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SIGNALING THE DAWN OF A NEW ERA: **2023 ANNUAL MEETING**

SEVEN PILLAR STRATEGY TO END ALS

DAN DOCTOROFF: CLOSING STRONG

TARGET ALS

LETTER FROM THE CEO

Signaling the Dawn of a New Era:

2023 ANNUAL MEETING

MANISH RAISINGHANI, M.B.B.S., Ph.D.
CEO, Target ALS

Dear Friends of Target ALS,

Thank you for your steadfast support and encouragement as we continue to implement our seven-pillar strategy to reach our goal of a world where no one dies of ALS. We are excited to share with you the concrete progress we continue to make on all fronts. However, I first want to tell you about the extraordinary atmosphere that reigned at the Target ALS Annual Meeting. Despite its traditional name, this event is a unique strength that lies at the very heart of the Target ALS ecosystem. Since our launch in 2013, this scientific conference has been both a reflection and a driver of the Target ALS values of bringing different constituencies together to openly share new scientific breakthroughs and to forge new collaborations with the aim of accelerating ALS drug development.

The Annual Meeting, held in Boston in early May each year, has multiple goals:

First, the work done by funded consortia and investigators over the previous year is shared with the **worldwide community** at the Target ALS Annual Meeting. This also provides an opportunity for members of the Independent Review Committee (IRC) to provide direct, unfiltered feedback on both the strengths and weaknesses of each presentation.

Second, **academic scientists deepen their integration with biotech/pharma and venture capital partners**. This occurs not only through discussions of the breaking data at purposefully curated tables in the meeting room, but also by a series of calendared, preplanned 1:1 meetings to initiate new deals or collaborations. The largest meeting anywhere of the biotech/pharma industry is the annual J.P. Morgan Healthcare meeting in San Francisco, and we like to think of the Target ALS meeting as the **J.P. Morgan of ALS.**

Third, we share detailed information about the Target ALS **core scientific facilities** available to the worldwide ALS community. Importantly, this is also an opportunity for investigators to tell us what else they need to accelerate their efforts, and to provide critical feedback on how we could further enhance our support of the community.

The May 2023 Target ALS Annual Meeting was both a continuation of this tradition and **a quantum leap forward**. Over 830 attendees joined us in person and virtually, reflecting the remarkable diversity and expansion of our constituency. There were representatives from **126 academic institutions, 125 pharmaceutical and biotechnology companies, 13 venture capital firms, and 17 non-profit organizations**. There was intense participation in the discussion sessions of all 57 scientific presentations. Their impact was further strengthened by the vision and emotion shared by Dan Doctoroff in his open platform discussion with David Rubenstein, founder of the Carlyle Group, philanthropist, master interviewer, and a founder and major contributor to Target ALS's $250 million capital campaign, and Alisa Doctoroff in her moving plenary presentation.

But the numbers are just a start. This year's meeting was a seminal moment for the ALS research community. The plenary session left the audience with a **palpable sense of excitement** about the progress made, inspiring hope that for the first time, we are on the right path to finding effective treatments for everyone with ALS in the next decade.

Familial ALS:

The meeting began with a remarkable presentation of results from an ongoing clinical trial to treat a familial form of ALS caused by mutations in the FUS gene. The treatment uses an antisense oligonucleotide (or "ASO"), a small piece of DNA/RNA that can bind to a specific messenger RNA and block its ability to make toxic mutant protein. For the first time, a reversal of symptoms was shown in a young person who was previously bedridden with tracheotomy and could now could climb stairs unaided by a ventilator. This has bolstered our commitment to partner with n-Lorem Foundation to leverage ASO technology with the aim of finding treatments for ultra-rare forms of the disease. The near-simultaneous decision of the FDA to award Accelerated Approval to the ASO developed by Biogen and Ionis for another genetic form of the disease — SOD1 ALS — led to a palpable feeling in the room of a glass ceiling that is at last being broken.

Sporadic ALS:

Further raising hope for all ALS patients, updates from **ongoing clinical trials relevant to the 90% of ALS cases** that are non-hereditary showcased a rich pipeline of new drug targets, of which some have emerged from the Target ALS ecosystem. Critically, they are based on our growing understanding of the biological mechanisms underlying the disease. It was particularly striking that these clinical trials are aiming to modify the course of the disease, instead of focusing on symptomatic relief. These developments reflect the successes of **Target ALS's pioneering approach** to incentivize collaboration between academic scientists and pharma/biotech companies.

