenues of study that are not typically associated with the disease, like role of the immune system or the microbiome in the gut – and demonstrated how our model derisks and accelerates ideas towards the clinic – sharing clinical trial milestones for new therapeutics developed with our support. **Some of the most exciting highlights include:**

- Two biotech companies have **advanced their active clinical trials**, which are based on early-stage funding from Target ALS, to the next phase.
- Multiple research groups funded by Target ALS are applying **cutting-edge gene editing technologies** to develop new treatment strategies for ALS.
- **An emerging generation of researchers** showcased their work exploring **novel areas of ALS biology** like the immune and digestive systems to find new drug targets.
- Exciting progress was presented on the gen-

eration of large multi-omic data sets, which we share publicly through our data portal. This is a necessary ingredient to accelerating the **application of Artificial Intelligence and Machine Learning** in ALS research.

- Promising research was presented on new biomarkers, which included blood-based and **non-invasive approaches to diagnose and monitor ALS** progression.

The work presented at the Annual Meeting has been made possible thanks to you and our Founder Dan Doctoroff's pioneering $250 million Capital Campaign, which he'll share more about in his concluding remarks. This bold endeavor has allowed us to **triple our research investment in the past three years alone** and with your support, we'll continue to make significant strides towards finding effective treatments for ALS.

Enclosed, we have summarized a few highlights from presentations made at the Annual Meeting. Their potential impact is astounding. However, beyond the science, perhaps the brightest highlight of the meeting for myself was meeting with **people living with ALS and their loved ones who offered their voices to inform and motivate our efforts.** In her remarks on the second day of the conference, Alisa Doctoroff gave the room a glimpse into hers and Dan's daily experience of life with ALS, a perspective that scientists don't often get to see firsthand. Her words underlined the urgency, but also the optimism, that herself and Dan lead us with every day.

Because of you, Target ALS will continue to be audacious and urgent in our approach. We will continue to fund the best ideas from the brightest minds across the globe, furthering the drug discovery pipeline toward effective treatments for ALS. **We believe that science driven by a meaningful mission can change the world**. And in our vision for a changed world, Everyone Lives. Thank you.

Manish Raisinghani
CEO, Target ALS

People ask me if I am taking care of myself and I am – doing the best I can. I think to myself – I can live with this; if it stays like this, I can handle it. And then I think I'm like the frog in the pot of water that's heating up. I don't know exactly how or when things will progress, but I know they will.

And Dan is only one case of many; I am only one spouse of many.

I know that you all know this. That many of you are here because of loved ones who have or had ALS or related diseases, that some of you treat ALS patients, that you encounter them in your research, that they reach out to you with hope for something that will slow the progress of their disease.

I'm here to thank you for being part of this amazing ecosystem and to ask you to keep pushing ahead relentlessly. To come here with the idea that maybe the NIH has rejected. To challenge each other with your questions, and curiosity. To use the new technologies that can speed up discoveries. To work with people in other disciplines. ***To be audacious and bold; unsatisfied and hungry."***

Alisa Doctoroff
Board Member, Target ALS

The Target ALS Annual Meeting: Updates from our Innovation Ecosystem

Drug Discovery and Development

Expanding the drug discovery pipeline to increase effective therapies for ALS

To date, many therapeutics for sporadic forms of ALS (the 90% of cases where there is no identified genetic mutation or family history of ALS) have been designed to target biological pathways or proteins, known as drug targets, that are not the initial causes of disease. These drug targets are considered to be downstream in the cascade of biological events that lead to ALS symptoms and motor neuron death. This approach may, in part, explain some of the recent failures of therapeutics in clinical trials and why current FDA-approved treatments have minimal impact; these therapeutics target consequences of disease, not the initial causes. The first wave of therapeutics which target upstream events in the biological cascade, including its causes, are now beginning clinical testing or will enter clinical trials in the coming years. Several of these programs are being funded by Target ALS through our Industry-Led Collaborative Consortia.

