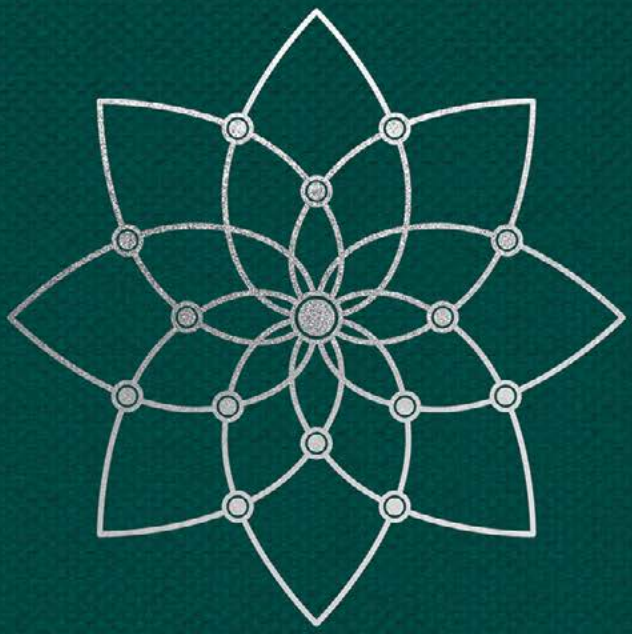

# RESILIENCE in the Fight AGAINST ALS

One Company's Journey of Courage, Commitment, and Ingenuity

Cytokinetics®

# RESILIENCE

# in the Fight

# AGAINST ALS

## One Company's Journey of Courage, Commitment, and Ingenuity

Cytokinetics®

MELCHER MEDIA

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To all those in the ALS community
who continue to fight relentlessly for hope,
change, and effective treatments.
Your courage, commitment, and tenacity
are an inspiration.

# Contents

FOREWORD

# An Urgent, Unmet Need

Discovery is built upon the foundation of our learnings

*The greatest journeys include opportunities to learn, connect,* adapt, reflect, and grow. Cytokinetics' quest to develop an effective new therapy for amyotrophic lateral sclerosis (ALS) is no different.

For the last 25 years, Cytokinetics has been at the forefront of the fight to discover new treatments for those with cardiovascular and neuromuscular diseases of impaired muscle function. We have spent much of that time working to discover an innovative therapy for individuals living with ALS—an extraordinary community that urgently needs and deserves both a cure as well as treatments that will meaningfully improve function and overall quality of life.

With the development of *tirasemtiv* and *reldesemtiv*, we have worked tirelessly alongside an awe-inspiring group of patients, clinicians, researchers, and advocates for 15 years. While a Cytokinetics medicine for ALS and other neuromuscular diseases still remains elusive, our company has achieved incredible milestones through our work in ALS. Our being welcomed into the ALS community has left indelible impressions on our company—and it has fundamentally altered the arc of what we do, and especially why and how we do it.

**OUR WORK IN ALS** has left us with the deepest level of gratitude to this incredible community. Gratitude for enabling us to define a strong company culture, based on values grounded in compassion, patient-centricity, and a "make it happen" urgency to do what's right for this extraordinary group of people living with ALS (PWALS). Gratitude for the opportunity to forge new clinical research pathways and scientific best practices to serve as a roadmap for those we hope will follow in our footsteps. And, most important, gratitude for the ability to share how to best engage with the community and bridge the gaps so often seen between sponsor, investigator, and patient.

Every success and every setback play a pivotal role in the journey—and, ultimately, they both take us closer to achieving our pursuit of effective therapies for neuromuscular disease. The next step for us is to educate and motivate those who will continue on. Every major discovery is built upon the foundation of many prior tries and the learnings they uncovered. In the following pages, we will share our leg of the journey—and what we learned along the way. It is our hope that it will inspire your own path forward.

***Above:*** **The Cytokinetics Research and Development team works tirelessly to develop potential medicines for cardiovascular and neuromuscular diseases of impaired muscle function.**

> Every ***success*** and every ***setback*** play a pivotal role in the journey—and, ultimately, they both take us closer to ***achieving*** our pursuit of ***effective*** therapies for neuromuscular disease.

***Above:*** **Robert Blum, President and Chief Executive Officer of Cytokinetics, has been with the company since it first opened its doors in 1998.**

Our experiences over the years demonstrate the critical importance of consistency, persistence, commitment, and community. The ALS community is composed of selfless individuals who are kind, thoughtful, deliberate, and compassionate. We take our lead from them—and are grateful to PWALS for providing us with our North Star. They continue to guide, inspire, and amaze us, enabling and empowering us to put our purpose into action. They have shown us just what is possible when the best of academia, industry, and advocacy come together to help us better understand the nuances of this unrelenting neurodegenerative disease—and the potential research possibilities that may one day allow us to prevent, delay, or arrest its progression. There remains an urgent, unmet need to serve the ALS community—and it will take the best and brightest working alongside one another to finally conquer this disease.

Though the results of our Phase 3 trials of *tirasemtiv* and *reldesemtiv* in people with ALS—VITALITY-ALS and COURAGE-ALS—were not what we had hoped for, we remain grateful for the journey we traveled and the incredible relationships we forged along the way. We look to the science of gratitude to point us in a new direction for renewal of hope and commitments in the future. We have treasured our time working in the ALS space and look forward to seeing where others will take it in the future. And, most importantly, we look forward to rejoining you further down the road in this vital fight against ALS.

**—Robert Blum**
**President and CEO**

# Cytokinetics Core Values

## Patients Are Our North Star

- We seek to understand our patients' journey and proactively embed their needs in our goals, priorities, business, and community partnerships
- We keep the patient front and center in all we do—all actions and decisions are in service of the patient and their caregivers
- We advocate for the patient through our engagement in patient-centric activities like fundraising events, public policy initiatives, volunteering, and education

## Science Is in Our Soul

- We are committed to robust scientific thinking, grounded in integrity and critical thinking, and not polluted by politics or divisiveness
- We invite healthy debate, test hypotheses, encourage independent thought, and explore courageously the unknown—all in service of improving patient health and humanity
- We are problem solvers—we push boundaries and think beyond the norm to come up with out-of-the-box solutions that make a difference

## We > Me

- We are stronger as a team, valuing the power of diversity, rising together as one
- We insist on transparency, collaboration, and feedback
- We champion integrity, ethics, doing the right thing, and being our best selves

## Make It Happen

- We are tenacious, resilient, and confidently navigate ambiguity to deliver results
- We demonstrate courage by taking calculated risks, failing fast, and recovering quickly
- We hold ourselves accountable for our actions—without excuses or blame

1

# A Sparse Landscape

Twenty years of research and one treatment option


LINDSAY ABROMAITIS-SMITH

At present, the prognosis is grave. As far as I know, there is no case in which all the symptoms occurred and a cure followed. Is this an absolute block? Only the future will tell.

—JEAN-MARTIN CHARCOT, 1874

*ne-hundred fifty years after French neurologist* Jean-Martin Charcot first described the clinical symptoms of the muscle-wasting disease he named "*sclérose latérale amyotrophique*"—known in English-speaking countries as amyotrophic lateral sclerosis (ALS)—patients with this devastating diagnosis are still waiting for a cure.

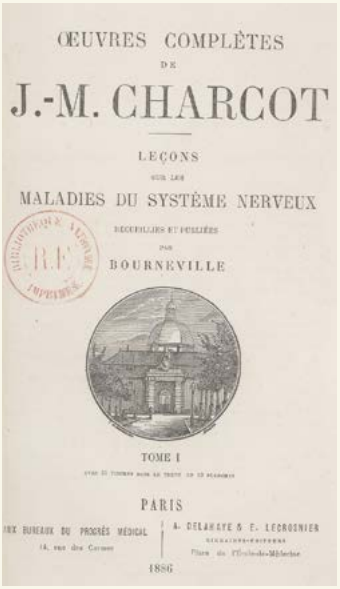
Unfortunately, even today, the vast majority of those living with this disease, which is also sometimes referred to as motor neurone disease or Charcot's disease, also lack effective treatment options. Despite remarkable advances in science and technology over the past decades, today's PWALS, much like Charcot's patients in the late 19th century, will experience the progressive death of motor neurons, leading to muscle weakness, paralysis, and, ultimately, death. Expected survival, too, is much like what was seen in Charcot's time. The majority of PWALS will only survive two to four years after an ALS diagnosis.

When Stacy Rudnicki, M.D., Vice President, Clinical Research & Therapeutic Area Lead, Neuromuscular, started her career as a neurologist treating PWALS in the early 1990s, she, like Charcot, had few options to help patients manage the disease's hallmark symptoms.

"There were no drugs approved at that time—zero," she said. "But while we couldn't cure patients of ALS, we could do our best to treat the symptoms with multidisciplinary care to address the malnutrition and breathing problems that many patients experienced. We always hoped that, eventually, there would be some type of disease-modifying treatment available."

That hope was amplified when Robert H. Brown, Jr., M.D., D.Phil, a neurologist at the Day Neuromuscular Research Laboratory at Massachusetts General Hospital, and colleagues discovered that the superoxide dismutase (SOD1) gene, an enzyme responsible for protecting cells from reactive oxygen species toxicity, was linked to the familial form of ALS. With the Human Genome Project already underway—and, with it, the promise of a biological blueprint to help researchers identify specific genes involved with different diseases—researchers and clinicians believed they would soon have the tools required to catalyze effective therapies for ALS.

There was only one problem—familial ALS, or the type of ALS known to be passed down through families—only accounts for approximately up to 10% of all ALS cases.

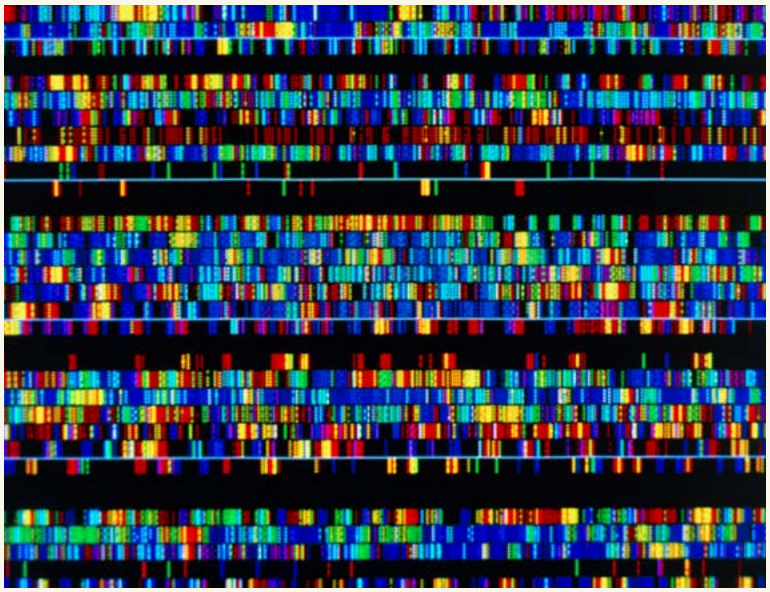



**THE REMAINING OF THOSE** diagnosed with the disease have what's known as sporadic ALS, meaning the disease appears to occur without a positive family history. While researchers now understand there are likely genetic contributors to this sporadic variety of ALS, they aren't as easy to identify. Dr. Brown and his collaborators were able to identify SOD1 thanks to a specific family line. Sir William Osler, a neurologist, recognized that the Farr family in Vermont had a strong inherited form of the disease back in the late 1800s. Dr. Brown used descendants of this same family to help detect SOD1 in his studies. While it may play a pivotal role in the familial form of the disease, it may not do the same for those with sporadic ALS. Since the discovery of the SOD1 gene, over 30 additional ALS-associated genes have been identified.

"This is one of the biggest challenges with ALS," said Caroline Ingre, M.D., Ph.D., a neurologist and ALS researcher at the Karolinska Institutet in Sweden. "We know where the disease is heading, but we still don't understand how it gets there in every person. There is a strong heterogeneity to this disease, despite the fact that symptoms can often look very similar."

Andrew Wolff, M.D., former Chief Medical Officer at Cytokinetics, remarked that the addition of strong epidemiological studies of ALS muddy the waters even further.

***Above, from left:*** **A copy of Jean-Martin Charcot's *Leçons sur les Maladies du Système Nerveux* (Lessons on Diseases of Nervous System), the leading medical text on neurodegenerative disorders, including ALS, back in the late 1800s. Hôpital Universitaire Pitié Salpêtrière, the leading hospital in Paris in the late 19th century. It was here that Charcot, one of the hospital physicians, first clinically described ALS, differentiating it from other muscle-wasting diseases.**



We know where the disease is ***heading***, but we still don't ***understand*** how it gets there in every ***person***.

***Above:*** **With the mapping of the human genome in the 1990s, scientists were optimistic that they would be able to find genes responsible for ALS — and, consequently, a cure.**

"There are probably a variety of different things that cause ALS. Some patients may have a genetic predisposition—and we may not know what that is for every patient," he said. "There are probably toxins and environmental factors involved in some cases. There's a strong implication that head trauma, and not necessarily severe head trauma, is associated with an increase in the incidence of ALS. We know that soccer players who hit the ball with their heads have a higher incidence of ALS. So do football players and members of the military."

Yet, for ALS researchers, the discovery of SOD1 provided them with something they never had before: the ability to model the disease. And Merit Cudkowicz, M.D., M.Sc, Chief of the Neurology Department at Massachusetts General Hospital, said that that advance buoyed the hopes of researchers across the globe. They thought they might finally have the tools at their disposal to come up with not just a treatment for ALS' relentless symptoms, but potentially a cure for the disease itself.

"When the SOD1 discovery came out, the mood regarding developing treatments changed," she said. "We could create an animal model of disease—the transgenic SOD1 mouse. We could come up with new ideas for drugs. We could use this model to test them. We thought that we'd be able to figure out how this illness works, and then find a way to cure it."

# A Brief History of Amyotrophic Lateral Sclerosis

## Early 1800s

Physicians across Europe begin publishing descriptions of ALS symptoms in medical literature. Many attribute symptoms like muscle twitches, spasticity, and slurred speech to hysteria.

## 1869

French neurologist Jean-Martin Charcot identifies ALS as a specific disease—and gives it its name. From the Greek, amyotrophic means "without nourishment to the muscles." While Charcot is the first to recognize ALS as a unique muscle-wasting condition, his observations were built on the back of scientific work by other leading scientists of the era including Scottish anatomist Charles Bell, British scientist Jacob Augustus Lockhart Clarke, and French physicians François-Amilcar Aran, Guillaume Duchenne de Boulogne, and Jean Cruveilhier.

## 1874

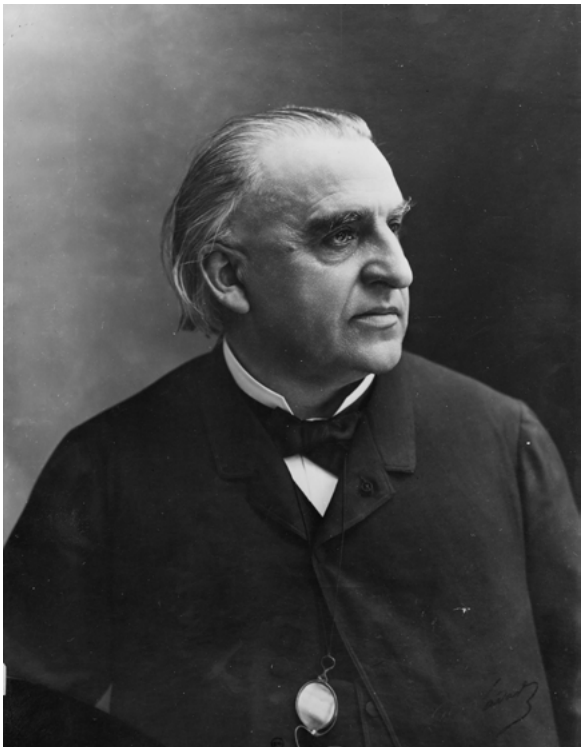
Charcot, today known as the father of modern neurology, publishes a treatise detailing the anatomic and clinical symptoms of ALS called *De la sclérose latérale amyotrophique*.

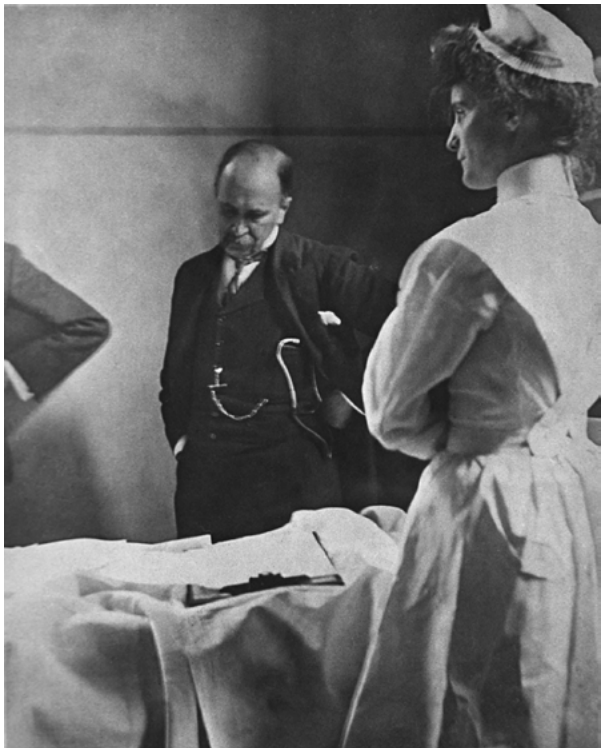
## 1880s

Sir William Osler, a Canadian physician and one of the founders of the Johns Hopkins Hospital, describes the familial form of ALS disease, describing a Vermont family, the Farrs, where many male members of the family developed ALS symptoms at an early age.

## 1939

Lou Gehrig, first baseman for the New York Yankees, is diagnosed with ALS at the Mayo Clinic. He makes headlines after announcing his diagnosis publicly during his retirement ceremony at Yankee Stadium, declaring, in his speech, that he was "the luckiest man on the face of the earth." He passed away two years later.





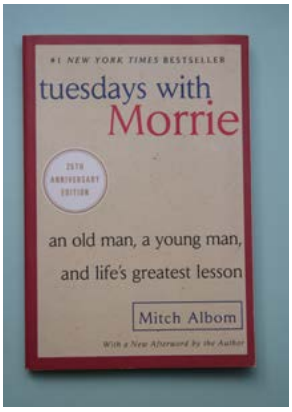
*Top left:* Jean-Martin Charcot, the French physician who is known today as the father of modern neurology.

*Center:* Sir William Osler, one of the founders of the Johns Hopkins Hospital, who was the first physician to describe the familial form of ALS in a Vermont family back in the late 1800s.