Biomarkers:

We continue to advance on new frontiers to find a toolkit of biomarkers, a critical unmet need that will enable early diagnosis, help track disease progression and reliably assess the effects of new treatments. Collaborations between academia and industry, funded through our **partnership with Gates Ventures and Alzheimer's Drug Discovery Foundation** presented encouraging updates on biomarkers that range from **analyses of blood samples to non-invasive digital tools** to assess speech and gait.

Biosample repository:

The research community also learned about progress of our groundbreaking initiative to create **the most comprehensive biosample and dataset collection for ALS anywhere**. Over the course of the next 5-10 years, this initiative will collect biofluid samples at different stages of the disease from approximately 1000 individuals with ALS and healthy controls. The biosamples and datasets will be **accessible to the worldwide research community with no strings attached**, galvanizing the application of artificial intelligence and machine learning tools to discover new therapeutic targets and biomarkers.

There was a definite, deeply motivating sense of a new page being turned at this year's Annual Meeting. We are just at the start of a decade-long battle and in this newsletter, I want to share exciting new developments on all fronts of our seven-pillar strategy.

Target ALS Seven-pillar Strategy

PILLAR

01

Diversification and Expansion of Talent

As the frontiers of ALS biology expand, it is imperative to continue to diversify and expand the talent and technologies working on the disease. We are committed to supporting ideas from scientists and clinicians at critical stages of their career to ensure emerging talent continues to work on the disease, leading the way for breakthroughs of tomorrow.

A key stage for **emerging scientists** is their ability to transition from a postdoctoral fellowship to establishing themselves in an independent faculty appointment leading their own lab. **Target ALS Springboard Fellowships** facilitate this transition through mutually reinforcing mechanisms: a **portable 3-year grant** that allows the awardee to move the funds to any institution worldwide where they secure an independent faculty appointment and a **6-year free-of-cost period of access to Target ALS core facilities**, paving the path towards advancement of their ideas as the next generation of leaders in ALS research.

This year, we awarded Springboard Fellowships to **seven talented postdoctoral fellows** who are working on different aspects of ALS biology: selective vulnerability of motor neurons in ALS, leveraging zinc finger nuclease technology (a gene editing approach) or reducing abnormal protein aggregation to treat the C9orf72 form of ALS and development of strategies to ameliorate TDP-43 pathology in ALS.

One of these Springboard Fellows is **Dr. Jose Norberto (Jobert) Vargas, Ph.D., at University College London**. His Target ALS-funded project focuses on how TDP-43 (a protein that moderates function of RNA molecules and is found aggregated postmortem in the brain of ~97% of ALS cases) and dysfunction may lead to aberrant chemical modification of RNA transcripts in motor neurons to drive neuronal death during ALS. This work has the promise of not only yielding fundamental findings on how motor neuron axons fail during ALS but may also provide novel therapeutic targets that may someday enhance the lives of people with ALS.

> “The Target ALS Springboard Fellowship is a marvelous funding scheme that provides support for my work and catalyzes the steps towards my scientific independence. As an early career researcher, I aspire to lead an independent laboratory and mentor the next generation of passionate researchers, including clinician scientists, who are devoted to discovering the molecular underpinnings of ALS. Furthermore, as a first generation Filipino-American immigrant, I am extremely grateful for the privilege of finding a path into academic research. I am thus fully committed to creating an environment in my future laboratory where aspiring scientists from marginalized groups can thrive and succeed. As a Target ALS Springboard Fellow, I am one step closer to achieving these goals.”
>
> **—Dr. Jose Norberto Vargas, Ph.D.**
> *University College London*

PILLAR

02

Maintenance and Expansion of Scientific Core Facilities

With the increasing application of artificial intelligence and machine learning for drug discovery, it has become more important than everto create comprehensive big datasets that can unleash the true potential of these emerging technologies.

We have launched an ambitious **initiative to create the most comprehensive collection of biosamples and datasets from people with ALS and healthy controls**. A natural history study following ALS and healthy control cases over the course of their disease is currently in progress. Biofluids, including cerebrospinal fluid (CSF, the fluid that bathes the brain and spinal cord), blood and urine samples will be collected from all cases at the clinic.

Big datasets, including whole genome sequencing (analysis of the entire genome), proteomics, lipidomics, metabolomics (mapping changes in networks of proteins, lipids and metabolites, respectively), neurofilaments (the first biomarker for ALS, considered reasonably predictive of clinical benefit) will be generated from all samples.

These big datasets will be placed on a **central data platform** and all investigators will be able to access, visualize, mine and analyze them using a data portal being created by Target ALS. Scientists worldwide will have **no-strings-attached access** to the biosamples and datasets.