Industry Highlight: Denali Therapeutics

Denali Therapeutics is rapidly moving potential therapeutics targeting stress granules towards the clinic. Stress granules are bundles of dysfunctional RNA and protein that aggregate when a cell is under stress, like motor neurons are in ALS. By preventing formation of these stress granules, the proteins they trap can perform their necessary functions in the cell. One of these trapped proteins, TDP-43, is found aggregated in 97% of ALS cases, a hallmark of the disease.

In the Clinic

Denali's investigational drug, DNL343, is a small molecule that puts the brakes on an overactive cellular stress response by binding to a protein. This protein was identified through research conducted by a Target ALS-funded consortium including scientists from Denali, UCSF, and UCSD from 2017-2020. The treatment quickly entered successful early stage clinical trials showing safety and tolerability. **Denali achieved a major milestone recently: complete enrollment of its phase 2/3 clinical trial to evaluate benefit of DNL343 in ALS patients.** Significantly, this treatment targets an upstream biological pathway believed to be a key driver of ALS pathology, rather than downstream effect of disease. The rapid pace at which this work transformed from an idea in the lab to a potential disease-modifying treatment demonstrates our Innovation Ecosystem model successfully at work.

Approaching the Clinic

Denali is following up their success with a second program targeting another protein that contributes to formation of stress granules. The consortium shared the rapid progress they've made in just one year in their Annual Meeting presentation. The group reduced levels of this protein by using an **antisense oligonucleotide (ASO)**. **This approach led to reduced formation of stress granules and reversed several other negative effects associated with ALS.** Early stage testing of ASOs for this protein in mice demonstrated good activity and was well-tolerated with no side effects. With this exciting momentum, the team is gearing up to test the molecule for benefit in animal models of ALS before considering human trials. Further, the team has already identified candidate biomarkers to confirm activity of the drug in human patients, a critical factor in clinical trials to prove a treatment's efficacy to the FDA.

An **Antisense Oligonucleotide (ASO)** is a small piece of DNA or RNA that can block formation of a protein.

Further Studies

In 97% of ALS cases, the protein TDP-43 clumps together, or aggregates, in the motor neurons. Since this is such a common occurrence in ALS, TDP-43 is a popular target for research efforts. Beyond our work with Denali, Target ALS is funding additional companies targeting TDP-43 directly, including Dewpoint and Neumora. **Our grants and resources are currently supporting these companies as they develop plans to enter clinical trials.**

I've had the pleasure of being at every Target ALS meeting since the first one. I can see it's been incredibly impactful to be involved, not just through the consortia that we've been a part of, but through the relationships we've built at this meeting."

Dr. Joseph Lewcock, PhD
CSO, Denali Therapeutics

Industry Highlight: QurAlis and Trace Therapeutics

QurAlis and Trace Therapeutics are developing treatments aimed at **cryptic exons**, an underlying mechanism of disease that Target ALS-funded research helped identify in 2015. Since the discovery of cryptic exons, we have helped drive several programs aimed at restoring normal, healthy forms of genes towards the clinic.

Cryptic Exons are sequences of RNA that are only present when TDP-43 dysfunction occurs, as it does in 97% of ALS cases. These aberrant RNA sequences lead to aberrant proteins that can affect neuron health.

Neurotransmitters are signaling chemicals that allow neurons to communicate with each other. They are released at the **synapse**, or junction, between neurons.

QurAlis

Quralis is developing an ASO treatment, ARL-201, to correct a cryptic exon and restore normal, full length levels of Stathmin 2, a gene critical to neuron growth and repair. **Currently, the company is enrolling ALS patients in a Phase I study** to understand the treatment's safety and tolerability and to demonstrate proof of activity.

Trace Neuroscience

Trace Neuroscience is developing an ASO treatment targeting a cryptic exon in the gene Unc13a, an incredibly important **synapse** protein involved in the release of **neurotransmitters**.