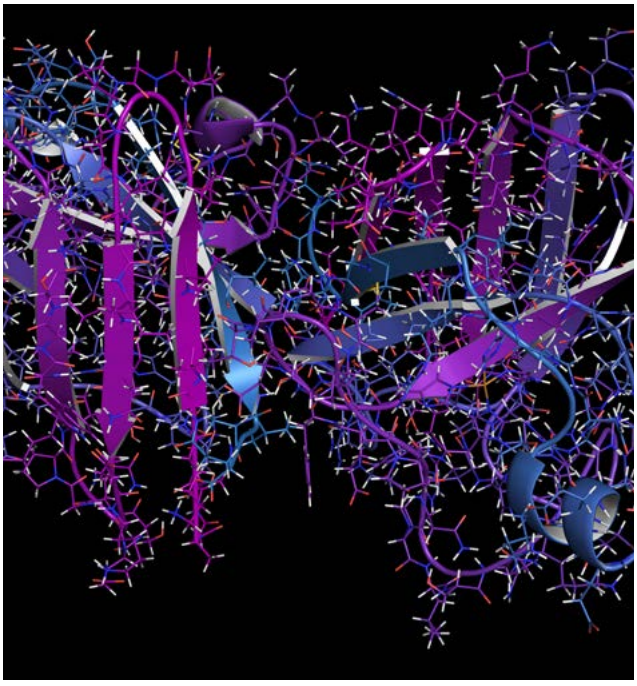
*Bottom left:* Lou Gehrig, a famous baseball player known as the "Iron Horse" was diagnosed with ALS in 1939. He is one of the most well-known celebrities who lived with the disease.

*Right:* Famed theoretical physicist Stephen Hawking was diagnosed with motor neurone disease (MND) at the age of 21. ALS is the most common form of MND. Most people usually live only a few years after diagnosis—Hawking lived another 50 years.

*Below:* A rendering of the superoxide dismutase (SOD1) gene, the first gene to be linked to the familial form of ALS, in 1993.




*Above:* In the *New York Times* best-selling memoir *Tuesdays with Morrie*, author Mitch Albom chronicled the critical life lessons he learned from Brandeis University sociology professor Morrie Schwartz, who was diagnosed with ALS.



## 1993

Dr. Robert H. Brown, Jr., a prominent neurologist and clinical researcher, and his colleagues at the Massachusetts General Hospital identify the superoxide dismutase (SOD1) gene in familial ALS using descendants of the Farr family first described back in the late 19th century by Sir William Osler. SOD1 codes for an enzyme that protects cells from oxidative stress. The familial mutation makes motor neurons more susceptible to neurodegeneration.

## 1995

The first drug to treat ALS, *riluzole*, is approved by the Food and Drug Administration (FDA). It works by blocking the release of glutamate, a neurotransmitter, which can damage nerve cells in large amounts. Its effects, however, are modest, at best—increasing survival time in patients by two to three months.

## 2000–2017

Dozens of different drugs for ALS are tested in clinical trials to no avail—one after the other, despite promising preclinical studies, they fail to meet their endpoints.

## 2017

The FDA approves *edaravone* (Radicava), only the second drug available to PWALS. It helps to prevent oxidative stress, which damages nerve cells.

## 2021

President Joseph R. Biden signs the Accelerating Access to Critical Therapies for ALS Act into law. The bill provides funds for expanded access programs, a rare disease grant program, and a new public-private partnership to try to accelerate the development of new therapies for ALS.

## 2022

The FDA approves AMX0035 (Relyvrio) to treat ALS. It works by protecting mitochondria in motor neuron cells. It also approves an oral version of *edaravone* (Radicava).

## 2023

The FDA approves *tofersen* (Qalsody) for patients with the familial SOD1 form of ALS disease.

## 2024

The Phase 3 trial for AMX0035 (Relyvrio), despite its prior FDA approval, fails to meet its primary and secondary endpoints. At the time of writing this book, the status of the drug—and whether it will remain on the market—remains unknown.

# One Step Forward . . .

**THE DEVELOPMENT OF THE** transgenic SOD1 animal model led to a research renaissance in ALS. Experimental studies identified several potential targets for drug development, ranging from glutamate toxicity to oxidative stress. Researchers believed that, if they could stop one or more of these processes, they could save motor neurons from certain death—and, as a result, slow, if not stop, the progression of ALS disease.

That belief was bolstered when a new drug, *riluzole*, which inhibits the release of glutamate in the brain, showed modest success in clinical trials. It was the first ALS drug to be granted approval by the Food and Drug Administration (FDA) in 1995. The clinical trial demonstrated that the drug could increase tracheostomy-free survival for, on average, three months in PWALS.

"We finally had something we could offer to patients—and that was exciting," said Dr. Rudnicki. "But the benefits were really quite modest, and the drug did not help slow symptoms."

PWALS certainly appreciated the potential promise of increased survival time—patients still had to reckon with an average 2- to 4-year survival time frame—but they wanted and deserved so much more.

"There's data to show that good multidisciplinary care, the kind that you can find at academic ALS centers of excellence, with respiratory, nutrition, speech and language

> We ***finally*** had something we could offer to patients—and that was ***exciting***.

***Left:*** **Lindsay Abromaitis-Smith, a PWALS, describes herself as a "sparkling goddess witch cat." Here she stands outside her home.**

> That's what we want to see with ***drug treatments***—something that will provide ***improved*** quality of life.

pathology, social work, and pulmonary care, can not only extend survival but also quality of life in ALS patients. Frankly, it does more so than any drug out there right now," said Andrea Pauls Backman, former Chief Executive Officer of the Les Turner ALS Foundation who is now an independent ALS advocate and strategist. "So, that's what we want to see with drug treatments—something that will provide improved quality of life and help people living with ALS maintain function for as long as possible."

With new basic research studies uncovering new potential disease-modifying targets throughout the 1990s and into the 2000s, the ALS community felt certain that those sorts of life-changing treatments must be on the horizon.

# Andrea Pauls Backman

*Andrea Pauls Backman* was working as an institutional real estate portfolio manager when her mother, Sally, was diagnosed with ALS in 2006.

"I think I had heard of ALS before then, but I really didn't know that much about it," she said. "But my mother's three-year journey with this disease was so profound to me and my family. And I began to get very involved with advocacy work while still working and raising my family. A few years after she passed away, the national ALS Association asked me to join the board as a trustee."

After serving in different volunteer leadership roles over the years, Pauls Backman decided to move to full-time advocacy work as the executive director of the Les Turner ALS Foundation.

"I approached the ALS space a little differently than others had before me because of my business background," she said. "It was important to me to find areas of alignment and collaboration among the various ALS organizations so we could

By creating more cohesion among the different groups, I felt that we could do a lot more for the patients we serve.

work together to pull in new sources of funding. By creating more cohesion among the different groups, I felt that we could do a lot more for the patients we serve."

Today, Pauls Backman leads her own ALS advocacy group, ALS Strategy Consulting, with the goal of bringing together ALS organizations, as well as government and industry players, to allow all of these different stakeholders to work together more effectively.

"ALS is such a horrific disease. There's something about the relentlessness and the aggressiveness of it that is just overwhelming. We don't have time to be off working in our own silos," she said. "We have to be aligned. We have to share what we know. We have to have shared goals. And we have to work together. There's no other way to help the patients diagnosed with ALS."

Pauls Backman first became acquainted with Cytokinetics when *tirasemtiv* was going into Phase 2 trials. She said she was very excited about its unique muscle-based approach to treatment.

"No one else in the pharmaceutical industry was working in that way," she said. "At the time, there was only one drug approved for ALS, *riluzole*. It only had modest effects. There had been a multitude of clinical trial failures, including *dexpramipexole*, in 2012. At that point, no one was all that excited about getting into ALS therapy development. But Cytokinetics was quite dedicated—and even very early on was engaged with the patient community to ensure they understood what they could really offer to patients living with the disease."

While both *tirasemtiv* and *reldesemtiv* trials did not bring the hoped-for results, Pauls Backman remains optimistic that new therapies for ALS are on the horizon. She credits Cytokinetics for setting a high bar for its science—as well as showing an unparalleled commitment to the greater ALS community. Its work, she said, will help facilitate tomorrow's discoveries.

# Two Dozen Steps Back

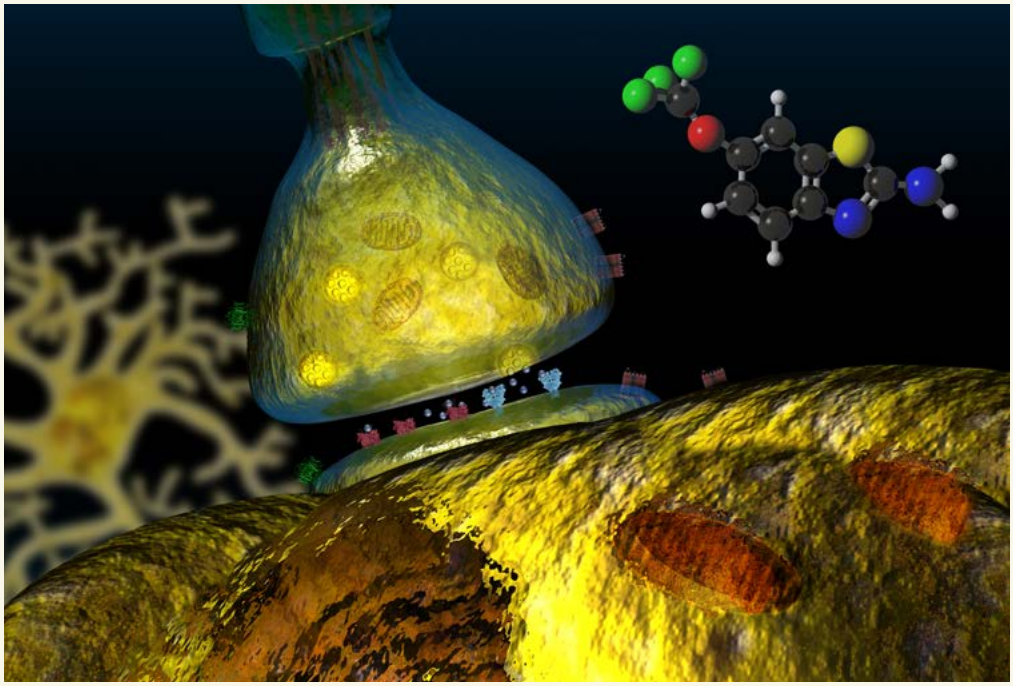
**OVER THE NEXT TWENTY** years, more than two dozen clinical trials—which included the testing of drugs designed to reduce inflammation, increase neurotrophic factors, and protect neurons from oxidative stress, just to name a few—all yielded negative results. Dr. Rudnicki said all those failures were very hard to take, not only for PWALS but the doctors who treated them.

"The good old days weren't necessarily so good. We had such limited options to offer patients and we just had so many failures in clinical trials," she said. "It wasn't for want of looking. There were a number of different trophic factors that were looked at. There were repurposed drugs that were looked at. There were novel drugs, with completely new targets, which proved to be busts. And each failure was just heartbreaking."

Orla Hardiman, M.D., a neurologist and ALS researcher at Trinity College Dublin and National Neurology Clinical Lead for Ireland's Health Services Executive, attributes all these trial failures to an overreliance on the SOD1 preclinical models.

"There was a tendency to slavishly follow this SOD1 preclinical model and assume that the clinical scenario for all ALS disease could be deduced from it," said Dr. Hardiman. "I think we made a lot of mistakes because of that. Because while we learned a lot about the cell biology of SOD1 ALS disease, and a lot of the related epiphenomena,

***Above:*** **Chuck Schretzman, a PWALS and Army veteran, walks outside with his wife and children.**



***Above:*** **An illustration of how *riluzole*, the first medication to be approved by the FDA for treatment of ALS, works in the body.**

our learnings did not necessarily translate into other types of ALS disease. These models were simply not as translatable as we hoped—and we saw, time and time again, that a positive animal study did not result in a positive human study."

Enter *dexpramipexole*. This new drug, developed by Knopp Biosciences and Biogen, acted on cellular energy by improving mitochondrial function to extend the life of motor neurons, and showed great promise in preclinical models. When it then yielded positive results in a proof-of-concept Phase 2 study, Dr. Cudkowicz said the excitement about the new drug was infectious.

"It was a small study, but the results were positive. And there really wasn't any other potential drug around at the time with positive Phase 2 data," she said. "Biogen quickly put together a global clinical trial to try to repeat the results. Despite the risk, people wanted to participate. That Phase 3 trial enrolled incredibly fast—we had something like 800 people in 15 months."

This ***new*** drug showed great ***promise*** in preclinical models.

Dr. Rudnicki, who enrolled PWALS herself into that trial while working at the University of Arkansas, said the early results seemed like a turning point for ALS therapies.

"One of the most exciting things about the Phase 2 study with *dexpramipexole* was that it definitely seemed to show benefit in slowing disease progression," she said. "This was something patients desperately wanted. And the thinking was, since it was a short trial, if it slowed disease progression in a short trial, you would see that and improved survival once it was tested in a longer trial. We had a lot of hope about *dexpramipexole*."


Unfortunately, EMPOWER-ALS, the Phase 3 trial, which enrolled 943 PWALS across 81 sites, did not meet its primary endpoint, a combination of function and survival for PWALS, when compared to placebo. Against all hope, the study found no difference in scores on the revised Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRS-R), a well-validated metric which assesses functional outcomes in ALS including walking, swallowing, and breathing, between the start and end of the trial. Dr. Rudnicki said the results were "a crushing blow" to the entire ALS community.

"It was like this huge balloon just popped. It was so deflating," she said. "It hit everyone really hard."

Dr. Cudkowicz agreed. She said she and the other researchers who worked on the clinical trial hadn't anticipated a negative result, despite the fact that so many clinical trials in ALS ended in failure. They believed *dexpramipexole* would make history as the second drug approved by the FDA for ALS treatment. Those combined hopes and beliefs made the top-line results even more disappointing to the greater ALS community.

"We really kind of hit a brick wall with that one," said Dr. Cudkowicz. "In retrospect, drug failures in ALS happen a lot. There are a lot of Phase 2 studies that just don't repeat. But the worst part was that there weren't really all that many other trials coming out at that point in time. It wasn't clear what targets might be viable, and where we should look next for treatment development."

***Left:*** **To develop *tirasemtiv* and *reldesemtiv*, Cytokinetics' scientists did exhaustive preclinical studies to understand how the molecule worked on muscle.**

# A Different Approach

**WITH THE FAILED *DEXPRAMIPEXOLE*** trial, Biogen announced it would cease development of the drug. Brian Dickie, Ph.D., Director of Research Development at the Motor Neurone Disease (MND) Association based in the United Kingdom, said this was not a surprise. He said, historically, drug companies see ALS as a "high risk proposition" for drug development—and, because of that, tend to dip in and out of the space.

"ALS, like other neurodegenerative diseases, are tough nuts to crack," he explained. "There's not one single cause. The reasons for its development are multifactorial—and there are likely a number of different events that must occur over many, many decades to kick off whatever processes lead to motor neuron death. It's only then that disease symptoms start to manifest. With ALS, you also often have a diagnostic delay of often up to a year, so maybe patients are so far down that slippery slope that we shouldn't be too surprised that these different drugs don't work."

Unlike other diseases, Dickie said, there isn't a straightforward strategy for how to treat ALS either—and that makes it harder for pharmaceutical companies to put the disease at the "front and center" of their research and development (R&D) planning.

More than five years earlier, the Cytokinetics team had synthesized a fast skeletal muscle troponin activator, CK-2017357. Unlike other drugs that had been

***Above:*** **Brian Dickie, Ph.D., Director of Research Development at the Motor Neurone Disease (MND) Association, speaks at the 2023 International Symposium on ALS/MND in Basel, Switzerland.**

***Left:*** **For people living with ALS, an everyday act as simple as putting on shoes can become an enormous challenge. A therapy preserving muscle function could promise a greater quality of life for PWALS.**

tested previously, this molecule did not attempt to target the motor neurons directly. Instead, it worked directly upon muscle—enhancing whatever muscle innervation remained.

"At the time, we were doing research on a whole bunch of different disease indications, but ALS kept coming up on the top of our list for potential development," said Scott Jordan, Senior Vice President, Global Marketing and Commercial Strategy at Cytokinetics. "I was excited that we might have something to help these patients. I knew there wasn't much out there. I also knew it was a risky proposition because 25 of the last 26 drugs that had gone through clinical trials had failed."

Pauls Backman said most biopharmaceutical companies were wary of getting involved with ALS drug development at this point. *Dexpramipexole*, after all, had shown great promise in preclinical models and in its Phase 2 trial. It would be difficult to get pharmaceutical players, especially newer, smaller companies, to make a strong investment in testing new therapies.

"Instead, it worked directly upon ***muscle—enhancing*** whatever muscle innervation ***remained***."

> ***Company*** scientists believed its muscle-based approach could ***support*** better ***function*** and quality of life for PWALS.

"After decades of failures, there was no question that it was a gamble to try to get into this market," she said. "The bigger companies were not successful, so how is a company that is a smaller biotechnology or early-stage pharmaceutical development company going to get a positive result? It was such a big risk to take."

Yet, it was during this time, when the ALS treatment landscape looked most bleak, that Cytokinetics, a small South San Francisco–based biopharmaceutical company decided it was time to invest in developing a unique drug with focus to enhancing muscle performance and endurance. Company scientists believed its muscle-based approach could support better function and quality of life for PWALS. Jordan said, as the company did more research on CK-2017357, it became clear that a fast skeletal muscle troponin activator could potentially make a difference for PWALS—if not as a standalone treatment, as a complementary add-on to other therapies. The potential reward would be more than worth the risk.

"The more we discussed it, the more we realized that we're in this industry to take those kinds of risks," he said. "We worked hard to assess the underlying biology of the disease. We understood how our mechanism worked. We thought we could set up clinical trials in the right way so we could minimize our risks there. And we decided, based on what we learned during those assessments, to go all in."

For his part, Blum, who had recently moved to the role of President and Chief Executive Officer at Cytokinetics, said, as daunting as others may have found ALS therapy development, he felt CK-2017357 could potentially make a significant difference in the lives of PWALS. Even as a smaller organization, Blum said he felt compelled to move forward, come what may.

"I remember thinking that this is what we were meant to do," he said. "I was cognizant of the fact that this was a disease for which the etiology was very unclear. But I felt like we understood what our muscle-directed research was all about. These are patients who have a neuromuscular disease where neurons are dying. Everyone else is focused on why the neurons are dying. But when the neurons die, the most immediate impact is on muscle, leading to weakness and dysfunction. So, we believed that if we focused on that aspect of the disease, looked at the issue from a different perspective, we could make a difference for these patients who desperately needed more effective therapies."