A lack of diversity is an enduring challenge for all biomedical research initiatives. Understanding the **role of ethnic differences on disease biology and genetics** can lead to greater insights into biomarkers and more efficient clinical trials in the future. With this in mind, we are pursuing a **multi-pronged approach to promote inclusivity**: cover travel and lodging for people with ALS and their caregiver to visit ALS clinics for care; engage an outreach coordinator at Target ALS-funded clinics to work with the local community and encourage participation; partner with patient care and support organizations to spread awareness about the initiative.

PILLAR

03

Applying the Target ALS Model to Related Diseases

We continue to exploit the talent and technologies that are part of the ALS research community as an approach to related neurodegenerative disorders that share overlapping genetic causes and disease biology. This is especially true for **Frontotemporal Dementia (FTD) — the disease with which Bruce Willis was recently diagnosed — which can manifest with ALS in the same family, can be triggered by the same gene mutations that cause familial ALS**, and can feature the same underlying pathological hallmarks seen in ALS. While ALS is characterized by pathology in motor neurons (nerves that send signals from the brain to muscles), FTD is characterized by pathology in cortical tissue (the cortex is the outer layer of the brain that performs higher order processing and communication between multiple brain regions). Understanding how and why these diseases share their biology, pathology, and genetic risk factors — and why they ultimately differ — can potentially lead to identifying new drug targets and biomarkers for ALS and FTD.

One pathological feature shared by ALS and FTD is the aggregation of TDP-43 (a protein critical for maintaining proper production and function of RNA molecules in cells).

A collaborative project funded by Target ALS is applying a new technology called "RNA aptamers" (protein-binding RNA molecules that facilitate detection and visualization of very small molecules at high resolution). **This multi-disciplinary international collaboration** involves Drs. Jenna Gregory, University of Aberdeen; Neil Shneider, Columbia University; Matthew Horrocks, University of Edinburgh; and Gian Gaetano Tartaglia and Elsa Zacco, Italian Institute of Technology. This group has **developed and is applying a novel technique to detect TDP-43 aggregates** in human tissue well before ALS or FTD symptoms appear, a significant improvement on the available technologies for detecting this pathology. They are currently working to adapt this technology to detect aggregates in biofluid samples from people with ALS. An early detection of ALS and FTD pathology would enable early diagnosis and treatment.

> We are delighted to be part of the Target ALS community. We have been particularly impressed by the breadth of research being conducted ranging from basic science all the way to translational studies with an emphasis on real world impact to improve the lives of people living with ALS. We are so happy to be able to contribute our work to this incredible endeavor."
>
> **—Dr. Jenna Gregory, MB Bchir, Ph.D.**
> *Senior Clinical Lecturer & Consultant Histopathologist at University of Aberdeen*

PILLAR

04

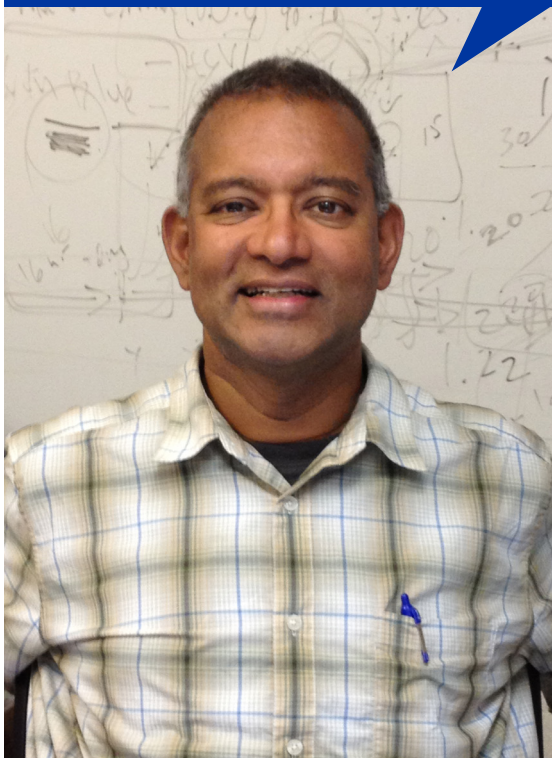
Discovery and Development of New, Effective Treatments

We have pioneered an approach based on cross-sectoral and multi-disciplinary collaborative consortia that provides a framework for **pharma/biotech-based scientists to lead programs that also have the necessary involvement of academic scientists**. These collaborative efforts leverage complementary strengths of each constituency: a deep understanding of disease biology and expertise in drug discovery.