▶ Dr. Claire Clelland, UCSF, presents her research on CRISPR for ALS

▼ Dr. Chris Henderson, Target ALS Chief Advisor, asks a question during audience Q&A

Therapeutics focused on C9orf72 form of ALS

Familial ALS, defined as presence of family history or identified genetic cause, accounts for 10% of all ALS cases. The most common familial form of ALS, stems from a **repeat expansion** in the gene C9orf72. Early clinical trials designed to treat C9orf72 mutation carriers by WAVE and Biogen targeted only the **sense RNA strand** and its resulting aberrant proteins, not the **antisense RNA strand**. These trials failed to show benefit in patients, leading to new therapeutic hypotheses on whether the sense, antisense, or both strands should be targeted in future treatments. **Target ALS is funding all possible gene therapies for C9orf72 mutation carriers, approaching the disease from all angles for the best possible chance of success.**

A **repeat expansion** is a repeated sequence of DNA that significantly affects a gene's length and function.

When the mutated gene is transcribed to RNA from both strands of DNA (the **sense** and **antisense strands**), the resulting RNAs are aberrant.

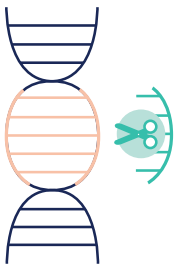
Aberrant proteins are created from each of these aberrant RNAs, both of which could be toxic and lead to motor neuron degeneration.

Gene Editing with CRISPR

Dr. Claire Clelland of UCSF is studying the use of CRISPR, a gene editing technology, to identify and cut out the entire repeat expansion in the c9orf72 gene, thereby removing the disease-causing DNA. **This would be an optimal therapy for patients, as it aims to resolve the initial cause of disease.**

Excitingly, this approach has **potential benefits beyond ALS and can be applied to a wide range of genetic diseases.**

Take a look at the diagram below to learn more about how CRISPR works.



1 Search

The CRISPR molecule finds the specific sequence of DNA to cut, for example, the repeat expansion in c9orf72 ALS carriers.

2 Cut

The CRISPR enzyme cuts out the targeted DNA segment. In our example, the entire repeat expansion.

3 Edit

In some cases, a new, corrected segment of DNA can be inserted. In our example, the repeat expansion has been removed, so the DNA is simply repaired.

▲ Dr. Kathyrn Morelli presents her research on zinc finger nuclease technology as a gene-editing tool for c9orf72 ALS.

Targeting Antisense RNA

Two companies, Ionis and Atalanta, are developing treatments targeting the antisense strand of RNA using different technologies.

Ionis is developing an ASO targeting the antisense RNA strand. **Given the success of Qalsody, a recently FDA-approved therapy for people living with another genetic form of ALS, this therapeutic is promising**.

Atalanta is targeting the antisense RNA strand with **disiRNA** technology. **Using disiRNA has some potential benefits,** including better distribution of the treatment throughout the central nervous system, longer lasting effects, fewer intrathecal (in the spinal cord) injections, and less tolerability issues compared to ASOs.

Zinc Finger Nuclease Technology

Dr. Kathryn Morelli of the University of Vermont, a Target ALS Springboard Fellow, is using **zinc finger nuclease** technology to target both the sense and antisense RNA strands, eliminating the guess as to which strand is actually toxic. This exciting research is moving to additional animal studies **to support an investigational new drug application (IND) with the FDA, the first step to beginning clinical trials in ALS patients.**

Zinc Fingers are small sections of protein that serve many functions, like regulating how DNA is copied.

Zinc Finger Nucleases combine Zinc Fingers and an enzyme to cut and edit DNA. Recent studies have found that these can edit RNA as well, unlocking new therapeutic avenues.

disiRNA is a short sequence of RNA that can identify aberrant RNA in a cell and bind to it. This tags the aberrant RNA for destruction.

This technology works similarly to ASOs, blocking production of aberrant proteins, which can be toxic.

Treatments for people with ultra rare forms of ALS

ALS drug discovery efforts are focused primarily on more prevalent forms of familial ALS and sporadic ALS. Genomic sequencing continues to reveal new ultra-rare (affecting <30 individuals worldwide) genetic forms of ALS. Development of new therapeutic approaches like antisense oligonucleotides (ASOs), small interference (siRNAs) and others, which can specifically modulate expression of targeted proteins, has opened the possibility of treating them, both to save lives and to apply learnings to all forms of ALS.