As Jean-Martin Charcot wrote in his 1874 treatise on ALS, *De la sclérose latérale amyotrophique,* only the future could tell the ALS community when a disease-modifying therapy for this devastating disease might come to pass. With a novel and unique approach to ALS treatment at the ready, Cytokinetics decided it was ready to join the fight—and see what the future might bring.

# The Cytokinetics Story

After working in the same field of cytoskeletal biology and molecular motor proteins for over a decade, four distinguished academic research scientists decided to get together and start a biotechnology company.

James Sabry, M.D., Ph.D., then a post-doctoral fellow in the biochemistry department at Stanford University, helped to uncover how motor proteins are regulated during cell division, a process fundamental to cellular function and health. James Spudich, Ph.D., founder and first director of the Stanford Interdisciplinary Program in Bioengineering, Biomedicine, and Biosciences—better known as Bio-X—had made a name for himself by uncovering the structure and function of the molecular motor that powers muscle contraction, myosin. Ronald Vale, Ph.D., a professor at the University of California, San Francisco (UCSF), discovered a new class of molecular motors, the kinesins, that move cargo down axons and around the inside of a cell, and power cell division. And, finally, Lawrence S. B. Goldstein, Ph.D., a professor of pharmacology at the University of California, San Diego (UCSD), first cloned the gene for kinesin and studied how dysfunctional proteins in nerve cells contribute to neurodegeneration. Together, these pioneering researchers had collected different pieces of a fascinating scientific puzzle regarding the movement of cells—and the insights they had gleaned had the potential to spur new therapies for a variety of diseases.

"The founders wanted to start a company focused on the science of the cytoskeleton," said Fady Malik, M.D., Ph.D., Executive Vice President of Research and Development at Cytokinetics, who worked in Vale's UCSF laboratory in the 1980s. "They saw their research had translational potential. They wanted to take their research from the bench to the bedside and develop therapies to help patients. That's how Cytokinetics started."

When the company was founded in 1998, Sabry stepped up as the first President and CEO. But Robert Blum, who is President and CEO of the company today, said the original founders understood that they needed the guidance of seasoned industry leadership to assist them. That's why Blum signed on at the beginning to be the company's Vice President of Finance and Business Development prior to the launch of company operations and the opening of South San Francisco laboratories.



***Top:*** **The original Cytokinetics headquarters in South San Francisco.** ***Bottom*****: The current Cytokinetics headquarters located on Oyster Point Boulevard in South San Francisco.**

***Right:*** **One of Cytokinetics's corporate values is Science Is in Our Soul. The company's research and development department spends its working hours committed to robust scientific thinking and problem solving—all with the goal of improving patient health and humanity.**

"When I met the four scientific founders, I was inspired by a vision they had in this unique area of biology and biochemistry," said Blum. "They had this incredible camaraderie and collaboration from their academic roots. After being recruited to join them by venture capitalists who were interested in supporting their work, I was very excited to work with them to help establish the company."

During its first years, the company focused on research directed towards inhibiting cell division, including a molecular target called kinesin spindle protein (KSP). After discovering a KSP inhibitor called *ispinesib,* they believed it could be developed for the potential treatment of cancer. In the background, however, Dr. Malik had conceived and launched a new discovery program focused towards activating the molecular motor responsible for cardiac muscle contractility as a potential way to treat heart failure.

At the same time, Blum was taking a hard look at where the company could best allocate resources to enable competitive advantage for the future. When Blum took over the President and CEO role in 2007, he decided to pivot and focus the company's efforts on muscle biology, an emerging field that Cytokinetics, based on its scientific strengths, could


pioneer and lead. Since then, Cytokinetics has developed a pipeline of muscle-directed therapies to potentially treat medical conditions characterized by muscle weakness and dysfunction, including hypertrophic cardiomyopathy (HCM), heart failure, and amyotrophic lateral sclerosis (ALS).

In 2023, only 9 months after Cytokinetics learned *reldesemtiv*, its fast skeletal muscle troponin activator, had failed to meet its endpoints in a Phase 3 trial in ALS, the company announced its investigational medicine for the potential treatment of HCM, *aficamten*, a cardiac myosin inhibitor, was a success. The Phase 3 trial was positive, making way for it to potentially become a therapy for people living with obstructive HCM. The drug is not yet approved by any regulatory agencies, including the FDA.

"If you look back at our history since 2007, we've had many successes and setbacks," Blum said. "At some points in time, our cardiovascular programs were in front of neuromuscular and at other points in time, neuromuscular was in front of cardiovascular. But we have always been dedicated and intentional in our pursuit of muscle-directed therapies, advancing both programs in parallel, to develop potential medicines for patients with great unmet need."

2

# Science Is in Our Soul

Cytokinetics' unique scientific approach to ALS


AJAY SAMPAT, M.D.

*The vast majority of human diseases are influenced, in some* way, by the kinetics of cellular function. Cells are the building blocks of human life. When the processes that help them grow, disseminate, and differentiate go awry, disease takes hold. Cancer is the byproduct of unchecked cell growth. Hypertrophic cardiomyopathy involves excess thickening of the heart muscle and changes to the heart muscle cells that can restrict blood flow. And dysregulation of cellular processes is also at the heart of multiple neurodegenerative diseases, including ALS.

When Cytokinetics started operations in 1998 in South San Francisco, its founders had collectively contributed to key academic research discoveries relating to the cytoskeleton and its role in cellular mechanics, and how different molecular proteins support cellular functioning. These breakthroughs provided an initial foundation to support the building of discovery programs to support the development of new medical therapies. But it would be the company's work on the sarcomere that would ultimately give rise to a novel approach involving the potential treatment of ALS.

The sarcomere, simply defined, is the basic contractile unit of a muscle cell. It is the functional component of muscle that allows muscle tissue to lengthen and shorten. The sarcomere is composed of two protein filaments, actin and myosin. When the brain's motor cortex sends a signal down the spinal column to motor neurons instructing muscle

to activate, a complex of proteins orchestrate together to coax the thin actin filament to slide against the thicker myosin fiber, resulting in a contraction, an elegant symphony of physiology. Every movement starts with these crucial cellular actions. Dr. Malik, the first employee of the company, said founder James Spudich's, Ph.D., academic work purifying and reconstituting the parts of the sarcomere laid the groundwork for the company's foray into discovering therapies for both cardiovascular and neuromuscular diseases. Those original insights were what informed Dr. Malik's team to look for new ways to activate muscle contractility. That eventually led to the discovery of activators of troponin, one of the muscle proteins that regulate actin and myosin interactions, as a promising new drug development target for diseases affecting skeletal muscle.

"We didn't pursue troponin necessarily when we screened the sarcomere and looked for tractable targets," he explained. "We let the biology lead the way and that is what led us to find a troponin activator to increase muscle contractility."

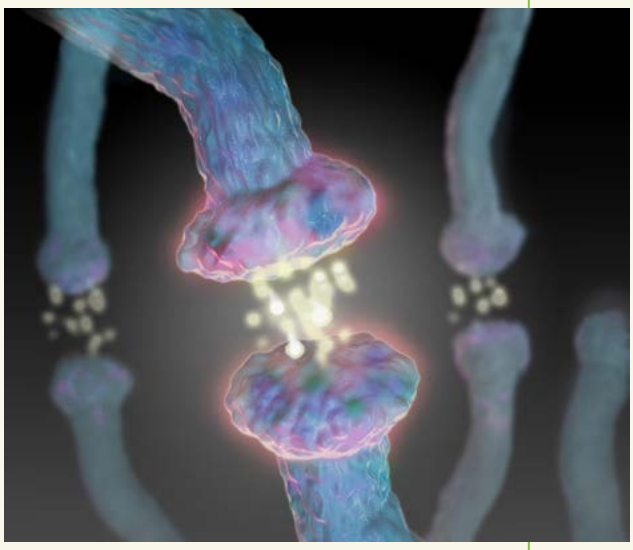
It would be the company's work on the sarcomere that would ultimately give rise to a novel approach involving the treatment of ALS.

# A Shift in Focus

**WHEN CYTOKINETICS FIRST OPENED** its doors, the scientific team focused on applying its knowledge of cytoskeletal proteins to explore potential new treatments in oncology. Nearly a decade later, in response to initial progress in its research on the sarcomere, company leadership decided to revamp its strategy. The cancer care biopharmaceutical market was becoming increasingly crowded, while treatments for muscle related diseases, including rare and orphan diseases, were often left unaddressed. Blum, at the time overseeing Cytokinetics' R&D activities, believed the company could make more of a major impact by focusing exclusively on the discovery and development of therapies anchored in muscle biology for underserved markets.

The research team was beginning work on drug discovery programs focused on activating cytoskeletal proteins that could help treat cardiac muscle diseases like heart failure, and Dr. Malik believed that seminal work identifying new approaches to activating proteins in heart muscle—including the creation of a sarcomere system to screen for new drug candidates—could be useful in finding new approaches to treating diseases affecting skeletal muscle, too.

"There are so many diseases where skeletal muscle is impaired. We wanted to see if we could find ways to modulate the skeletal muscle," he explained. "We put a fast



***Above:*** **A motor neuron sends a signal to the muscle, instructing it to contract. In ALS, motor neurons waste away, depriving the muscle of vital neural input.**

skeletal muscle system together—actin, myosin, and the proteins that regulate the muscle contractions like troponin and tropomyosin—so we could screen it and find a hittable target. Interestingly enough, the most hittable target in the fast skeletal muscle sarcomere was troponin."

Troponin, historically, is known as a protein that is released in large quantities as a result of heart damage. The greater the damage to the heart muscle, the higher the amount of troponin released into the bloodstream. If you head to the emergency room with chest pain, in fact, the physician on call will likely order a troponin test to help determine whether you are having a heart attack. But this protein also plays a pivotal regulatory role in skeletal muscle contraction.

When motor neurons send a signal across the neuromuscular junction into the sarcomere to initiate a movement, it leads to the release of calcium in the cell. The stronger the neural signal from the motor neuron, the greater the amount of calcium released. The sarcomere system needs a biological sensor to keep an eye on how much calcium is in the system—and, consequently, how strongly the muscle should contract. Troponin acts as this sensor, letting the muscle fibers know to contract in a proportional response to the amount of calcium in the sarcomere.

Understanding troponin's role in muscle contraction, Dr. Malik and colleagues started to screen libraries of compounds with the power to activate troponin—and convince the muscle to strengthen contractions—even if the signal input from motor neurons might be diminished.

"Calcium, when it is released into the muscle, binds with the troponin and basically acts as a gas pedal," he said. "The more calcium released, the harder your foot is pressing on the gas pedal, and the more myosin fibers in the sarcomere are engaged in a muscle contraction. The end result is a stronger contraction in the muscle even when signal transmission from the motor neurons isn't that strong. The skeletal troponin activator basically amplifies the response of the sarcomere to the signal it's getting and makes it stronger."

***Troponin***, historically, is known as a ***protein*** that is released in large quantities as a result of ***heart*** damage.

After Blum led a strategic planning initiative in 2006—and subsequently took the helm as Chief Executive Officer the next year—Cytokinetics pivoted. With preclinical research successes in both cardiovascular and neuromuscular diseases, the company decided to focus solely on areas where it could make an outsized contribution to the future of patient and medical care.

"We re-engineered the company away from oncology toward muscle," said Blum. "Since 2007, we've focused on both cardiovascular and neuromuscular research and development. At the time, the cardiac programs were getting more traction relative to the skeletal muscle programs, but we continued to advance them in parallel. It was intentional that we did that together."

# Leveraging the Two-Way Signal

Far too often, neuromuscular signaling is described as a one-way street. The motor neuron sends a signal to the muscle. The muscle then relies on the strength of that signal to determine the force of the resulting contraction. Today, however, researchers are learning that the neurobiology involved in this signaling is far more complex. The latest studies show that once the muscle gets a signal from the neuron, the muscle sends chemical messengers of its own back to the nervous system.

"There's a fair amount of literature to show that the muscle itself releases different factors that go back to the nerve to help modulate the neural signal," said Darren Hwee, Ph.D., Senior Director of Pharmacology at Cytokinetics. "The interface where that happens is the neuromuscular junction—or the synaptic space between the motor neuron and the muscle."

Given that studies have shown some of these chemical messengers include positive factors like brain-derived neurotrophic factor (BDNF), often referred to as brain "fertilizer," many in the scientific community hypothesize that this form of neuromuscular junction retrograde signaling (that is, the factors sent from the muscle to the nerve) may help strengthen the connections between neurons and muscles—and help preserve function. Conversely, if the muscle shows defects, as it does in neuromuscular diseases like ALS, the muscle may not be sending adequate factors back to the nervous system, spurring cell death from an unexpected direction.

Research conducted by Luc Dupuis at France's prestigious INSERM institution, for example, suggests that muscle abnormalities in energy metabolism may, in part, contribute to the death of motor neurons seen in ALS. When the mitochondria are not working as they should, the muscle cannot send the right signals back to the nerve cells, leading to atrophy—and hastening motor neuron death. Other studies have shown that defects in muscle tissue can also interfere with this vital bidirectional signaling between nerve and muscle, which may also affect the motor neurons. That

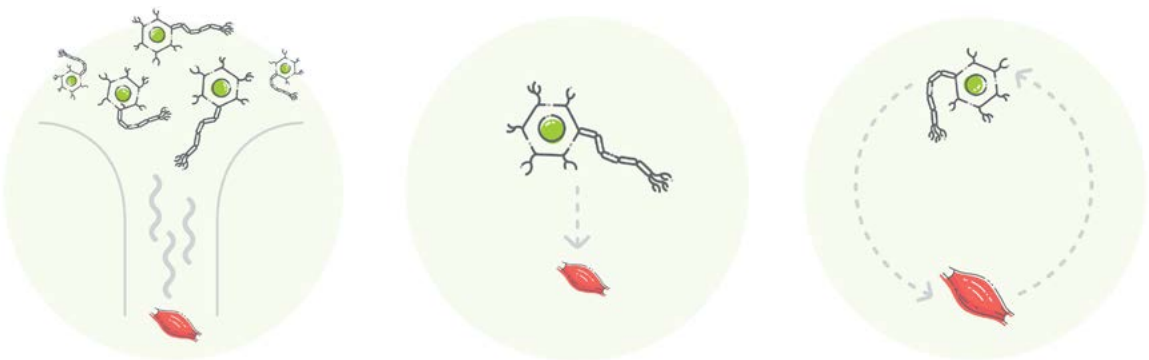
led Cytokinetics to work with scientists at the University of Montreal to look at the long-term treatment effects of *reldesemtiv* in a mouse model of ALS to see what it was doing at the neuromuscular junction. Some hypothesized that, by strengthening the muscle, it may support this important bidirectional relationship between muscle and nerve cell.

"We were hoping to see whether there was any kind of preserved integrity of muscle in the mice who were treated with long term treatment of *reldesemtiv* versus those that were treated with placebo. The idea was to see whether a muscle-targeted therapy might modify disease specifically at the neuromuscular junction to help promote this kind of retrograde signaling," said Dr. Hwee.

While early results showed that the mice treated with *reldesemtiv* showed preserved function over the animals in the placebo group—they showed a stronger gait and could get around more easily than the animals who received the placebo—the study was deprioritized when COURAGE-ALS failed to meet its endpoints in March 2023. Yet Dr. Hwee maintains that a better scientific understanding of the different chemicals that are passed through the neuromuscular junction may provide new insights—and targets—for ALS therapies in the future. Despite the fact that *reldesemtiv* failed in trials, he believes there is promise in muscle-targeted therapies in neuromuscular diseases.

"There's still a lot to learn about the neurobiology of ALS and how it affects the muscle over time," he said. "So, while we, as a community, should of course continue to look at nerve-directed therapies to treat ALS, there is likely a lot we can do to try to address the inherent defects seen in skeletal muscle, too—and there may be more to discover as we learn more about neuromuscular junction retrograde signaling."

***Below:*** **Over the past decade, scientific understanding of the relationship between motor neuron and muscle has evolved. They now understand that it is not a one-way street. Rather, there is a reciprocal relationship, with muscles sending important factors back to neurons to help keep them healthy.**



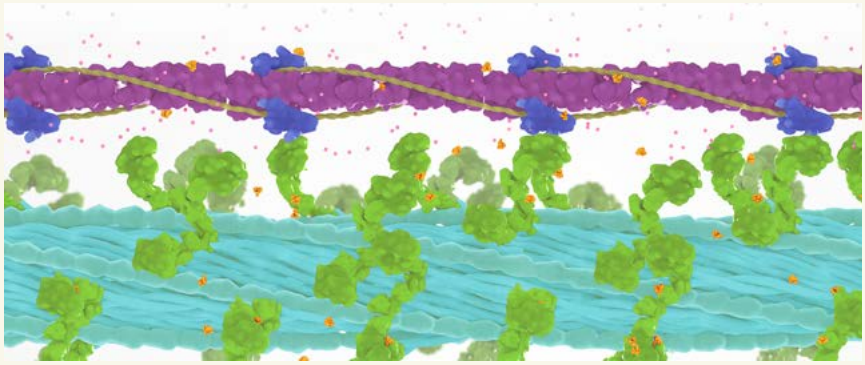
# A Novel Approach

**AT THIS POINT IN** time, the ALS community continued to suffer from a lack of treatments. While many biopharmaceutical companies had attempted to bring new therapies to market, their efforts led to dozens of failed clinical trials, culminating in the early 2000s. The vast majority of these compounds were designed to stave off motor neuron death and/or preserve motor neuron function.

Leaders at Cytokinetics believed a new approach was in order. A small molecule fast skeletal muscle troponin activator could potentially work as a therapy for a number of neuromuscular diseases. The question was: Which one should they pursue? While diseases ranging from myasthenia gravis to spinal muscular atrophy (SMA) were possibilities in these early days, the lack of available treatment options for PWALS quickly made ALS a priority for the company.

"We basically started listing different neuromuscular diseases on a blackboard and then discussed where we should put our efforts," stated Dr. Malik. "We looked at medical need, the infrastructure for developing a drug with different diseases, and what kind of endpoints we could use in clinical trials. Given the high unmet need in the ALS population—as well as the existing network of investigators and clinical research centers out there for ALS in both the U.S. and in Europe—we realized this was the right path to take forward."