This year, **we have funded six industry-led collaborative consortia that are working to bring forward novel drug targets that are based on deep understanding of biology of the disease.** These projects are led by a range of companies from emerging biotechs like Atalanta Therapeutics, Prosetta Biosciences and Maze Therapeutics as well as larger, more established companies like Denali Therapeutics and Biogen. These collaborative groups are focused on different approaches to treat ALS that include targeting RNA biology in cells under stress, deleterious effects of aberrant RNA molecules, as well as a pathway within cells that is responsible for destruction of damaged proteins called autophagy and C9orf72 form of ALS.

A **collaboration led by Prosetta Biosciences** that also includes Drs. Leonard Petrucelli, Mayo Clinic, Jacksonville, and Steven Finkbeiner, University of California, San Francisco are working together to address the cause of the most common pathology observed in ALS, presence of aggregates of TDP-43 protein in ~97% of brain and spinal cord from people with ALS. This group is **looking for new drugs that can interfere with the pathways that lead to TDP-43 aggregation**. Prosetta, a small start-up from the San Francisco Bay Area, has already shown that some of their drugs have a unique ability to interfere with TDP-43 aggregation in stem cell models of ALS.

> We are grateful to Target ALS for providing a mechanism for our novel hypotheses on ALS pathogenesis and treatment to be tested by world-class basic scientists like Professors Finkbeiner and Petrucelli."
>
> **—Vishwanath Lingappa, M.D., Ph.D.**
> *CEO and CTO of*
> *Prosetta Biosciences*



TARGET ALS

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05

Discovery and Development of Toolkit of Biomarkers

An enduring challenge for ALS is the lack of biomarkers to enable early diagnosis, reliable disease tracking, and treatment evaluation in trials. A pivotal development this year occured when the FDA Advisory Committee voted unanimously that strong reductions in plasma levels of neurofilament, a side-product of neuronal degeneration particularly prominent in ALS, are "reasonably predictive" of clinical benefit in SOD1 ALS. Broader application could significantly expedite Go/NoGo decisions in clinical trials of many drugs, saving time and costs. It would also enable the community to concentrate expensive late-stage trials on drugs that have a higher probability of success.

However, neurofilament alone is not sufficient. We're actively advancing biomarker discovery through various means: supporting academic-industry collaborations, providing access to disease-related biospecimens and datasets collected during the disease's progression. These already bring together different constituencies around pre-competitive biomarker projects that share data and new research tools with the broader research community, once again with no strings attached for academia or industry.

An exciting cross-disciplinary project we've co-funded with Gates Ventures and the Alzheimer's Drug Discovery Foundation involves a collaboration led by Drs. Pietro Fratta (University College London), Leonard Petrucelli (Mayo Clinic), Michael Ward (NIH), and Kevin Eggan (BioMarin Pharmaceuticals). They're investigating the **use of abnormal RNA molecules and proteins as potential ALS biomarkers**. These abnormal RNA molecules and proteins form when TDP-43, a protein regulating RNA function and expression, aggregates and loses its function. **One consequence of loss of TDP-43 function is the emergence of abnormal RNA molecules, which, if not destroyed, result in formation of abnormal proteins that can lead to deficits in motor neuron function**. These abnormal RNA and protein molecules have significant potential as biomarkers of TDP-43 dysfunction and could help early disease diagnosis, progression tracking, and new treatment assessment.

> "TDP-43 cryptic exons are turning out to be incredibly useful in getting a handle on ALS. They really just occur in the brain during active disease, and if we were able to detect these in CSF or blood, this would allow us to gain insight in the disease process happening in brain and spinal cord. This would be incredibly important in clinical trials. Detecting these cryptic exons is indeed the primary goal of our consortium. Working with Target ALS has really been great. Their annual meeting is one-of-a-kind in the ALS world with its translational focus and its ability to bring together academia and private sector internationally."
>
> **—Dr. Pietro Fratta, Ph.D.**
> *University College London*

PILLAR

06

Treatment of Ultra-Rare Forms of ALS

Target ALS has committed to finding treatment for all forms of ALS, including the **ultra-rare familial forms of the disease, each of which affects a handful of individuals worldwide.**

ASOs (antisense oligonucleotides) can be used to directly interact with — and destroy — mutant disease-causing RNA. Excitingly, recent clinical trials have shown reversal of symptoms following treatment with ASOs in people with ALS who carry mutation for SOD1 and FUS genes (see Familial ALS on page 3). We have therefore partnered with the n-Lorem Foundation to leverage its expertise in ASO technology to expand therapeutic development for ultra-rare forms of ALS. In 2022, we funded nonclinical and clinical studies which allowed for treatment of an ALS patient with an ultra-rare form of mutation in the TDP-43 gene. This event represents the first ALS patient to be treated with n-Lorem's technology platform. We have now expanded our funding to support the generation of a second ASO therapeutic targeting a distinct ultra-rare ALS mutation.