Target ALS works closely with other nonprofits whose mission and values align closely with our own, including the n-Lorem Foundation, an organization focused on developing ASO therapeutics for people living with ultra-rare genetic forms of disease. Working with n-Lorem allows us to treat people living with ALS more quickly, specifically those living with ultra-rare forms who are not traditionally prioritized by pharmaceutical and biotech companies, while also developing technology that has broader applications in ALS and beyond.

Target ALS funded a consortium led by the n-Lorem Foundation for their preclinical work to discover an ASO for a single patient with a unique TDP-43 mutation. The consortium has already identified ASO candidates that bind well to the mutant form of TDP-43, blocking its activity. These candidates are undergoing testing in mice for tolerability and additional toxicity data will be gathered later this year, enabling dosing of the patient as early as next year. **By focusing on a single patient with a single genetic cause of ALS, this process is significantly shorter than a typical drug discovery program,** which can take 5 to 10 years just to get into clinical trials.

We have individuals that have these unique mutations. We have technology that we know and understand very well. How can we leverage this technology in a non-profit fashion - only focused on the patient, efficiency, quality, and safety? We focus on a single patient's genotype and ask: how have we made a difference for individual patient phenotypes? "

Dr. Sarah Glass, PhD
COO, n-Lorem Foundation
Presenting on n-Lorem's model to rapidly develop treatments ultra rare forms of ALS

Identifying Novel Drug Targets

Understanding environmental and biological causes of ALS

At the beginning of the drug discovery pipeline, scientists must identify drug targets for potential therapies. Discovery of drug targets with high potential of success in future clinical trials relies on a strong understanding of the biology of the disease. Most ALS research is laser-focused on the biology of the central nervous system and motor neurons, as they are the cells that are affected by the disease. However, other systems in the body, like the immune system or metabolism, may play a role in how ALS manifests. Target ALS encourages researchers from various scientific backgrounds to join our Innovation Ecosystem, widening the lens with which we analyze the disease. At the Annual Meeting, collaborative consortia funded by Target ALS presented updates on their work which included projects that are drilling further into pathology in the nervous system by applying cutting-edge techniques as well as new areas of exploration, like the role of immune and digestive systems in ALS, to find novel targets for development of ALS therapies.

The Nervous System

Leveraging big data to find new drug targets

Scientists from the University of Sheffield, Stanford University, the University of Pennsylvania and the Weizmann Institute of Science are **leveraging big data to identify genetic changes that occur in specific cell types in tissue from ALS cases**. Using high-throughput screens, a technique to rapidly test thousands of samples at a time, the group has narrowed down to characterizing two new potential drug targets.

The first target is found only in astrocytes, support cells in the brain and spinal cord. The consortium found that increasing its activity was protective for motor neurons in ALS.

The second target is found only in motor neurons. The consortium found that reducing levels of this target is protective in motor neurons in cell cultures.

Masking a drug target to treat ALS

Scientists from the Swiss Federal Institute of Technology and Ludwig-Maximilians University are studying a new drug target found on some **synapses** that sends an "eat me" signal to the immune cells of the nervous system. The consortium is developing a therapeutic approach with a protein that will mask the drug target on the synapse. By masking the target, immune cells cannot recognize its signal, thus preventing the synapses from elimination. In a live mouse model, this approach showed spinal cord protection and improvements in motor function.

Synapses are connections between neurons. During development, our neural circuits are refined in a process called "synapse pruning".

In adults, excessive synapse elimination can lead to impaired cognitive and motor function, a process implicated in ALS.