***Below:*** **Sarah Coglianese, a PWAL who unfortunately did not survive the disease, reads a letter about Cytokinetics' mission to find an effective treatment for ALS, to her daughter, Scarlett.**



***Left:*** **An artist's rendering of the sarcomere, the basic unit of a muscle fiber. It is composed of two protein filaments, actin and myosin, which move against each other as the muscle contracts.**

While some were skeptical that a muscle-targeted therapy would be beneficial for those living with ALS, Dr. Rudnicki, who at that time was a Professor of Neurology and the Director of the ALS MDA Center of Excellence at the University of Arkansas Medical Center, said she was excited about the possibility of a different kind of therapy—especially after so many failed clinical trials with neuronal targeted drugs. While the ultimate hope was for a drug or cocktail that could cure ALS, or at least modify the course of disease, Dr. Rudnicki said the aggressive progression of ALS also called for treatments that could help arrest or delay the loss of muscle strength. A muscle-targeted therapy that could help PWALS preserve muscle function longer, even as the motor neuron signal input declined, would be a boon. It would help PWALS remain independent longer—and thus help improve their quality of life.

"One of the things that impressed me about this approach was that a muscle-targeted therapy is agnostic to what's going on in the brain. We still don't really understand what's happening in the brain in ALS—what is going awry that results in the death of all those motor neurons," she said. "But we do know that everyone with ALS eventually ends up with weakened muscles. So, if you could increase the force of muscle contraction with a troponin activator, it wouldn't matter if you have familial or sporadic ALS, or if you have glutamate toxicity, or if you have some kind of genetic mutation, or if there is some other issue that is what leads to disease. A muscle-targeted therapy could be potentially effective for everyone with ALS—and help these patients keep their motor function for a longer period of time."

Dr. Hwee added that the scientific team also thought it was possible that a troponin activator could potentially slow the progression of disease. Multiple studies in the scientific literature demonstrated that PWALS not only showed motor neuron degeneration—they also had "toxic" abnormalities in their muscles that led to weakness and atrophy. That might well mean that muscle issues were also involved with the disease pathophysiology.

"There's a perception that muscle is kind of a bystander in ALS and that it's the loss of the motor neurons that is wholly responsible for the symptoms seen," said Dr. Hwee. "So, it was clear to us that while the biopharmaceutical industry should certainly continue to look at different neuron-directed therapies, a drug that could address inherent defects in the muscle could also potentially help patients retain muscle strength and function for a longer period of time."

# An Increase in Endurance

**ARMED WITH THE KNOWLEDGE** that a troponin activator could bolster the mechanics of skeletal muscle contractility, Cytokinetics synthesized a first-in-class muscle activating compound named CK-2017357 in 2007. The R&D team immediately started a series of preclinical studies to determine its feasibility as an ALS treatment. They also started work on the development of a next-in-class molecule with the goal of providing incremental therapy improvements.

"One of the big challenges for us was to describe to clinicians and regulators what the activator did to muscle function. We knew that it bound to troponin and fundamentally increased the calcium sensitivity of the sarcomere but to what end?" said Dr. Malik. "We ultimately were able to articulate three primary functions. One, it increased muscle response to calcium. Meaning, it amplified the nerve signal that came in from the motor neurons. Modulating troponin was like turning the amplifier knob on a record player—it allowed us to get more force output out of the same amount of nerve input coming into the muscle."

That, Dr. Malik said, is vital in conditions where that innervation signal is limited, as it is in ALS. The second thing that preclinical studies of the fast skeletal muscle troponin activator showed was that it could also improve the endurance of the muscle.

***Bottom right:*** **Cytokinetics research scientists work to create potential medicines to address muscle dysfunction and weakness.**

> ***Modulating*** troponin was like turning the ***amplifier*** knob on a record player—it allowed us to get more ***force*** out of the same amount of ***nerve input*** coming into the muscle.

***Below:*** **Chuck Schretzman, a PWALS, works with a physical therapist to help retain strength and function in his leg muscles.**

> Just a ***single dose*** of CK-2017357 ***improved*** both muscle ***force*** and ***grip strength***—outcomes that could be game-changing for PWALS.

"When calcium's released into the muscle, it needs to be pumped back to where it came from. That takes a lot of energy," he said. "If you need less calcium to get more force, the muscle can keep contracting for longer. With the troponin activator, we actually saw the stamina of muscles improve, too."

Finally, the researchers also saw a third benefit: fast skeletal muscle troponin activators increased the power output of the muscle. Just a single dose of CK-2017357 improved both muscle force and grip strength—outcomes that could be game-changing for PWALS, allowing them to continue to do things like grip objects and walk independently for a longer period of time. Dr. Wolff said, when they brought their initial data to ALS thought leaders, many were very enthusiastic about a therapy that could offer "more bang for the buck out of what skeletal muscle innervation was left."


kinetics

***Left:*** **Safety and tolerability studies demonstrated that CK-2017357, which would later be called *tirasemtiv*, was well tolerated by ALS patients—the first hurdle in developing it as a therapy for ALS patients.**

***Above:*** **As ALS progresses, PWALS often have difficulty with grip strength and must rely on adaptive utensils like these so they can remain independent longer.**

"This was a very novel approach—and, all things considered, a quite reasonable way to try to improve patient function," he said. "I remember the first time we went to see Jeremy Shefner, M.D., Ph.D., one of the founders of the Northeast Amyotrophic Lateral Sclerosis Symposium (NEALS), a network of clinical centers of excellence that support clinical trials. We went through a presentation of this early clinical data. Dr. Shefner listened intently, asked a few questions, then sat back in his chair and said, 'Wow, this is amazing. My whole professional career, the most I thought we could do is keep patients from getting worse. But you are showing me something here that might improve patient function.' It was an inspiring thing to hear someone of that stature in the ALS community say our therapy held that kind of promise."

Dr. Shefner added that those early results provided him with tremendous hope that this kind of approach could help PWALS who desperately needed something to help them strengthen their muscles.

"I was excited by the findings," he said. "Clearly, it wasn't going to be a cure for ALS. But to the extent that any ALS patient still had functioning nerve connected to muscle, this therapy held promise to improve function in these people. I thought that this molecule should do that and was glad that it was going to go into clinical trials."

After safety and tolerability studies demonstrated that CK-2017357 was well tolerated by PWALS—and also improved voluntary ventilation (a measure of breathing capacity) and handgrip endurance—it seemed that this muscle-targeted therapy might provide some much-needed light at the end of the ALS clinical trial tunnel.

"Ultimately, PWALS die because the loss of muscle function leads to a loss of breathing function which increases the risk of pneumonia. These patients become prisoners in their own body as their muscle function shuts down both locally and peripherally," said Blum. "It appeared that our unique perspective on therapies had provided us with a potential way to make a real difference for these patients."

With these strong early results in hand, and the support of key opinion leaders in the ALS community, Cytokinetics was ready to move CK-2017357 into a Phase 2 clinical trial. It was at this time that the United States Adopted Names (USAN) Council provided the drug with a generic name: *tirasemtiv*.

# Testing the Science

**AFTER PROMISING PHASE 1** trial results in 2009, which demonstrated that *tirasemtiv* worked to improve muscle strength in healthy human participants, Cytokinetics immediately got to work on a Phase 2 trial, known as BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with *Tirasemtiv* in ALS).

"The ability of this agent to hit the target and impact the isolated contractile apparatus of the muscle was confirmed in this early work," said Dr. Shefner. "We saw that the release of calcium by the muscle cell produces more force with *tirasemtiv* on board than without it."

Cytokinetics started enrolling PWALS into the BENEFIT-ALS trial in 2012, recruiting 711 participants over the age of 18 to receive either 250, 375, or 500 milligrams of *tirasemtiv* per day over a 12-week period. The inclusion criteria were typical of the time—a score of 2 or 3 on at least 4 items on the ALSFRS-R scale, a slow vital capacity (SVC) of greater or equal to 50%, an ALS diagnosis, and diminished but measurable grip strength. The primary endpoint was a change in ALSFRS-R score, but the study also examined respiratory and muscle function.

"The study did not meet its primary endpoint," said Dr. Shefner. "But what we did see was what looked to be an impressive effect in vital capacity. We asked ourselves whether it was a positive enough result to go forward and, after a lot of discussion, the decision was made to continue with a Phase 3 study."

That study, VITALITY-ALS (Ventilatory Investigation of *Tirasemtiv* and Assessment of Longitudinal Indices After Treatment for a Year in ALS), recruited 744 adult participants for a year-long study to determine whether *tirasemtiv* improved respiratory function, with the primary

> We saw that the release of ***calcium*** by the muscle cell produces more force with ***tirasemtiv*** on board than without it.

endpoint being change in SVC. Unfortunately, Dr. Shefner said, the drug had significant tolerability issues, with strong side effects including dizziness and fatigue, which meant many of the participants stopped active treatment before the conclusion of the trial.

*Reldesemtiv* (also known as CK-2127107), the next-in-class molecule that Cytokinetics already had waiting in the wings, had been specifically designed to address the tolerability issues seen with its precursor. Its chemical structure meant that it did not cross the blood-brain barrier—and it would not cause the dizziness that so many people experienced when taking *tirasemtiv*. Its preclinical studies, too, showed promising results. That's why, Dr. Rudnicki said, Cytokinetics decided to conduct a Phase 2 trial, FORTITUDE-ALS (Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints in ALS) with SVC as its primary endpoint, before seeing the final results of VITALITY-ALS.

Unfortunately, *tirasemtiv* did not achieve its endpoint in VITALITY-ALS and the decision was made to discontinue development. But, as those results could be attributed to the number of people who discontinued treatment because of the side effects, the company had high hopes that *reldesemtiv* would succeed where *tirasemtiv* had not. And the results from FORTITUDE-ALS, said Dr. Shefner, were very promising, despite the fact *reldesemtiv*, too, failed to meet its primary endpoint.

***Left:*** **Jeremy Shefner, M.D., Ph.D., was the principal investigator of the COURAGE-ALS trial.**

When the data analysts pooled all of the PWALS who received active treatment and compared them to placebo, they saw a 27% change in vital capacity, a 25% change in the ALSFRS-R score, and a 21% change in muscle strength. These were tangible effects that, if replicated in Phase 3, could point to a new therapy for ALS to help PWALS lead more independent, higher quality lives.

"All of this happening in a three-month period of dosing was extremely encouraging," said Dr. Shefner. "And it was deemed appropriate that we carry our work forward, with a Phase 3 trial for *reldesemtiv* called COURAGE-ALS (Clinical Outcomes Using *Reldesmtiv* on ALSFRS-R in a Global Evaluation in ALS)."

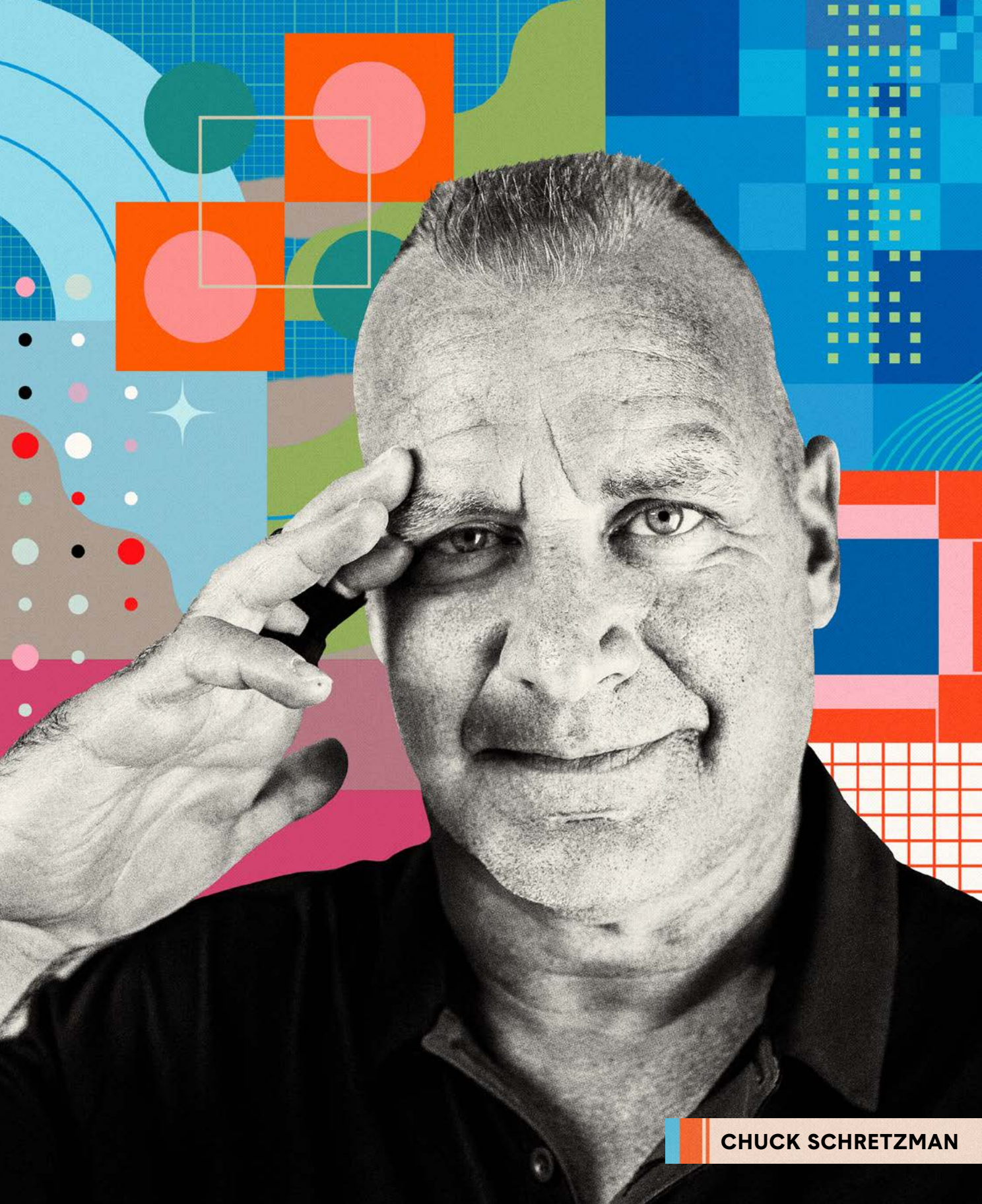
One of Cytokinetics core values is Science is In Our Soul. The company puts scientific thinking and critical thinking at the heart of everything it does. Unfortunately, despite promising Phase 2 data with *reldesemtiv*, the future would bring more disappointment to those hoping to find a treatment for ALS. *Reldesemtiv* did not meet any of its endpoints in COURAGE-ALS. In March 2023, the trial was stopped due to futility following the second interim analysis. After more than a decade of dedicated work, Cytokinetics would not be able to bring forward a new therapy to the ALS community as company employees had so fervently hoped.

Despite this result—which some might summarize, far too simply, as a defeat—Blum said he and his colleagues learned vital lessons about collaboration, innovation, perseverance, and commitment—all thanks to the remarkable community of PWALS, caregivers, advocacy groups, researchers, and clinicians who make up the greater ALS community.

3

# We > Me

How Cytokinetics became an active and trusted member of the greater ALS community


CHUCK SCHRETZMAN

*To understand those lessons, it's important to go back in time* to when the early clinical data suggested that *tirasemtiv* might be a viable therapy for ALS. It was then that Cytokinetics began to engage with the greater ALS community to help move the molecule forward. While ALS remains a relatively rare disease—the Centers for Disease Control and Prevention (CDC) estimates there are approximately 5,000 new diagnoses of ALS in the United States each year, with around 31,000 people living with ALS at any one time—its ferocious progression has led to the development of a committed group of researchers, clinicians, PWALS, caregivers, and advocacy organizations working to drive new therapies and treatment options.

Blum said he was immediately struck by the mission and passion of the tight-knit ALS community—as well as the work it was doing in order to advance ALS therapies.

"It is an inspiring community," he said. "I've often said that ALS patients are the best versions of ourselves. They are courageous, selfless, and they give of themselves far beyond what would be the norm. They are also dedicated to the science and research, largely knowing that any advances that may occur are going to benefit others, as opposed to themselves. The patient advocacy groups reflect those attributes, too. Then, there are the ALS clinicians and researchers. They, too, have a tenacity and a purpose to help patients that is just unyielding."

Historically, the pharmaceutical industry has not been viewed as being quite as dedicated to the cause. Dr. Dickie said for decades, pharmaceutical companies wouldn't make large investments in development because the disease is so challenging to treat.

"As a rare disease, ALS has just not been a big market for Big Pharma. If something happened to come along that might fit as an ALS therapy, companies would come in and test it," he said. "But, generally speaking, once it didn't work out, the companies did not stick around—and the different patient associations were treated as an afterthought."

Dr. Dickie added that, too often, many of these companies also did not see a need to engage with the research community regarding their study findings either.

"These companies might do a quick and dirty study of a drug that might keep sick nerve cells alive in a preclinical model, but then it would ultimately fail in clinical trials," he said. "At that time, many industry companies did not feel obligated to share what they learned over the course of their trial with the research community so others might build on that work. It was kept close to the vest."

Dr. Wolff said, Cytokinetics' introduction to the greater ALS community was paved by its interaction with an "established, tightly knit, and organized constellation of global ALS investigators who cooperated on clinical trials."

# The Power of Networking

**WHEN CYTOKINETICS STARTED PLANNING** clinical trials for *tirasemtiv*, the Northeast ALS Consortium (NEALS), the network of clinical centers of excellence, had been around for at least a decade—and had since grown beyond the northeast United States and continues to expand its geographical reach. The European Network to Cure ALS (ENCALS), a consortium of more than 70 ALS research centers and hospitals across Europe, the United Kingdom, and beyond, formed about the same time. Both would prove to be instrumental in helping Cytokinetics connect with the greater ALS community both within the United States and ultimately abroad.

"We were very lucky to be working with this experienced cadre of investigators, study coordinators, and clinical sites. But one of the unexpected advantages of working with NEALS and ENCALS is that they were, by then, associated with every kind of stakeholder in the ALS community," said Dr. Wolff.

NEALS was founded in 1995 by Dr. Cudkowicz and Dr. Shefner, leading clinical researchers in neurodegeneration and ALS. Dr. Shefner said he and Dr. Cudkowicz were inspired after the Chair of the World Federation of Neurology, Ted Munsat, M.D., called for physicians and academics to get more involved in ALS therapy development the year prior.

"Just before we started NEALS, Dr. Munsat gave a presidential address at the World Federation of Neurology meeting where he basically called for academics to take more responsibility for clinical development," recounted Dr. Shefner. "He was the one who suggested the idea of creating an academic consortium for ALS therapies."

***Right:*** **Brian Wallach and Sandra Abrevaya, founders of I AM ALS, at the San Francisco debut of the documentary *No Ordinary Campaign,* which chronicles their advocacy work for the ALS community.**


> The ***different*** ALS people from those sites would regularly meet, talk about the gaps in clinical ***trials***, and ***figure out*** how to fill them. It all grew, really, from us ***talking*** a lot.