PILLAR

07

Prudent Growth of Target ALS Capacity

We continue to broaden and deepen the scope of our initiatives. This requires that we expand all aspects of our organization to ensure efficient and effective implementation of our strategy. A critical factor in the success of our approach is the role played by our **Independent Review Committee (IRC)**, which **makes all funding decisions**. This committee consists of **experts from different scientific disciplines**, reflecting the evolving nature of ALS research. Uniquely in the field, **no member of the IRC can apply for, or receive, Target ALS funding** for their own research, removing any potential conflict of interest.

We continue to expand the IRC to engage experts in emerging technologies and related neurodegenerative disorders. We are proud to introduce one of the new members of the IRC. Fanny Elahi, M.D., Ph.D. is a physician-scientist and Assistant Professor in the Departments of Neurology, Neuroscience, and Pathology at the Icahn School of Medicine at Mount Sinai in New York City. Her work focuses on understanding vascular aging, examining the link between disease of the brain's small blood vessels and neurodegeneration. She is passionate about translating laboratory discoveries into clinical applications, with the goal of extending the brain's longevity and preventing dementia due to neurodegenerative diseases.

"I joined the Target ALS IRC because Target ALS is doing everything right to bring treatments to those affected with ALS or at risk of developing disease based on genetic risk. They have brought academic and industry researchers together and funded multi-disciplinary teams including basic scientists, tool makers, clinicians and clinical trialists to drive the development of treatments for ALS. As a neurologist-neuroscientist specialized in neurodegenerative diseases, it's an honor to help Target ALS fund the best science to one day end this terrible disease."

—Fanny Elahi, M.D., Ph.D.
Assistant Professor, Icahn School of Medicine at Mount Sinai

Dan Doctoroff

IN OCTOBER 2021, OUR FOUNDER AND chairman, Dan Doctoroff was diagnosed with ALS. Ever the optimist, he never expected to get the disease. But upon receiving the news, he knew exactly what he should do: spend more time with his family and friends and scale up Target ALS. He resigned from the company he created with Alphabet and stepped back from other activities to fully focus on our mission. At the same time, members of the Target ALS team worked to develop a more ambitious strategy for the organization.

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Over the next six months, under the leadership of CEO Manish Raisinghani and with input from board members, Target ALS Senior Advisor Chris Henderson, and intensive consultations with the Target ALS ecosystem, a **seven-pillar strategy** emerged that expanded on the successful model of collaborative research that Target ALS had pioneered when it was founded in 2013. The team set a **goal of raising $250 million, which would be spent over the next nine years**, enabling Target ALS to implement its strategy and increase its annual spending at least three-fold. At the same time, the team designed a presentation highlighting Target ALS' historical approach, achievements, and the seven-pillar strategy for the future. By May 2022, Target ALS was ready to launch the capital campaign.

At the **Target ALS annual meeting in May 2022, Dan spoke to the over 830 assembled investigators**, both in person and virtually, and described the strategy. He candidly admitted that he didn't have a clue whether he would be able to raise the funds, since no one had ever raised that much money for ALS research. At that point, he still hadn't given a single presentation. A week later, he had his first meeting with Bloomberg Philanthropies, Dan's co-founder and steadfast partner in the growth of Target ALS. Bloomberg Philanthropies quickly made a new commitment of $75 million, setting the tone for the record-breaking campaign. **Over the past fifteen months, Dan, his wife Alisa, and Manish have raised nearly $230 million**, $30 million of which has been raised in the few months since the annual meeting in May 2023. The majority has been raised from friends of Dan and Alisa through individual presentations and a series of four intimate events hosted by Dan and Alisa in New York and one in Boston by their cousins, Jeff and Lynda Bussgang, in their homes. The fundraising strategy has now broadened to include a Corporate Council (www.targetALS.org/corporate-council). Target ALS also held its first Foundation Leaders Breakfast at Bloomberg Philanthropies. We are now working to expand our donor family to raise the remaining $20 million to meet our $250 million goal by the end of 2023. You can be part of the crucial group of supporters who help us close strong by making a donation at **www.targetALS.org/donate**.


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