The Immune System

Drs. Caroline Ingre, Jenna Gregory, and Mai Yamakawa are taking different approaches to study the role of **T cells** in ALS, a concept that **gained popularity across medical research due to breakthroughs in cancer treatment.** In ALS, specific T cell subtypes grow in number in the blood and **cerebrospinal fluid (CSF)**, indicating that they are fighting off disease factors, and have been found infiltrating the brain and spinal cord. These scientists aim to answer this question: can the balance of T cell types or the specific proteins expressed by **T cells impact disease progression and allow for therapeutic intervention in ALS?**

T cells are a part of the immune system that help fight off infection. In healthy individuals, T cells are very rarely found in the brain, but they exist in the cerebrospinal fluid (CSF) to protect the brain against intruders like viruses.

Cerebrospinal fluid (CSF) is the fluid that bathes the brain and spinal cord. Doctors look at CSF to learn about the health of a patient's nervous system.

Reactivating exhausted T cells

Recent studies have shown that the increased T cell response in ALS can lead to T cell exhaustion and suppression. Through our Early Stage ALS Clinician program, Dr. Jenna Gregory of the University of Aberdeen in Scotland is studying methods to **reactivate these exhausted T cells, so they can return to performing normal functions.** Her lab is studying the soluble form of a protein that suppresses T cell activation and is elevated in both ALS model systems and in human postmortem tissue. She is developing an antibody to block this protein, **avoiding suppression of the T cells as a treatment option.** Further, Dr. Gregory is analyzing whether the protein is also elevated in the blood or CSF of ALS patients **as a potential biomarker to detect presence of disease.**

▼ Dr. Eran Hornstein, Weizmann Institute of Science, answers a question on his consortium's work.

▼ Dr. Jenna Gregory, University of Aberdeen, presents on her research to reactivate T cells for therapeutic benefit.

Balancing T cell subtypes for therapeutic benefit

While studying the role of T cells in a large group of ALS patients, Dr. Caroline Ingre of the Karolinska Institute in Sweden, also funded through our Early Stage ALS Clinicians program, found that specific T cell subtypes (effector T cells) are elevated in disease, while others (regulatory T cells) are reduced in disease. Further, patients with slow-progressing ALS had higher levels of regulatory T cells and lower levels of effector T cells than fast progressing patients. Based on this interesting finding, **Dr. Ingre initiated a trial to restore the balance of these two cell subtype populations using an antibody.** The study will be completed in one year and will evaluate the potential benefit to patients.

▲ Dr. Caroline Ingre, Karolinska Institute, presents her research on restoring balance of T cell subtypes in ALS.

▼ Dr. Mai Yamakawa, UCLA, presents her work to create an organ chip model to analyze immune response in ALS.

An ALS "Organ Chip" to Model Disease

Dr. Mai Yamakawa of UCLA, a Target ALS New Academic Investigator, is studying the infiltration of T cells in postmortem tissue from ALS and Frontotemporal Dementia (FTD) cases and their effects on the resident immune cells and neurons in the brain. In parallel, based on the inability of mouse models to properly replicate human immune response, Dr. Yamakawa is **creating a new organ chip model to study the interaction of these cells.** The organ chip uses stem cells and peripheral blood mononuclear cells (PBMCs) from living ALS/FTD patients, recreating a microcosm of their nervous systems and immune responses so that candidate therapeutics and biomarkers can be reliably tested.

The Digestive System

The Microbiome and ALS

Dr. Aaron Burberry of Case Western Reserve University presented on the **role of gut microbiota as an environmental risk factor for ALS and FTD.** Dr. Burberry is trying to determine if we can co-opt the naturally existing "good" microbes to prevent development of disease. His exciting research showed that **the gut microbiome differs in ALS** versus healthy controls. Dr. Burberry bred mice without the C9orf72 gene (mutation in this gene is responsible for ~40% cases of familial forms of ALS) to replicate an ALS population in two locations, at a Harvard University laboratory and at a germ-free facility at the Broad Institute. When bred at Harvard, these mice were unhealthy and died early. However, the mice at Broad were healthy and lived longer, indicating that **environment plays a factor in disease progression.** Dr. Burberry tested the fecal matter of each mouse population, which showed that the differences in their health were related to gut microbes. Immune cells were highly reactive to the fecal matter of the Harvard mouse population, releasing toxins, but not the Broad population. Dr. Burberry also showed that probiotics are protective in cell cultures. He is in the process of **identifying new probiotics that might become part of treatment regimens for people living with ALS.**

Gut microbiota, the microorganisms that live in the digestive tract, are critical to several biological processes like digesting food to produce the nutrients we need, helping to train the immune system to fight off infections, and generating neurotransmitters. Both "good" and "bad" microbes exist.