Dr. Cudkowicz added that, with the development of the SOD1 preclinical models, researchers were now hard at work identifying targets for potential new drugs—but lacked the infrastructure to conduct the necessary clinical trials to test them for efficacy. Researchers who were working on Parkinson's disease had been able to set up their own clinical trial consortium—and, after winning a National Institutes of Health (NIH) grant to test *topiramate*, an anticonvulsant medication, as a possible treatment for ALS, Dr. Cudkowicz and Dr. Shefner brought together trial sites across New England.

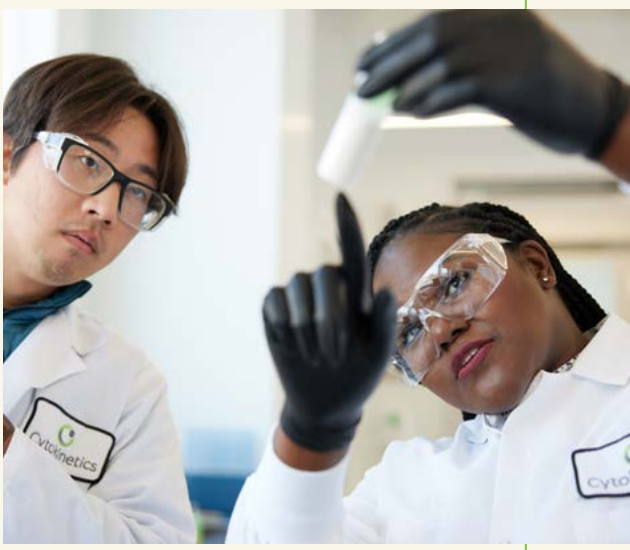
"We were actually the New England ALS Consortium at that point, I think," she said. "We started with nine centers across New England. The different ALS people from those sites would regularly meet, talk about the gaps in clinical trials, and figure out how to fill them. It all grew, really, from us talking a lot. Talking not only with other clinicians and research scientists, but with patients and caregivers."

That led to strong relationships with PWALS and advocacy groups across the country. To both educate and recruit PWALS for studies—as well as understand what

kinds of therapies they were most interested in seeing come to market—NEALS became a hub in the greater ALS ecosystem. Beyond supporting clinical trials, it also worked with different players in the ALS space to facilitate better care and support for PWALS, promote public policy change, and raise both awareness and desperately needed research funding. NEALS even created a clinical research learning institute, which trains PWALS and other ALS stakeholders as research ambassadors.

"We all have to work together, otherwise we're just reinventing the wheel every time someone comes up with a new idea," said Dr. Cudkowicz. "Advancing effective therapies is all about knowledge sharing and efficiency. And, to get to that point, you need everyone on deck. The fact that we need therapies is something that has really connected doctors, patient advocates, and now, companies. It's created this army of committed people who really care about ALS research and are out there advocating in different ways to make a difference."

Like NEALS, ENCALS, now led by Dr. Hardiman and Dr. Leonard van den Berg, a neurologist and motor neurone disease researcher at the University Medical Center Utrecht in the Netherlands, was founded with the understanding that finding a viable treatment for ALS would require strong collaborations and teamwork. Despite the fact that most small biopharmaceutical companies might not venture outside the United States to conduct trials, Cytokinetics understood the value of including European investigators in its programs to develop new therapies—particularly given that its muscle-targeted approach was so novel. Dr. Wolff said that the company relied on the experience and knowledge of key opinion leaders in the field, both in the U.S. and Europe, to not only guide them as they developed trial protocols, but to introduce them to other leading voices in the ALS community.




***Above:*** **Cytokinetics' R&D team works in a coordinated, collaborative manner to discover and develop potential new medicines.**

> ***Advancing*** effective therapies is all about knowledge ***sharing*** and efficiency. And, to get to that point, you need ***everyone*** on deck.

# Beyond Trials

**IN 2011, CYTOKINETICS** connected with NEALS to discuss its impending Phase 2 trial for *tirasemtiv*. Dr. Shefner said he was struck by the company's dedication in bringing the drug forward. "From the very beginning, Cytokinetics showed to be really unique in the ALS community," he said. "They invested in large, well-powered, and well-designed studies. They looked at things incredibly carefully and it was clear they were really committed to doing things the right way."

Jordan said the company wasn't just interested in supporting strong clinical trials. It was also dedicated to connecting with other stakeholders in the community.

"In any disease area, you have to go all in to really understand the journey for patients living with the disease," he explained. "Some of that is good market research, I suppose—but, through that process, you really get to know the community and the people there. They became more than just a valuable resource in terms of connecting and understanding the lived experience of disease. They became our inspiration."

Blum agreed. He said what started as a company philosophy to meet PWALS where they are transformed into finding new ways to demonstrate Cytokinetics' value to patients, caregivers, and clinicians. And they made sure they weren't just working with ALS organizations within the U.S.—they also made sure to connect with key opinion leaders and patient advocacy groups across Europe. Patrizia Allegra, Senior Director of Marketing for ALS at Cytokinetics, said she and her colleagues made a point to frequently meet with clinical experts in the European centers of excellence and the various advocacy organizations overseas.

"This started in the early days of *tirasemtiv*," she said. "For a small company to dispatch people to understand this whole other world and the needs of PWALS was significant on its own. Dr. Rudnicki and I spent a lot of time engaging with different centers of excellence to understand how they managed things and what PWALS needed. We knew those voices were important to include—and could help us make sure we were developing our trials in a meaningful way to help more people."

The group also participated in master classes hosted by the Translational Research in ALS and Neurodegenerative Diseases (TRICALS) organization, founded by Dr. van den Berg in 2012.

These annual informal meetings bring together PWALS, researchers, regulatory bodies, and industry representatives to brainstorm ways to improve clinical trials. Dr. Rudnicki said it was an invaluable learning experience.

"This meeting was a great way to get all these different stakeholders to talk to one another and see where they could work together toward the goal of advancing new therapies," she said. "We talked about meaningful outcome measures, how to better design ALS clinical trials, and the latest research findings. It was just this incredible opportunity to get together with all the people involved with ALS in Europe to see how we could all work better together toward the common good."

Blum said, in retrospect, that kind of commitment, especially so early in drug development, may seem odd to some. But it was important to the company that it showed up in a way that indicated a longstanding commitment and authenticity from the very beginning.

"We were just hoping to enter the tent where leading academics were convening and ask where we can be of most service," he said. "These groups represented the center of gravity for ALS, centralizing discovery sciences and clinical research. It's where you want to be—and it's where we committed to join forces with all stakeholders in the ALS community to help bring about new treatments, shape public policies, and do the work needed to make ALS a treatable condition."

For those reasons, Dr. Cudkowicz said Cytokinetics quickly differentiated itself from other biopharmaceutical companies. The organization's early and steadfast commitment stood out from the rest of the industry.

"While Cytokinetics was doing their studies, they were also doing what they could to help the community," she said. "If there was a run or a bike ride to support ALS in California, they were always there supporting the local chapters. They commissioned groups to work on different research papers, including several studies that looked at respiratory measures and different trial endpoints. These things helped with their trial, but also helped the field. Most importantly, they never kept their data to themselves. They really worked to share data and help the whole field learn. And they made it a point to go to all the meetings, get to know people, and do what they could to help fill gaps in knowledge because it was important for the entire community."

These groups represented the ***center*** of gravity for ALS, centralizing ***discovery*** sciences and clinical research.

***Right:*** **Ryan Farnsworth, who sadly has passed on, with Robert Blum, Joanna Siegall, and members of what is now The ALS Network at an ALS Awareness Day hosted by the San Francisco Giants in 2017.**

**MOMENTS THAT MATTER**

# Robert Blum, President and CEO

Blum said meeting Ryan Farnsworth, who was only 29 when he was diagnosed with ALS, crystallized for him why it was so important to go all in when developing *tirasemtiv* and *reldesemtiv*.

"It was one of those pure moments where we were just walking together and randomly connected. Through our conversation, I felt in him a kind of superpower. He was a young man who was wise beyond his years: reflective, introspective, and very self-aware. In many ways, he had transcended his disease and rose above himself to speak about ALS in terms that I had not heard from any other patient before," he said. "He was accepting of his diagnosis and disease prognosis. He was considered in his way of addressing his mortality, frankly, confronting it in a very courageous way. But he also saw beyond it—and was doing what he could to bring more awareness to the needs of people living with ALS and the need for more effective therapies. In his presence, I felt I had an even stronger duty and obligation to help him do just that."

# Working Together

**MANY PHARMACEUTICAL COMPANIES TRY** to build relationships with ALS organizations as they look to recruit for clinical trials—but Fred Fisher, President Emeritus of The ALS Network (formerly The ALS Association Golden West Chapter) said that the entire ALS community benefits when industry players more actively participate in those relationships beyond clinical trial enrollment.

"At the most rudimentary level, there is an opportunity to partner with an organization like ours, which serves about 2,000 people living with ALS, to find people to be in your trial. Some significant percentage of our members will likely be eligible," he said. "But when you are more proactive in your relationships in this greater ecosystem, everyone benefits."

He applauds Cytokinetics for always seeing PWALS as more than potential customers—but as human beings that have significant unmet needs that must be addressed more broadly.

"Cytokinetics cares deeply about the ALS community. They recognize the terrible situation that patients and families are in and have real empathy for the different challenges that people diagnosed with ALS are living with," Fisher said. "They routinely engaged the patient community. They embraced opportunities to participate in events where the ALS community comes together. They


***Top:*** **The unveiling of the Wall of Heroes, a display of patient photos, at Cytokinetics headquarters in 2016.**

***Bottom:*** **Cytokinetics would often bring in PWALS, like Sarah Coglianese, to talk to the company about the lived experience of ALS.**

***Below:*** **Cytokinetics started participating in the annual Walk to Defeat ALS event in 2010, often bringing dozens of employees, family members, and friends to show their support and raise money and awareness for the cause.**



> As a ***company*** in the biopharmaceutical industry for the ***right*** reasons, it was important that we ***committed*** ourselves to people with ALS and the larger ***community*** in any way that we could.

helped raise money; they provided sponsorships for different programs. And they also engaged around our public policy activities. Let me tell you, when the CEO of a company like Cytokinetics comes with me on visits to key legislators, not to talk about the company or their drug, but to talk about the needs of ALS patients and why supporting ALS-related legislative priorities is important, it makes a difference."

Blum said he does not understand why more companies are not engaging with the greater ALS community in this way.

"As a company in the biopharmaceutical industry for the right reasons, it was important that we committed ourselves to people with ALS and the larger community in any way that we could," he said. "By doing these things, we identified more and more with this community and felt very privileged that we could join forces with them in the fight against ALS. It gave us a higher calling and a higher conviction—and a higher urgency that we needed to do everything we could to help bring forward potential new medicines to serve patients."

# Philip Green

*At first, Philip Green,* a former athlete who played football for the University of Washington and then later tried out for a Major League Soccer team, didn't take much notice of the twitching in his triceps. The busy executive and father of 4 thought it might be the byproduct of too much caffeine. But when the twitching continued—and started to spread to other parts of his body—he became more concerned. Soon after, he noticed a significant loss of pinch strength in his fingers. He could no longer clip his own toenails. It was at this point that the man who once bench-pressed 360 pounds on a regular basis realized something was amiss. In August 2018, after nearly a year of referrals and specialist visits, he was diagnosed with ALS. Soon after, he got involved with patient advocacy efforts.

"I'm a fixer and problem solver by nature," he said. "As a patient, I saw the ALS ecosystem was broken in a bunch of different areas. It still is. I couldn't just sit there and accept that. I had to do something to try and change it." Green considers himself lucky—he was able to participate in a clinical trial. But that experience made him realize how difficult it is for many PWALS to gain access to investigational medications. He also noted that many clinical trials are often quite burdensome for participants—and Green realized this was one issue he could apply his problem-solving skills to immediately. He joined I AM ALS' clinical trials committee as co-chair, educating biopharmaceutical companies about how they could make their trials more patient-friendly.

In addition, Green has worked to highlight the potential link between chronic traumatic encephalopathy (CTE), a neurodegenerative brain disorder thought to be caused by repeated head injuries. Epidemiological studies have shown that there is a higher incidence of ALS in football and soccer players who have experienced repeated concussions. In fact, Lou Gehrig, who, until recently, was likely the most well-known public figure diagnosed with ALS, was reported to have suffered from multiple concussions over the course of his baseball career.

Since his diagnosis, Green has worked directly with different biopharmaceutical companies. And he said he's witnessed, firsthand, how the patient voice can make a difference in how they communicate with the greater ALS community and conduct their trials. Talking about his lived experience with this disease has not only assisted companies who are trying to bring a new treatment to market increase their clinical trial enrollment numbers, it has also helped to reduce the burden of PWALS who sign up to participate.

Green was an integral part of Cytokinetics' Patient Advisory Council for *reldesemtiv* development. He said that the company's willingness to listen to patients, doing whatever it could to accommodate patients, was what helped the company receive a 5-star rating from I AM ALS' Patient-Centric Trial Design Committee for COURAGE-ALS.

"Our voices matter. We can have an impact to change things," he said. "My good friend Sandy Morris, who also had ALS and worked with I AM ALS, would often say 'what we allow will continue.' So, if we don't use our voices to inspire change when we see things that could be done better, nothing will change. We need to speak up so we can get the good changes we need to help companies develop new treatments more efficiently. And we appreciate companies like Cytokinetics, who are always willing to listen."

# Paving the Way

**BECOMING MORE INVOLVED WITH** the greater ALS community demonstrated many of the systemic barriers industry players faced when trying to bring a new drug therapy to market. Even if a drug is successful in clinical trials—and it was well understood that is a big "if"—there is still the matter of gaining approval from regulatory agencies and convincing payers to cover the drug so it will be accessible to PWALS. While many organizations may not talk to these stakeholders until long after clinical trials have begun, Cytokinetics understood the importance of having those conversations early.

"Of course, you want to talk to patients and caregivers—and the clinicians and researchers, too," said Dr. Rudnicki. "But you will not be able to get any medication into the hands of patients unless you also talk to the regulatory agencies and insurance companies."

Allegra said the company made sure to immediately open the lines of communication with regulatory agencies like the FDA and the European Medicines Agency (EMA). The company engaged in payer initiatives early on, too, to get input on clinical trials in the United States. But one thing that really stood out from other biopharmaceutical companies was the decision to meet with the health technology assessment (HTA) bodies in Europe very early in the therapy development process to help pave the way for *reldesemtiv* if it proved effective in COURAGE-ALS.

You will ***not*** be able to get any medication into the hands of ***patients*** unless you also talk to the ***regulatory*** agencies and insurance ***companies***.

"If you are successful in your trials, it's not just about getting the regulatory approval. You also need payers to say, yes, we will cover this drug. It's a tough process, especially in Europe, where you have healthcare for all," she said. "We knew how important this step would be to getting *reldesemtiv* to patients if we were successful in our trials. And we thought we needed to go to these important decision makers early to make sure that we understood what they would want from us."

HTAs are responsible for determining whether the value of a particular therapy reflects the benefits it provides to patients. Upon a product's approval by the HTA, they are involved in a multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of that specific health technology. Dr. Rudnicki said HTAs are independent of the EMA—and there is currently really nothing to parallel their decision-making process in the United States. Organizations working to get a drug authorized must go through a rigorous approval process, and understanding the HTAs' assessment of a clinical trial protocol early on is extremely useful.

"This is a unique system that looks at your outcomes and how clinically relevant they are to patients," she said. "They also want to see a cost effectiveness model—you need to show them that your therapy is something that really provides value."

Cytokinetics spent seven months putting together a dossier, including clinical, regulatory, biometric, health economics, and other key data, for HTAs in the U.K., Germany, and France to review. The company then set up meetings with each body to answer questions and gather feedback from the HTAs to help guide the protocols for the company's upcoming Phase 3 trial.

"Speaking with the HTAs so early was a very controversial decision at the time—and not everyone within the company initially agreed that we should do it," said Allegra. "But our therapeutic approach was so new that we needed to make sure the HTAs would understand how a muscle-targeted therapy could help patients so they could get it as soon as possible if it proved to be effective."

Allegra credits Blum's vision for understanding how important it was to start these dialogues with so many of the different ALS stakeholders early and often. But Blum said this should be what all industry stakeholders do when they are developing a potential medicine for PWALS.

"Our obligations go beyond getting a medicine approved. We need to do our part to ensure equitable access to that medicine," said Blum. "The team's work in getting us in front of HTAs so we could understand what needed to be done to overcome the barriers and impediments to access was just as important as everything else we did. We needed to bring these other stakeholders into the conversation, align with their interests, much like we aligned with the interests of patients, so everyone is working together in unison to bring new therapies forward."

Our ***obligations*** go beyond getting a ***medicine*** approved. We need to do ***our part*** to ensure ***equitable*** access to that medicine.

# The Ice Bucket Challenge

Rewind back to 2014. The Winter Olympic Games were held in Sochi, Russia. NASA managed to land the Philae probe on the back of a fast-moving comet. Janet Yellen made history when she was named the first woman to lead the Federal Reserve. Marvel's *Guardians of the Galaxy* hit it big at the box office. And, during the summer of that year, it seemed that you could not escape the latest viral social media sensation taking over Twitter and Facebook: the ALS Ice Bucket Challenge. Celebrities from Taylor Swift to LeBron James all doused themselves with a large bucket of ice-cold water—on video no less!—to help raise awareness and money for ALS.

While the Ice Bucket Challenge is now somewhat synonymous with ALS, it didn't start out that way. The challenge rules were fairly simple. You nominate up to three people to participate in the challenge. They can either donate $100 to their charity of choice—or dump a bucket of ice water on their heads. According to *Time* magazine, when Chris Kennedy, a former professional golfer from Florida was nominated to join the challenge, he selected The ALS Association as the beneficiary for his challenge. He had a cousin, Jeanette Senerchia, whose husband had been diagnosed with the disease.

While Jeanette originally planned to just donate money when Chris nominated her, she saw an opportunity to raise money for a newly formed baseball tournament started to honor her husband, Anthony Senerchia, Jr. She posted her own video—and then started challenging people to join in the fun, including Pat Quinn and Pete Frates, two well-known (and well-connected) PWALS and advocates. From there, the Ice Bucket Challenge grew exponentially, with millions of people across the globe participating in the viral sensation. The Ice Bucket Challenge ultimately raised more than $15 million that summer for ALS charities—and has pulled in hundreds of millions of dollars since.

Robert Blum takes part in the first Ice Bucket Challenge, dousing himself with ice cold water, along with approximately 50 other Cytokinetics employees, in 2014.

**Since 2014, Cytokinetics has participated in the Ice Bucket Challenge every August, with large numbers of the growing company joining in the fun.**

"Building awareness really is essential in trying to get support and research dollars—but I also think it plays a role in helping to improve time to diagnosis and getting more people interested in developing new therapies," said Diane Weiser, Senior Vice President, Corporate Affairs at Cytokinetics. "And the Ice Bucket Challenge managed, somehow, to do this to the nth degree. We were proud to take part in it."

On August 19, Cytokinetics was challenged to join the Ice Bucket Challenge by The ALS Network. Nearly half of the company's employees at the time—about 50 people—stood in front of company headquarters and endured the ice-cold showers from buckets filled to the brim. The event was then posted on YouTube and shared widely.

Cytokinetics' employees not only withstood the icy waters, they also collectively donated about $1,500 to the cause. That amount was then matched by the company. Since then, Cytokinetics has continued the tradition each year, said Mary Pomerantz, Senior Director of Patient Advocacy and Engagement.


"We realized early on that the more people are aware of what ALS is, the more hope there is for the ALS community," she said. "The challenge has resulted in more money being raised by non-profit organizations, more successful legislation regarding advancing ALS therapies at the federal level, and more funding for ALS research."

Pomerantz added that, beyond the public awareness and fundraising such campaigns can provide, there was also a vital human component to the Ice Bucket Challenge that, she believes, made it stand apart from other non-profit fundraising.

"So often, these individuals and their families suffer in silence," she said. "This challenge helped to give them more of a voice. It helped to increase better access to information to ALS associations and to ALS care, so that patients diagnosed with this disease can better navigate the journey ahead, no matter how short or long that may be."

# Real Commitment

**OVER THE PAST 15** years, Cytokinetics has embodied its corporate value of We > Me as company employees worked across the ALS ecosystem, expanding this value to external stakeholders as well. The company has done the utmost to serve PWALS—committing to help this vibrant, courageous community and, in doing so, helping it gain new knowledge, funding, awareness, and, perhaps most importantly, hope for the future.

Here are just a few of the ways Cytokinetics helped to fill gaps in the greater ALS community as it worked to develop two fast skeletal muscle troponin activators, *tirasemtiv* and *reldesemtiv*:

## Silicon Valley Walk to Defeat ALS

Each year, the various chapters of The ALS Association host a Walk to Defeat ALS event to help move the national community forward in their mission to find a cure. Since 1999, The ALS Network has held its own gathering in the Bay Area to raise both funds and awareness. Individual walkers and teams raise monies to help support care service programs, advocacy and public policy efforts, and ALS-specific research. Cytokinetics joined the Silicon Valley walk in 2010 as a team—within a few years, it became one of the event's leading sponsors.

"Cytokinetics always has a big group participating in these events—and that presence goes beyond any

***Below:*** **The Napa Valley Ride to Defeat ALS, held each year in California's picturesque wine country, offers routes for cyclists of all ages and abilities. In 2023, Cytokinetics clocked in more than 2,000 miles as a team, raising more than $42,000 to support The ALS Network.**

> It ***shows*** the community that the ***company*** and its employees are really engaged and ***care*** deeply about the people who ***live*** with this disease.

sponsorship that the company may provide," said Fisher. "It shows the community that the company and its employees are really engaged and care deeply about the people who live with this disease. They show up to make a difference."

### Napa Valley Ride to Defeat ALS

The ALS Network also hosts an annual bike ride fundraiser to raise money for ALS support and research in California's picturesque wine country. This one-day cycling event is designed for everyone—there's a century (100-mile) route for hardcore distance bikers, as well as other routes ranging in length and difficulty to appeal to cyclists of all ages and abilities. Cytokinetics first joined the Napa Valley Ride in 2015 as an unofficial participant. But, as with the Walk to Defeat ALS, the company became more involved over time, entering teams each year, as well as providing different levels of sponsorship. In 2023, nearly 60 employees, family members, and friends of the company joined the ride, clocking in more than 2,000 miles as a team. The group also raised more than $42,000 to support The ALS Network's many programs to support people living with ALS, as well as their families, friends, and caregivers.




## Ringing NASDAQ Bell in Recognition of ALS Awareness

To usher in ALS Awareness Month, Cytokinetics, together with The ALS Association, rang NASDAQ's closing bell on May 2, 2016, reaffirming the company's commitment to the greater ALS community. This symbolic action helped to spur ongoing efforts to grow public awareness, education, and research activities to help PWALS. In a press release announcing the honor, Blum said, "These are promising and hopeful times for both our company and the ALS community, and we are honored to ring in ALS Awareness month in recognition of the great strides we are taking to urgently advance the development of an investigational medicine for the potential treatment of ALS."

*Left:* **Fady Malik, M.D., Ph.D., and Leo Kim after the Ice Bucket Challenge in 2016.**

*Center:* **Robert Blum rings the NASDAQ Bell in honor of ALS Awareness Month on May 2, 2016.**

## ALS on the Hill

Over the past 10 years, Cytokinetics has joined other key members of the ALS community to meet with members of the United States Congress to encourage them to pass critical legislation that will improve the lives of PWALS. The company has worked with other stakeholders, including I AM ALS and The ALS Association, to advocate for increased education and awareness regarding ALS—as well as to push for increased funding for research and patient support.



## Donation of Placebo Data to PRO-ACT

To help further research, especially the search for reliable biomarkers in ALS, NEALS created a unique repository, the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database. Researchers and industry partners who conduct clinical trials have the option to donate their placebo data to this database—which can include blood, cerebrospinal fluid, and other biological samples—to build up a data bank as well as a specialized biobank of clinical specimens to spur basic science research. (All patient data and samples are managed in accordance with applicable U.S. state and federal, or national European, requirements.)

"Cytokinetics was one of the first companies to donate data to this open data source—and they did so without hesitation." Dr. Cudkowicz said. "We ask everyone doing clinical trials to donate their placebo data, but many won't because they feel it's proprietary information. But it was never in question with Cytokinetics. The database now contains data and clinical specimens from over 20,000 people—and researchers from all over the world can use it to help us better understand this really complex disease."

***Above:*** **President Joseph R. Biden signs the Accelerating Access to Critical Therapies for ALS Act into law on December 23, 2021.**


*Above:* **Members of the ALS community meet outside the U.S. Capitol before meeting with lawmakers as part of the annual ALS on the Hill event.**

## FDA Consensus Document for Advancing ALS Therapies

In 2018, the FDA published draft guidance regarding the clinical development of new therapies for ALS, with a focus on efficacy and safety in the *Federal Register*. The FDA requested comments from community stakeholders about the suggested framework. Given the fast progression of ALS—and the lack of available therapies—the greater ALS community banded together and called upon the FDA to exercise its "regulatory flexibility" to support clinical trial designs that will help get treatments to patients faster. Blum said that Cytokinetics started working with key opinion leaders and advocacy groups to help the FDA understand the value of adaptive study designs to help fast track approval for new drugs to benefit PWALS.

"We joined with the academics to help the FDA understand the willingness of patients in this community to accept more risks in order to potentially benefit from more medicines," said Blum. "Dr. Wolff worked with many of these leading researchers to create a position paper in 2019, which laid out a framework by which clinical trials for ALS treatments

could be conducted more efficiently, with trial endpoints that would be meaningful to patients but also approvable. This position paper helped the FDA sharpen its thinking and provide more clarity on what was expected of industry and researchers in order to bring new medicines forward for patients with ALS. That paper has provided more focus in our conduct of clinical studies, eliminating many of the questions and uncertainties about what should be acceptable for FDA approval in the future."

There's a lot to be ***learned*** from ***looking*** at the patient and caregiver ***experience***, especially as we work to ***advance*** new medicines.

## Voice of the Patient Initiative

In 2017, Cytokinetics, in partnership with The ALS Association as well as a number of other industry and community stakeholders, sponsored IMPACT-ALS, a survey designed to capture the perspectives of PWALS, as well as their caregivers, about the burden of living with ALS, what they see as important functional outcomes for potential treatments, and their thoughts on clinical trials. After surveying more than 1,500 people, the stakeholders came together to publish the *ALS Voice of the Patient* report in 2019, which communicated the needs and desires of PWALS and their families. It was the first time such data had been collected across such a diverse group of people affected by this disease.

"We thought it was important to participate in initiatives to help bring more uniformity to clinical research—and help the FDA understand the voice of the patient and what really matters when it comes to treatments," said Blum. "We worked with investigators to figure out how to better communicate with patients so they could understand the availability of clinical studies. We worked with advocacy groups to help make patients more aware of clinical studies, available care services, and ways to find one another. This was just one part of being a meaningful member of this community. We even brought other industry partners together, convening stakeholders, so they, too, could understand how to better join forces within this remarkable ecosystem to make a difference for patients living with ALS."

Cytokinetics then supported a similar initiative in Europe, presenting findings to the EMA. Dr. Hardiman said this effort was very important to helping regulatory agencies and policy makers understand what PWALS really need from future therapies.

"This kind of contribution is very valuable," she said. "And it gives a voice to people who might not usually have one at these levels. And there's a lot to be learned from looking at the patient and caregiver experience, especially as we work to advance new medicines."

Brian Wallach, a PWALS and founder of I AM ALS, an ALS advocacy organization, agreed—and added that it can offer a perspective that many have never been privy to before.

"I've found that many researchers who are working on this disease had never met a person

living with ALS until they met me," he said. "But when they do meet someone—and they learn more about what it's like to live with this disease—it helps to make clear why we must move so urgently. Most of us only have two to three years after diagnosis. That sense of urgency is everything—and must inform everyone's work so they can move further and faster and help get people the therapies they need."

## Accelerating Access to Critical Therapies for ALS Act

With so few treatment options available, I AM ALS spearheaded new, groundbreaking legislation to help advance new therapies for the disease. In 2020, the United States Congress introduced a new bill, the Accelerating Access to Critical Therapies for ALS Act (often called the ACT for ALS Act). The bill called for expanded access programs to provide promising treatments to patients who might not be eligible for clinical trials, an FDA-NIH partnership to help speed the development and approval of new therapies for rare neurodegenerative diseases, and a new grant program to fund ALS research programs. Wallach credited Cytokinetics for not only advocating for this act—but also for being open to providing open access programs even before ACT for ALS was signed into law in 2021.

"Ninety percent of people living with ALS cannot qualify for any clinical trials," he said. "The law provides $75 million every year for five years to fund expanded access programs—that's enough to provide funding for almost every biopharmaceutical company to have an expanded access program along their Phase 3 trial. Not only does this bill help patients who might not be eligible to receive these investigational treatments, these expanded access programs also provide important data to the FDA that can help validate data from the clinical trial when the new treatment comes up for approval."

## EUpALS Formation

Cytokinetics was also instrumental in helping Evy Reviers, then President of ALS Liga België, a Belgian advocacy group, develop an overarching European advocacy organization, the European Organization for Professionals and Patients with ALS (EUpALS). After meeting Blum at an International Symposium on ALS/MND meeting, she said they discussed the importance of creating an umbrella organization to ensure that PWALS across different European countries had the same access to information about clinical trials—as well as appropriate access to potential treatments coming to market.

> ***Most of us*** only have two to three years after diagnosis. That sense of ***urgency*** is everything—and must inform everyone's work so they can move further and ***faster*** and ***help*** get people the ***therapies*** they need.


***Above:*** **Attendees of the 2019 International Symposium on ALS/MND in Perth, Australia, including the Cytokinetics *reldesemtiv* team, came together to take part in an awareness walk during the meeting.**

"We talked about the different gaps we saw in Europe, especially when it came to including Eastern European countries in the community, and how important it was to find a way to bridge them," she said. "It was the encouragement I got from Robert that made me realize how important it was to create this umbrella organization—and that I could be the one to do it."

Blum, for his part, said he was immediately struck by Reviers' passion for ALS advocacy. He knew, that with the right support, she could be successful in creating this much-needed new group. The organization opened its doors in 2020.

"[Reviers] has an extraordinary talent for bringing people together—she just needed a little bit of support to make this idea that she had into something actionable," he explained. "We wanted to provide corporate contribution support to help enable her to form an organization with a legal structure, financial support, and some of the best practices that we had learned to help channel her passion into something fruitful."

**MOMENTS THAT MATTER**

# Andrew Wolff, M.D., Former Chief Medical Officer

Once Cytokinetics started working on *tirasemtiv*, Dr. Wolff was a regular at the International Symposium on ALS/MND meeting. On the first day of the conference, there is a special session for the International Alliance of ALS/MND Associations, including organizations like The ALS Association. At his first meeting, Dr. Wolff went to that session—and was surprised to see he was the only person from industry in attendance.

"This session seemed quite relevant to me. But when I looked around, I quickly realized I was the only person there from a biopharmaceutical company. Everyone else there was from one of the ALS organizations. I sat in the back of the room and just wanted to hide at first because I thought that I had overstepped by coming," he said. "But, at the first coffee break, all of these people came up to me to thank me for coming. They told me I was the first person from industry to ever come to this part of the meeting. Person after person said they were happy I was there, that they wished more industry professionals would come. Well, I quickly realized the benefit of being there and listening to what they had to say about trials and therapies. Today, a lot of industry representatives go to that session, likely because I've told this story so many times. What I thought initially might be a mistake has helped to foster a lot of incredible relationships over the years."

"When I looked around, I quickly realized I was the only person there from a biopharmaceutical company."

## Grants and Sponsorships

Throughout its ALS journey, Cytokinetics has also provided a variety of sponsorships for different research meetings and advocacy events, as well as grants for different organizations. This included sponsoring the annual International Symposium on ALS/MND, administrated by the MND Association in the United Kingdom. Cytokinetics has provided lead sponsorship for this important annual meeting for more than a decade.

"The ALS community is this intimate, dedicated community—and any opportunity to bring healthcare providers, advocacy organizations, key opinion leaders, and people living with ALS together benefits everyone," said Laura Gschwind, Director of Marketing and Communications at Cytokinetics. "And our decision to get so involved was really driven by Robert. He set the tone so we could create meaningful partnerships to help enhance the greater community."

The company also started an annual communications grant program in 2018, providing five grants of $20,000 each to different advocacy organizations to support increased capacity in communication, awareness building, and community engagement. The grants support projects to help increase access to resources, grow organizational reach, and launch new educational programs. Grant winners in the ALS space have included NEALS, the ALS Therapy Development Institute, and the Les Turner ALS Foundation, just to name a few.

"As we worked with these incredible organizations over the years, we came to this revelation that many of these groups do not get a lot of budget or resources to support patient-focused communications," said Weiser. "We created this grant program so we could be a strong partner to the advocacy community and to support these different organizations in as many ways as we could. And, as a result, we've been able to develop some wonderful collaborations between ourselves and other organizations to help improve outreach and education."

This list of community involvement is far from exhaustive. Cytokinetics, said Jordan, has taken its place as a trusted member of the greater ALS community thanks to its core values of "commitment and consistency." He added that the company's success in connecting with so many different community players can be chalked up to wanting to be a partner, rather than just a sponsor. The company's networking and community efforts have provided a clear blueprint for others to follow in the future. Jordan said it all starts with two intentional steps: showing up and listening.

"To solve any problem, you have to work with the people who are directly dealing with it. You can't just show up and say, 'Look, I've got a solution!' and take a step back. We were able to become part of this community because we knew, when we started, that we were a guest," said Jordan. "When we started to do trials with *tirasemtiv*, we understood that we were there to listen and to learn. And, over time, by showing up in that way, we became a friend to the community—and then, as more time went by, we became part of the family. From there, we were in a position to really contribute to improve things in ways beyond bringing a potential new therapy to market. We were able to partner within this greater ecosystem to help make things better for people living with ALS whether we ever brought a therapy to market or not."

4

# Patients Are Our North Star

Ensuring that “patient-centricity” is more than just an industry buzzword

**SHELLEY HOOVER**
with her niece

*In 2010, the Patient Protection and Affordable Care Act (ACA)* was signed into law—and, with it, a mandate to make healthcare, including the development of new treatments for diseases, more "patient-centric." Simply defined, patient-centricity involves open and sustained engagement with patients to better understand their needs. In centering their work around patient needs, clinicians, researchers, and biopharmaceutical companies can help drive better healthcare experiences and outcomes for individuals who are diagnosed with both acute and chronic disease.

In the years since, "patient-centricity" has become a bit of a buzzword in the drug development space. Many companies talk about patients being at the center of all they do. However, there is a stark difference between talking about patient-centricity and developing new therapies, conducting clinical trials, and creating patient support and education programs that truly keep the patient both in mind and at heart. Cytokinetics understood, from the very beginning, how important it was to "walk the walk." Moreover, the company remained an active part of the ALS community even as *tirasemtiv* and *reldesemtiv* failed to meet clinical efficacy endpoints in Phase 3 trials—continuing to honor its commitments and sponsorships in the ALS space more than half a year after the results of COURAGE-ALS were released.

For Blum, "patient-centricity" involves much more than just fostering a symbiotic relationship with PWALS to help facilitate drug development. It's about doing the right and ethical thing.

"We have a strong moral compass, and we do work that is rooted in good science—both things illuminated our way forward," said Blum. "Once you meet these patients, and you hear their stories, you can't help but do right by them. Because if you are doing right by them, you are doing right by the company and your business."

Many companies talk about patients being at the center of all they do. However, there is a stark difference between talking about patient-centricity and developing new therapies, conducting clinical trials, and creating patient support and education programs that truly keep the patient both in mind and at heart.

# Finding Inspiration

**BECOMING AN ACTIVE MEMBER** of the greater ALS community helped Cytokinetics leaders, from R&D to Marketing, better understand PWALS and caregiver needs—as well as what PWALS specifically needed (and wanted) from any future therapies. Blum said it was clear, from the beginning, that those lessons needed to be shared with the entire organization. There was no point in developing a particular drug if patients did not see the value in it—or would not be able to access it.

"Early into our journey, it was clear to me that, if we were going to have a real impact, we needed to do more than just speak to patient-centricity. We needed, as a company, to live it," said Blum. "That started by inviting PWALS to engage with our scientists so they could also see the future in our research—and, equally as important, they could inspire our scientists, providing a catalyst to ignite their creativity of thought and push the boundaries of our work."

Ryan Farnsworth, whom Blum met at an ALS fundraising event, was one of the PWALS who visited company headquarters. Trisha Rice, his mother, said that he spoke about his diagnosis—and his personal experience living with ALS—back in 2017.

"Ryan talked and he shared some of his poetry—and I just remember all the love that we felt from the people listening," said Rice. "People who work in science have a

***Above:*** **Farnsworth, and his mother Trisha Rice, standing with Cytokinetics employees after sharing his story at a company town hall meeting.**

***Right:*** **Ryan Farnsworth and Robert Blum at the Muscular Dystrophy Association Toast to Life Gala in 2018.**

***Below:*** **Cytokinetics hosted an Every Drop Adds Up Arts Festival in 2017, as a spin on the Ice Bucket Challenge. There, Farnsworth read from poems from his book *Seeds of Light Sown*.**


> Having the ***privilege*** of hearing these stories, of talking to patients firsthand, of sitting in on patient checkups on ***clinic*** days—it shows us what really ***matters***.

passion for science. We all understand that. But when you can listen to someone talk about their lived experience with a disease, I think it really brings home how real it is and just how urgently people with ALS need therapies to help them. It can help guide that passion for science. It can help make the science even better."