Dr. Aaron Burberry, Case Western Reserve, presents his work on the gut microbiome as an environmental risk factor for ALS.

Lipids are a class of fatty compounds. Recent studies have shown that triglycerides, one type of lipid, are positively associated with survival in ALS, while cholesterol, another lipid, is negatively correlated with survival. Higher body mass index (BMI) is also associated with a better prognosis.

Lipids and ALS

A consortium between scientists from Ulm University, Université de Strasbourg, and University of Alberta is studying the role of lipids in subtypes of ALS versus healthy controls. They found a correlation between a specific lipid and the size of the hypothalamus, the region of the brain that controls appetite, which is decreased in ALS. The consortium plans to identify whether this family of lipids might be a good biomarker for disease or a therapeutic target. Building on a German clinical study which demonstrated that a high caloric, fat-rich diet improved survival time in ALS patients, **a second larger study will be launched this year to measure the benefit of a high fat diet on survival in ALS** where levels of this specific lipid family will be analyzed.

Identifying and Developing Biomarkers

Finding the key to successful clinical trials through biomarkers for ALS

Since we can't directly look into the brain of someone living with ALS, we have to dissect clues, called biomarkers, from biological fluids like blood or urine, imaging like MRIs, or functional measures like breathing or speech tests to get an accurate picture of when and how the disease is manifesting and changing over time. However, finding reliable biomarkers for ALS has proven difficult. For example, while accumulation of aggregated TDP-43 protein occurs in the brain for 97% of people living with ALS, the levels of normal TDP-43 protein in the blood and cerebrospinal fluid (the fluid that surrounds our brain and spinal cord) remain the same in both people with and without ALS. Therefore, initial attempts to directly measure TDP-43 failed as a biomarker approach. Target ALS is funding several programs to drive development of a biomarker for TDP-43.

Biomarker Consortia

Several consortia presented updates on different types of biomarker assays, or tests, to detect levels of pathological forms or activity of TDP-43.

Nasal Swabs to Diagnose ALS

Scientists from the University of Zurich, the University of Verona, and the Trieste International School for Advanced Studies have developed an assay designed to detect TDP-43 using nasal swabs: **a method to diagnose ALS like we diagnose COVID**. Since their update last year, the group has made significant progress and is now able to detect TDP-43 using a non-invasive approach from nasal swabs. This approach has been implemented in Parkinson's Disease and is based on the similarities of neurodegenerative diseases that involve damaging misfolded proteins, or prions, that can be detected in the nasal cavity. This work is extremely encouraging as we strive **to develop low-burden, quicker, and more accurate methods of diagnosis.**

Detecting TDP-43 in the Brain

Scientists from the University of Edinburgh, the University of Aberdeen, the Italian Institute of Technology, and Columbia University demonstrated progress developing an **aptamer** approach to detect pathological forms of TDP-43 protein in the brain. Since TDP-43 dysfunction is so common in ALS, this method could **provide a path to diagnose and monitor ALS for the majority of people living with the disease.** The group has had success detecting TDP-43 in postmortem tissue, and they are now adapting the technology and generating initial data to demonstrate the feasibility of measuring TDP-43 in cerebrospinal fluid. Target ALS has connected this consortium to an industry partner with expertise to test the aptamers in relevant animal models of ALS.

Aptamers are small molecules that can bind to targets, like TDP-43, to help detect the target in tissue or fluid.

Dr. Magdalini Polymenidou, University of Zurich, answers questions on her consortia's work to diagnose ALS through the use of nasal swabs.

Dr. Mathew Horrocks, University of Edinburgh, discusses his consortia's work to detect TDP-43 in the brain using an aptamer approach.