Dr. Hwee agreed. He said those company visits were powerful reminders of why the R&D team's work on *tirasemtiv* and *reldesemtiv* was so critical.

"In the laboratory, you can sometimes get caught up on all the little day-to-day stuff you have to do. But you have to think in the long term—what is all this work really leading to?" he explained. "Having the privilege of hearing these stories, of talking to patients firsthand, of sitting in on patient checkups on clinic days—it shows us what really matters."

# Trisha Rice

***Trisha Rice*** welcomes any opportunity to talk about her son, Ryan Farnsworth. He was a poet. A lover of nature. An adventurer. A man who enjoyed hiking in the mountains, as well as snowboarding and cycling. He was also a strong advocate for PWALS.

"When Ryan was diagnosed in 2015, he was basically told to go live his best life—go do the things you can do while you can do them," said Rice. "It was done in a kind and loving way, but it really emphasized that there was very little that the doctors could do for him. The disease would progress, and he would have to make the most of the time he had left."

And that Ryan did. After moving home to California, he quickly connected with The ALS Network and began attending events. There, he became an active patient ambassador, telling his story to help raise awareness about the challenges of living with this relentlessly progressive disease.

After addressing the crowd at Walk to Defeat ALS in 2016, Ryan and Trisha first met Blum.

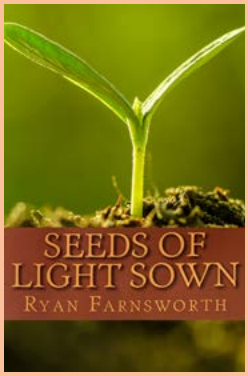
"Robert was at the very first walk we went to. At that point, Ryan was still able to stand at the podium to speak. He talked about his diagnosis and shared some of his poetry," said Rice. "This was actually his first time sharing his story. But Robert was so moved that he invited us to go to the Cytokinetics' office to share his story with the team."

Rice said that Ryan was initially a little reluctant. What could he tell seasoned researchers and industry folks that they didn't already know? But he decided to go anyway, Rice said, and enjoyed the experience immensely.

"It was a lovely little luncheon with the whole team that works there," she said. "They listened so intently to him—and it was clear that they were working so hard on trying to find treatments and cures for ALS. From there, Ryan started to do other events with Cytokinetics, and it was such a beautiful thing, to see this outpouring of love and support with so many people coming together in this fight against this disease."

Unfortunately, Ryan passed away in 2019. But Rice remains committed to the fight. She continues to share Ryan's story and his poetry, as well as educate people about the needs of people who care for those diagnosed with ALS.

"There's so much to caring for someone who is living with this disease—and there is a lot that people who are trying to develop treatments




can learn about what will make a difference as they start to lose more function," she said. "And I appreciate every opportunity to connect with other families affected by ALS, with the people who are trying to develop new therapies, because I remain dedicated to finding a cure, finding treatments, to finding whatever we can to bring more time and hope to the whole ALS community."

There's so much to caring for someone who is living with this disease—and there is a lot that people who are trying to develop treatments can learn about what will make a difference as they start to lose more function.

# Beyond the Norm

**CYTOKINETICS HAS ALWAYS** been at the forefront of patient-forward science. Yet, as the company started thinking about Phase 3 trials for *reldesemtiv*, it also wanted to expand advocacy initiatives. In 2020, the company recruited Pomerantz, a seasoned patient advocacy professional, to take that type of work to the next level as the Senior Director of Patient Advocacy and Engagement. She said she was inspired to join the organization because its work consistently demonstrated a strong belief that "a rising tide lifts all boats."

"What made it very easy to join the company was that the executives had long supported a strong culture of patient advocacy and had done so from the very beginning," she said. "But by having someone in a full-time role, it meant we could deepen the relationships we had with advocacy groups, build new relationships with emerging organizations, and continue our mission to help patients, families, and caregivers."

Weiser said, at this point, the company had developed official guidelines about how to engage with patients "as a part of doing business."

"Patient advocacy is more than just bringing in a patient to speak at a town hall meeting. Everybody does that," she said. "It's having patient advisory councils to provide perspective on all facets of the drug development process. It's adding a patient to a steering committee for

***Above:*** **Robert Blum speaking with Dr. Hermangi Sane, a PWALS, at the 2023 International Symposium on ALS/MND held in Basel, Switzerland.**

## Getting to the Heart of What Matters

The few approved ALS therapies on the market today offer PWALS one of two things: increased time of survival or longer maintenance of a score on a functional metric known as the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRS-R), which assesses functions ranging from walking to turning over in bed. Many patient advocacy groups, however, have said that these two endpoints aren't enough. Even if a cure for ALS is not possible at this point, they would like to see a therapy that can improve their day-to-day function—and allow them to live independently for a longer period of time.

Cytokinetics' Patient Advisory Council highlighted several important domains that PWALS would like to see in future. These domains include:

- Independence
- Autonomy
- Control over their choices, therapies, and healthcare provider interactions
- Self-dignity
- Focus on living today
- Quality of life over quantity of life
- A sense of hope and resolve

a clinical trial. It's getting patient input on pill size, packaging, and marketing efforts. It's about finding ways to appropriately get patient input on all critical business decisions."

That's why, Blum said, Cytokinetics even includes patient-centered criteria in performance evaluations for its employees.

"Being patient-centered starts with recruiting the right people and assessing that they are considering the patient in their work in a tangible way in our recruiting process," he said. "We are always working to evolve so that we can do more. It starts with listening to patients—as most biopharmaceutical companies do now—but also going beyond that. We constantly convene patients to speak with us about what they need and what they want, and we hold ourselves accountable to that."

He added that "living" patient-centricity also means constantly reevaluating what it is—and how it should best be done. "We are committed to further redefining our efforts because, if we are going to be developing and commercializing medicines, it's not good enough for them to just be approved by the FDA," he explained. "Those medicines need to address specific problems for patients and families—and they need to be accessible and affordable. There are major barriers to being truly patient-centric. But we continue to work, as an organization, to overcome them."

# Gwen Petersen

***Gwen Petersen*** was only 32 years old when she started having trouble with her balance. She noticed that her left foot was scuffing the floor as she walked—and falling was becoming a regular occurrence. When she went to see her primary care physician about those issues, he diagnosed her with anxiety. It would be another 18 months, with referrals to psychiatrists and neurologists, before a doctor would finally look at her walking and realize she had ALS.

"I had no medical history of anxiety. I was about to get married. I had just started a great new job as a recruiter for a big medical center. I had a great group of friends," she said. "I was essentially chasing my tail, despite having fairly obvious early physical manifestations of the disease and getting the wrong diagnoses. It was really frustrating."

Petersen channeled that frustration into advocacy. After participating in a clinical trial, she applied to a unique certification course offered by NEALS called the Clinical Research Learning Institute to gain the skills and knowledge required to become an ALS Research Ambassador.

"After my diagnosis, I had genetic testing and learned that I tested negative for all the known ALS genes. I have no family history of ALS, so I fall squarely into that more than 90% sporadic cohort," she said. "We simply don't know enough about why people like me get ALS. That's why I wanted to work with the researchers and the different community partners who were trying to find out. I also wanted to help move the needle toward real disease-modifying treatments that will either slow or stop the progression of disease."

After completing the NEALS program, Petersen met Pomerantz. She said she appreciated that Pomerantz, as well as Cytokinetics as a company, put a high premium on patient advocates. She joined the company's Patient Advisory Council for *reldesemtiv*, providing her lived experience with ALS to help the company design its upcoming Phase 3 clinical trial for the muscle-targeted drug.

"Mary really reinforced the value of patient advocates—who we are, what we are capable of, and what we can offer to companies. She's always put patient advisors on the same level as scientific advisors—and that's important," she said. "There aren't that many of us who have the strength and stamina to do this kind of work. ALS progresses so fast—and our time and experience is valuable. It is important to work with companies who understand that."

Today, Petersen remains actively engaged in advocacy work. But she also makes sure she has plenty of time to spend with her husband, Nathan,

her friends and family, and her dog, Annabelle. On weekends, you can usually find her walking with Nathan and Annabelle on the walking trails around her home in Connecticut. When asked what advice she has for PWALS, Petersen is quick to answer.

"Do what makes you happy. It doesn't have to be one thing," she said. "For me, that's advocacy. I'm inspired by the work and feel lucky that I still have the energy to do it. But my hope is that people living with ALS do whatever inspires them—and make sure their time, however long it is, is filled with the things they love the most."

There aren't many of us who have the strength and stamina to do this kind of work. ALS progresses so fast—and our time and experience is valuable.

# Elevating the Patient Voice

**ONE OF POMERANTZ'S FIRST** tasks was convening a patient advisory council to help guide *reldesemtiv* development— as well as provide insights on how to reduce patient burden in clinical trials. Gwen Petersen was one of the first members of the council—and she said she appreciated that Pomerantz put patient advisors on the same level as scientific ones.

"Mary, from the very beginning, was clear that we had worth not only as patients living with ALS, but as consultants to help companies make key business decisions," she said. "Mary's intent—both in terms of words and actions—were that patient advisors and scientific advisors were basically one and the same. We were contracted, paid for our time, and addressed as advisors as opposed to subjects. They made it clear that we had an important role in helping to advance new therapies."

Philip Green, a PWALS who also served on the patient advisory council, said he appreciated that Cytokinetics was very open to hearing the patient perspective.

"They really listened, and they did everything they responsibly could to accommodate our needs," he said. "Other companies often think they know what is best for patients without ever asking. They just assume. But Cytokinetics not only listened, but they also tried to incorporate our feedback and follow up to make sure they had it right."

***Above:*** **Even after her diagnosis, Lindsay Abromaitis-Smith knew how important it was to continue making art—and it became part of the way she advocated for the ALS community.**

***Left:*** **Sunny Brous and her husband speak with members of the Cytokinetics team at the 2023 International Symposium on ALS/MND in Basel, Switzerland.**

> Having regular ***access*** to the patient ***voice*** to get that feedback, to ***understand*** what really mattered, was ***invaluable***.

Dr. Rudnicki said the patient advisory council became the company's "built-in barometer," an important check and balance to make sure the organization was moving in the right direction as it developed protocols for clinical trials.

"One of the things we've always been open to exploring is new clinical trial endpoints. We were the first company to do an ALS interventional trial that included at-home vital capacity, a breathing assessment, to help reduce how often patients in trials had to come into the clinic," she said. "But we also knew how important it was to think about ways to measure things that really make a difference to patients living with ALS. Things like time until you need a wheelchair, a percutaneous endoscopic gastrostomy (PEG) tube for feeding, or a breathing machine. Having regular access to the patient voice to get that feedback, to understand what really mattered, was invaluable."

# Access Programs

**BEFORE POMERANTZ** joined Cytokinetics, the company had supported a managed access program for *tirasemtiv*. Managed access programs provide investigational drugs to eligible patients at the cost of the developing company. When Cytokinetics abandoned *tirasemtiv* because of its side effects profile—which included dizziness and fatigue—it immediately had *reldesemtiv*, the next-in-class fast skeletal muscle troponin activator, at the ready. But many trial participants felt they had gotten some benefit from the original drug. They did not want to stop taking *tirasemtiv*. Weiser said the company immediately convened an advisory board meeting with physicians, regulators, patient and disease advocates, and a bioethicist to talk about how to move forward.

"We didn't want to take away a drug that people thought was helping them," said Weiser. "But we wanted to do things the right way."

That input allowed trial participants who felt they had gotten some benefit from the original drug to continue receiving it.

"There are so many elements to patient-centricity. But it all comes down to serving patients," said Jordan. "That means you have to be very transparent. We have to share our data, show you why something worked or didn't work, and then, if you felt it did work and you took the risks to participate in our trial, we have some kind of obligation to continue to provide that therapy as long as we aren't putting you in harm's way."

Later, after thoughtful discussion and consideration, Cytokinetics decided it would also provide former trial participants access to *reldesemtiv*, too. Some patients had been receiving *tirasemtiv* through the managed access program for several years when COURAGE-ALS started enrolling participants in 2021.

"The *tirasemtiv* drug supply was almost depleted, so the people who were on that managed access program were going to be transitioned to a managed access program for *reldesemtiv*," said Pomerantz. "One of the things we keep hearing from patients is that it is hard to get into a clinical trial, they want access to these investigational drugs. We were actually going to open it up so that any patient who had been in a Cytokinetics ALS clinical trial would have the opportunity to enroll in the *reldesemtiv* managed access program. This was something I was really proud of—and it was patient advocacy that led the company to make the decision to support this program."

**MOMENTS THAT MATTER**

## Diane Weiser, Senior Vice President, Corporate Affairs

Weiser said she was always struck by the people that she met at different internal and external events to support the ALS community. She said they always reminded her—as well as her colleagues—about the importance of the work they were doing. But the work she did with an outside production company to create short documentaries about PWALS really hit home.

"The first one we did was with a military veteran. He had met his wife when he was a cadet at West Point and, together, they told the story of how they met—and then their adventures as a military family living all over the world," she said. "Just six months after he transitioned to civilian life, he was diagnosed with ALS. He's a fighter. His wife is a fighter. And they are fighting for a cure. Over the years, they have become my friends. We see each other when we are in the same town. I follow them on Facebook—they have grandkids now. These people just touched my life in so many ways. They show such courage and selflessness in sharing their stories. And while they were the first people who were affected by ALS that I got to know in this way, they weren't the last. We do what we do for them. All of them."

At the same time, however, patient advocacy organizations around the globe were also calling for pharmaceutical developers to provide expanded access programs for PWALS. Individuals who might not be eligible for any clinical trial could apply to participate—and, as a result, gain access to investigational medicines that might help slow the course of ALS disease. While the ACT for ALS Act provided funding for expanded access programs when it was signed into law in 2021, Cytokinetics had already committed to supporting its own expanded access program before then.

"Patient-centricity is also about remembering that patients living with this disease are human—they are people who want to be recognized beyond their disease," said Pomerantz. "Given that ALS is so physically debilitating, and it moves so quickly, providing access to an investigational drug through these kinds of programs can make a real difference. Unfortunately, our expanded access program was stopped in its tracks because COURAGE-ALS didn't meet its endpoints."

# Lending Expertise

**DR. DICKIE SAID HE** has been impressed by Cytokinetics' commitment to patient-centricity. "I've always used Cytokinetics as a yardstick to measure other companies regarding how to communicate with patient associations and work with patients living with ALS," he said. "Certainly, on the clinical, health, and social side of things, understanding the real-world patient experience is vital. Developing an effective therapy for ALS is a complex jigsaw puzzle—and we only have a limited number of pieces at the moment. But sharing information, working with the top researchers, being transparent about your work, and listening to what patients need—that, ultimately, is what will move us forward."

Cytokinetics' passion and expertise for patient engagement was so highly regarded in the greater ALS community, in fact, that the company offered its services on a consulting basis to other biopharmaceutical organizations.

"What we did could help other companies maybe get to a therapy faster," said Allegra. "We thought that we could loan our expertise and our wonderful team to help. It was a little bit of an off-the-wall idea. But we developed the skills to elevate the patient voice and to forge great and meaningful relationships with the entire community. If we could partner with other companies with the same goal of developing a new therapy, we could help. Because the patient is our North Star—and we are so committed to the ALS community—we thought our integrated strategy, which aligned everybody within our team—could make a big difference for others."

Blum said it illustrates just how dedicated the Cytokinetics team remains to patient-centricity, patient advocacy, and finding ways to help families affected by this devastating disease.

"From the beginning, we wanted to commit in a purposeful way to patients living with ALS and the larger ALS community. That started with meeting them where they are," he said. "It began with the patient and being inspired by patients and caregivers and doing everything we can for their benefit. And we quickly learned, if you are doing right by the patient, you listen—but you do much more than that. You elevate their voices so others can hear them, too. You find ways to serve them beyond just seeking new medicines."

***Right, top:*** **Monique Green and her mother, Pearl, photographed as part of the *Make Muscle Matter* campaign.**

> Cytokinetics' passion and ***expertise*** for patient engagement was so ***highly*** regarded in the greater ALS community, in fact, that the company offered its services on a ***consulting*** basis to other ***biopharmaceutical*** organizations.

***Left:*** **Lisa Bonahoom and her husband, Bob, demonstrate the importance of continued independence through muscle strength as part of the *Make Muscle Matter* campaign.**

5

# Setting the Gold Standard for Clinical Trials

In elevating the patient voice, Cytokinetics ushered in new clinical trial protocols to ease patient burden


RYAN FARNSWORTH

*Between the lack of effective therapies available to PWALS* and the relentless progression of the disease, many advocacy groups have called for reforms in the way that clinical trials are conducted. In consistently elevating the patient voice, Cytokinetics heeded that call—and looked for new ways to increase access to its investigational medicines as well as reduce the burden for those who participated in its trials.

"Patient advocacy organizations like I AM ALS, to their credit, looked at clinical trials and asked, 'Why does it have to be this way?'" said Blum. "Certainly, the FDA has certain expectations and requirements for how a trial should be run. There are certain statistical methodologies that must be considered when designing a study. But why should patients living with ALS, who have so few options and so little time, have to accept that they cannot participate in a clinical trial—or that, if they do, they may only get the placebo?"

There are myriad challenges involved with developing a strong clinical trial, particularly in the ALS space. Biopharmaceutical companies looking to test an investigational therapy for ALS must first consider just how heterogenous the patient population is. A therapy that works for a familial form of the disease may not work for those who fall into the sporadic category. Determining the right inclusion

criteria—that is, which PWALS are eligible to participate—is also difficult. Companies must weigh the need to show the efficacy of the drug in a target group with the need to offer "more seats on the bus," or more opportunities for patients to participate.

The rapid progression of ALS symptoms is also a barrier, with most people surviving only a few years after diagnosis, meaning that most PWALS will only be able to participate in a single trial. It makes it even more imperative that clinical trials provide not only hope, but strong potential of a positive outcome. Biopharmaceutical companies must also come up with the right endpoints for trials to determine efficacy. This is important not only to ensure that a particular therapy will meet the needs of PWALS but has strong enough data to garner both FDA and payer approvals. Then there's the matter of trial length—researchers must find a timeline that provides enough time for the human body to respond to a drug but isn't too short to provide scientific evidence of its efficacy. The trial also can't be too long—it would be nice for the PWALS who selflessly volunteered to participate to survive long enough to know the outcome of the study.