Dr. Jose Norberto Vargus Sagullo, a Target ALS Springboard Fellow, asks a question to the panel.

Scientists network at the event, an important part of the conference that encourages new collaborations.

Dan and Alisa Doctoroff listen attentively as scientists present updates on their innovative research.

TARGET ALS

Everyone Lives.

I say this often, but it's more than words. It's the vision of Target ALS.

Everyone Lives serves as our north star, underpinning our mission to break down barriers to accelerate ALS research forward.

At this year's Annual Meeting - our 11th – as I looked around the room, observing conversations and collaboration between all those we brought together - academics, pharmaceutical and biotech companies, people living with ALS, nonprofits, venture capital firms, federal funding agencies - **I clearly saw a future where everyone with ALS will live.**

Dan Doctoroff
Founder, Target ALS,
giving his opening remarks at our Annual Meeting on May 7

When Target ALS was first launched, we believed that collaboration was key to advancing ALS drug discovery. To accomplish this goal, we focused on three areas:

- Encouraging multidisciplinary and cross-sectoral collaborations
- Lowering the barriers to entry for investigators by providing tools and resources needed to conduct research
- Engaging and retaining industry in the ALS research space

Structuring our funding model and approach to achieve these objectives has led to remarkable progress in just 10 years. Today, of the 59 consortia we funded in our first ten years, 60% have led to drug discovery programs, seven clinical trials have been launched and five biotech companies have been formed. Over 1,100 projects have used our tools and resources. And just last month, we launched a first-of-its-kind data portal to provide free, no-strings-attached access to comprehensive datasets and analysis tools to fuel discovery of treatments and biomarkers for ALS.

In addition to the value of our funding model, we also saw an opportunity to host an Annual Meeting to bring stakeholders together to engage in dialogue, share ideas and challenge one another to advance drug discovery. At our first Annual Meeting in 2013, only eight

> *I'm not stopping. As long as I can, I will continue to fight and raise as much as possible so that we can stop ALS, once and for all."*

companies and no venture capital firms were present. This year, I'm proud to share that we had **over 132 pharmaceutical and biotech companies, 121 academic institutions, 14 venture capital firms and 37 non-profit organizations join us**.

Over the course of this year's Annual Meeting, we had consortia from 16 basic biology, 10 therapeutic discovery and 10 biomarkers projects, as well as three clinical trials, present their findings and engage in conversation around their approach, methodology, lessons learned and next steps. The room was filled with excitement and while there was some I didn't understand as a nonscientist, **I could feel the palpable sense of urgency and the hope that we are closer to unraveling the mysteries of ALS.**

When I was diagnosed with ALS in late 2021, I committed to spending the rest of my life focused on ALS. My dad and uncle died of the disease, inspiring me to start Target ALS in 2013, but I naively thought I would never get ALS. Being diagnosed myself made this mission even more deeply personal. **The risks to my children, grandchildren, brothers, and cousins were clear, not to mention the one in 400 people who are alive today who will develop ALS in their lifetime.**

I immediately called upon Target ALS CEO Manish Raisinghani, Target ALS Chief Advisor Chris Henderson, and our Board of Directors to take our successful model and scale up for greater impact. We determined that we would need $250 million over nine years to execute on our scaled-up strategy and drive progress.

When I embarked on this challenge to raise $250 million, I wasn't sure how I would accomplish such a bold goal, but I knew it was critical that we raise these much-needed funds. Two years later, I'm thrilled to share that **we have not only reached the $250 million goal, but we have exceeded it,** raising over $259 million. Over the next eight years, we will invest these dollars across our seven pillars focused on expanding the breadth and depth of the Target ALS Innovation Ecosystem, fueling scientific breakthroughs to develop effective biomarkers and treatments for ALS.

I am proud of this significant achievement made possible by so many, but I'm not stopping. **As long as I can, I will continue to fight and raise as much as possible so that we can defeat ALS once and for all.** Thank you for joining me in this fight. Every day, we get closer to a world where everyone lives. Thank you for helping make that world a reality.

Dan Doctoroff
Founder, Target ALS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