Dr. Ingre said that Cytokinetics, as compared to other biopharmaceutical companies pursuing new therapies, has always been "devoted" to helping the ALS community. From the very beginning, she said, they

spent a lot of time considering these challenges—and worked hard to ensure their clinical trials were centered around the PWALS so desperate for new treatments.

"[Cytokinetics] has always been concerned about the patient's experience in their studies—and learned from one study to the next about how to make things better," she said. "As a result, the patients who participated have been really pleased to be part of them."

In order to design sound clinical trial protocols, Cytokinetics looked to the people who understand the disease best. Those stakeholders included PWALS, of course, but also caregivers, key opinion leaders, regulatory agencies, health technology assessment (HTA) bodies, and others. The idea was to get input and advice throughout the development from all the stakeholders in the ALS field. And to listen to their voices by making possible necessary modifications to the protocols. By gathering these inputs, they could better overcome many of the barriers that their predecessors faced—and develop trials that PWALS could champion.

In order to design sound clinical trial protocols, Cytokinetics looked to the people who understand the disease best.

# Timeline of Drug Approvals in ALS

**1995**
**2018**
**2019**

***RILUZOLE*** (Tiglutik, a thickened liquid formulation of the drug, which can be taken orally or via PEG tube, was approved in 2018, and Exservan, an oral film formulation, was approved in 2019).

**Mechanism of action:** Inhibits glutamate release in the brain, preventing glutamate toxicity.

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**2017**

***EDARAVONE*** (Radicava)

**Mechanism of action:** Targets reactive molecules that lead to oxidative stress.

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**2022**

***ORAL EDARAVONE*** (Radicava ORS)

**Mechanism of action:** Targets reactive molecules that lead to oxidative stress.

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**2022**

**AMX0035** (Relyvrio)

**Mechanism of action:** Blocks stress signals in nerve cells, protecting mitochondria and endoplasmic reticulum in motor neurons.

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**2023**

***TOFERSEN*** (Qalsody)

**Mechanism of action:** Targets mRNA from SOD1 mutations, reducing the production of toxic proteins.

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# Reducing the Burden

**WHILE THE COMPANY WORKED** to include the PWALS voice at all steps of development of *tirasemtiv* and *reldesemtiv*, Dr. Rudnicki said that the addition of the patient advisory council, as well as more input from ALS advocacy organizations, inspired ways to further reduce patient burden as it developed the clinical trial protocols for COURAGE-ALS, the Phase 3 clinical trial for *reldesemtiv*. She added that they also had an unexpected accomplice in their efforts: the COVID-19 pandemic.

"We had been talking for a long time about ways we could make the trials more patient-friendly and were figuring out how to get the data we needed without patients having to come into the clinic for every test," she said. "But, with the pandemic, it was suddenly unrealistic to expect patients to come to the clinic every month to have their blood drawn or their breathing tested. We quickly pivoted so that our patients could do more things at home."

Jacqueline Lee, Senior Director of Clinical Operations for Cytokinetics, said, with the help of the patient advisory council, the company carefully examined every measure—and found ways to allow PWALS to do these assessments from home.

***Below:*** **To understand how its compounds work on the muscle, Cytokinetics' research scientists conduct experiments at the cellular and molecular levels.**

"Our primary endpoint for COURAGE-ALS was the ALSFRS-R, but we were also looking at changes in forced vital capacity (FVC), changes in the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), which measures quality of life, and handgrip strength," she said. "We had to be very pragmatic—what do we really need and what's just a nice to have? By focusing on how important it was to make things less burdensome for patients, we were able to do more remote

**MOMENTS THAT MATTER**

## Scott Jordan, Senior Vice President, Global Marketing and Commercial Strategy

More than 10 years ago, Jordan and colleague Patrizia Allegra attended an ALS clinic day at a local center of excellence. He said the experience opened his eyes to what PWALS must contend with on a day-to-day basis. Even going to a center of excellence to receive care can be a struggle for PWALS and caregivers.

Coming in once every three months to be assessed by a multidisciplinary team, undergoing tests to measure their pulmonary function, nutritional needs, speech/language capabilities, motor function, and other key functional skills takes a great deal of effort, Jordan learned.

"With their consent, we visited with patients learning about their disease progression in the physician's office and sat there with the patient for hours while they went through the different tests," he said. "It really taught us how much work it takes for these patients just to get into the clinic for the day. That shaped how we thought about clinical trial protocol design. We wanted to find ways that we could monitor patients remotely—other ways to get the data we needed but do so in a way that makes it easier for them to participate in trials."

home visits, provide them with study equipment so they could do respiratory measures at home, and send out companies to do their blood draws. We quickly learned that you could get the data you need while making the process easier."

Dr. Rudnicki said it made all the difference. PWALS were able to live their lives during the trial—and not overextend themselves with monthly trips to the clinic.

"We had people go on vacations during the middle of the trial and still do their check-ins remotely," she said. "They weren't tied up so they couldn't do the important things in their personal lives. They could go see friends and family. They could take those bucket list trips. And, as their disease got worse, they didn't have to worry about long car rides to the clinic, finding a driver, or the fatigue of a visit. Reducing the burden was clearly something that resonated with patients living with ALS and their caregivers. And I definitely think it helped not only with recruitment, but retention during COURAGE-ALS."

# A Five-Star Rating

**IN 2020, I AM ALS** rolled out a new clinical trial rating system, the Patient-Centric Trial Design (PaCTD) Rating, to assess the different clinical trials for humaneness and efficiency. For several years, a team of dedicated PWALS, caregivers, and other stakeholders worked together to come up with criteria for this new rating system with the goal of educating PWALS about what trials were available—and what they entailed for those who participated in them.

The resulting criteria look at three main categories of patient-centricity: optimizing access, colloquially referred to as "seats on the bus," based on how drug developers were expanding access to investigational drugs; advancing scientific progress, or new innovations to further the field's understanding of ALS; and patient-friendliness, or the ability to reduce participant burden. Blum said these new criteria acted as a catalyst for Cytokinetics, helping the company to "stretch" so they could do more for PWALS.

"Maintaining the integrity of the science and complying with the regulatory authorities was always important. But these criteria helped bring home that, at the end of the day, we are serving patients, and our studies need to be inviting of patient participation in a way that matters to them," he said. "We decided to do things differently in our design that, at the time, went beyond the norm."


***Above:*** **I AM ALS, the advocacy organization founded by Brian Wallach and Sandra Abrevaya, provides a patient-centric rating system for all clinical trials investigating ALS treatments.**

***Right:*** **The COURAGE-ALS trial's assessment by I AM ALS, which resulted in a 5-star rating.**

That work, and the push to make COURAGE-ALS as patient-centric as possible, resulted in the trial receiving a 5-star rating from I AM ALS—its top score. By minimizing placebo usage to 33% or less during the first half of the trial and having all participants on *reldesemtiv* in the second half, Cytokinetics designed COURAGE-ALS to optimally address patient needs. By planning both an open label extension and expanded access program, the company would be able to provide *reldesemtiv* to participants after they completed their participation in the Phase 3 trial in addition offering it to those eligible for expanded access. The use of scientifically supportable inclusion criteria, as well as the decision to look at potential biomarkers, gave COURAGE-ALS top marks in the scientific progress category. The combination of these features, as well as the decision to have trial participants do more from home with telemedicine visits, mobile phone applications, and remote labs and assessments brought the trial the coveted 5-star rating.

"This was an incredible stamp of approval to receive from I AM ALS," said Pomerantz. "It showed the ALS community that this company cares. It gives participants who are looking to enroll in a trial confidence that they are working with someone who is thinking about their needs. And it also helped let people know about our trial and what we were trying to do with this new type of therapy."

I AM ALS

**I AM ALS Patient-Centric Trial Design (PaCTD) Rating for Cytokinetics' Courage**

| **I AM ALS Patient-Centric Trial Design (PaCTD)** | **Cytokinetics Courage Reldesemtiv** | |
|---|---|---|
| Open Label Extension | Yes | 1 |
| Minimize placebo usage: 33% or less | 33% placebo | 1 |
| A side by side Expanded Access Program | Enrolling 550 in COURAGE. Alleligible for OLE+EAP participants in prior trials | 1 |
| **Part 1 Total** | | **3** |
| **Part 1 Rating-Seats at the Table** | | **0.6** |
| Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design | Yes; crossover | 1 |
| Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.) | Yes; Two years from symptom onset. Vital capacity of 65%. ALS-FRS-R of 44 or less. *Riluzole* and Radicava are allowed | 1 |
| Investigation of biomarker | Yes; serum (blood), DNA, DME, muscle strength, PROs | 1 |
| Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial | Yes; In the second interim analysis | 1 |
| **Part 2 Total** | | **4** |
| **Part 2 Rating-Advancing Science Quickly** | | **0.3** |
| Use of Run-In Observation Period: 3 months not acceptable, 1 month ideally | No | 1 |
| Use of novel methods: wearables, telemedicine visits, financial burden | Yes; Novel methods; telemedicine visits, mobile phone apps, home nursing visit: remote labs, spirometry | 1 |
| **Part 3 Total** | | **2** |
| **Part 3 Rating—Patient-Friendly** | | **0.1** |
| **Total Rating** | | **1** |
| **x5** | | **5** |
| **I AM ALS PaCTD 5-Star Rating:** | | **5-Star** |

# Brian Wallach

***Brian Wallach*** has always been someone who strives for excellence.

After graduating from Yale University and Georgetown Law, he worked for Barack Obama's presidential campaign, eventually taking a position in the White House counsel's office once the 44th president took office. Several years later, he worked as a federal criminal prosecutor in the U.S. Attorney's office—and there were whispers that he might one day run for office himself. He was happily married to Sandra Abrevaya, another Obama campaign alum, with one young daughter and another baby on the way.

Then, while working long hours on a gun smuggling case for the Department of Justice, Wallach found that his left hand was repeatedly cramping up, making it hard to maneuver a pen. He didn't know what might be wrong. Unfortunately, just a few months later, on the same day he and his wife brought their newborn daughter home from the hospital, he was diagnosed with ALS. The neurologist said the disease was progressing quickly—he might only have 6 months left to live. The news was devastating, Wallach said.

"For a few months, we did not tell anyone about my diagnosis. Instead, we grieved as a family," he said. "But just after Christmas, I started to think about founding an ALS non-profit. I asked my wife if she would be okay with me doing that and, at first, she said, 'Hell, no.' But then she gave me an out: she said if I flew around the country, met with ALS non-profits, doctors, and patients, and could come back with some clear ideas about what we could do to uniquely help the fight, she would think about it."

Wallach took on that challenge. After flying around the country and meeting with a wide range of ALS stakeholders, he realized he and Abrevaya's background meant they not only knew a lot of the D.C. elite with connections—they also knew how government worked. Thanks to the Obama campaign, they were also experienced with community organizing. And, Wallach added, they knew the power of a good story in recruiting people to the fight.

"I presented all of this to Sandra in a 40-page PowerPoint presentation. No pictures, just a lot of words," Wallach said. "We launched our non-profit, I AM ALS, on January 22, 2019. Over the past few years, we've been able to build an amazing community that has passed two pieces of legislation, helped increase federal funding for ALS by almost $1 billion, and changed the narrative of life with ALS from one that was hopeless to one that shows we have real reasons for hope."

Over the past few years, we've been able to build an amazing community that has . . . changed the narrative of life with ALS from one that was hopeless to one that shows we have real reasons for hope.

The organization, like Wallach, continues to fiercely advocate for legislative and research advances to support PWALS. I AM ALS was instrumental to bringing ACT for ALS to President Joseph Biden's desk in 2021—and has also worked with companies like Cytokinetics to ensure that expanded access programs are available for patients, like Wallach, who are not eligible to participate in clinical trials.

"I am truly hopeful, thanks to the progress we've made over the past 10 years, identifying some of the genes that cause ALS and the different molecular pathways impacted by ALS," said Wallach. "And with those discoveries, we have seen more treatments come into the clinical pipeline, including some that are slowing or even stopping certain types of ALS. And that, for me, is everything. Because once you are able to stop one type of ALS, it gives you a greater understanding of the disease and other types of ALS. It enables us to develop more targeted treatments for this disease in the future."

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# Make Muscle Matter

"I will make the most of what is."


MONIQUE GREEN

*Putting on your watch. Writing with a pen. Brushing your* teeth. Picking up a fork. Tying your shoes. Combing your hair. Working with your hands. Cradling your baby. Walking down the stairs. These seemingly simple actions are part of everyday living. And one's ability to do them becomes compromised as ALS progressively weakens the body's muscles.

As Cytokinetics pursued a muscle-targeted therapy for ALS, employees understood they were taking a revolutionary approach to treatment. One that, upon first glance, patients and clinicians might not fully understand.

"There were no other medicines being developed for ALS that target the muscle—the therapies being investigated were all drugs that worked on the neurons because this is a neurodegenerative disease," said Allegra. "As we did market research and advisory board meetings, it became clear that some stakeholders might not understand what we were trying to do. And we understood that we had to educate people about the disease and the impact of the symptoms and the functions at work in ALS."

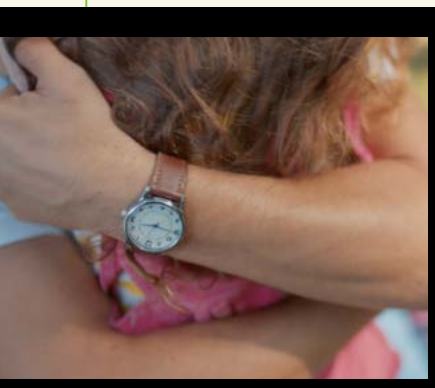
In 2020, Allegra and colleagues began to develop an education and outreach plan to help the greater ALS community grasp an idea of supreme importance: *Muscle preservation is an act of independence.* As Cytokinetics did with clinical trial protocol development, it reached

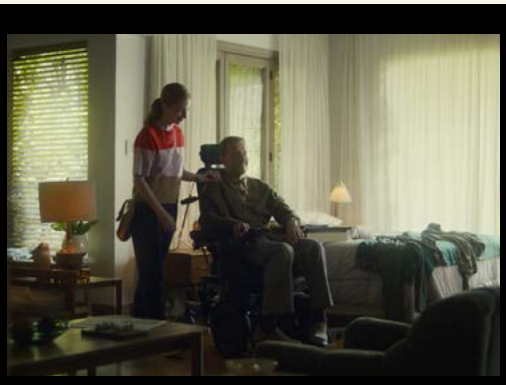
out to patients to help them craft a thoughtful campaign. The end result: *Make Muscle Matter*, a powerful, strategic, and heartwarming education program designed to emphasize the potential impact of muscle function in patients living with ALS.

"Patients need to preserve neurons—but they also need to preserve muscle to keep functioning," said Allegra. "Muscle is where the disease manifests itself. And without strong muscles, you will lose function, you will develop an impairment that gets in the way of doing the little things that allow you to remain independent and live life to its fullest."

The campaign included a compelling series of print images featuring real patients living with ALS. In one, a woman in her sixties, Lisa, holds a toothbrush. In another, Monique, in her forties, holds a fork. In the last image, Ajay, a neurologist who was diagnosed with ALS in his thirties, holds a pen.

"We worked closely with our patient advisory council (PAC) to guide this campaign," said Allegra. "And what we heard, time and time again, from the patients is that quality of life matters. They were very clear that they wanted to have and keep as much function as they could so they could spend their remaining time in the best possible way they could. In many ways, the patients saw the value in a potential muscle-targeted therapy that could help strengthen their muscles before many of the doctors did."





***Above:*** **Still images from *The Hands of Time*, the short film created to accompany the *Make Muscle Matter* campaign**

**GREEN, A MEMBER OF** the patient advisory council, said he appreciated Cytokinetics getting input from the PAC to emphasize the things that matter most to people who live with the disease day in and day out.

"Our voices matter—and we can have an impact and help change things," he said. "Our voices are instrumental in getting the kinds of therapies we need. Without our perspective, companies may not know what is difficult for us and what really matters to us."

In a short film developed for the *Make Muscle Matter* campaign, viewers see a man's disease progress over the course of his life. The story begins with him putting on his watch in the morning, kissing his wife goodbye, and heading to a woodshop to work. Later, you see him comforting his infant daughter when she wakes from her nap. Fast forward a few years, and the same man helps his young daughter snap on her helmet as she learns to ride her bike without training wheels. He quickly scoops her up into an embrace when she falls. Time jumps forward again—and now the same man, relying on a cane, walks his daughter down the aisle on her wedding day. In the final scene, the man, now confined to a wheelchair, attempts to put on his watch. His daughter, seeing him struggle with this small act, comes over to help him. The scene closes with the words, "Muscle has the strength to change the lives of people living with ALS."

> Muscle has the ***strength*** to ***change*** the lives of people living with ALS.

Lisa Bonahoom holds a toothbrush, demonstrating the importance of preserved muscle function, as part of the *Make Muscle Matter* campaign.

As PWALS lose muscle strength, the ability to grip can suffer. Here, Monique Green holds a fork—illustrating why preserved grip strength is important to maintaining independence in the *Make Muscle Matter* campaign.

***Left:*** **Monique Green sits with her mother, Pearl, before dinner. The *Make Muscle Matter* campaign wanted to highlight that muscle deterioration in ALS does not just affect PWALS, but also their caregivers.**

> It's a ***reminder*** that nothing stands ***still*** in this disease. There's much more at stake than just ***survival***.

Reviers, whose father was diagnosed with ALS and now leads EUpALS, a European advocacy group for patients living with ALS, said she found the campaign very moving—and said it shows the power of including the patient voice even in activities outside the clinic.

"People forget how the loss of these little abilities over time really matter," she said. "They all seem like something so easy—like brushing your teeth—but it becomes very important when you can't do it anymore. This kind of campaign is a real eye-opener, even for those of us who work with patients. It's a reminder that nothing stands still in this disease. There's much more at stake than just survival."

Allegra said that working with patients drove home the importance of independence, self-determination, autonomy, and quality of life for people living with motor neuron disease.

"Unfortunately, just as we were set to launch this campaign, we learned that our potential new medicine had failed in its Phase 3 trial," she said. "But even though *reldesemtiv* did not end up being effective in COURAGE-ALS, we think it is still important that others think about the future options that will help patients be self-reliant

***Right:*** **Ajay Sampat, M.D., is a physician who has been diagnosed with ALS.**

longer—and power more life into their days. That really became our mantra after talking to patients and it stood not just as a moment for the campaign but as the beginning of a movement."

That's why Blum sees *Make Muscle Matter* as much more than just a simple educational campaign. It is a call to action—a reminder to other biopharmaceutical players in the ALS space to remember the needs of the people for whom they are developing therapies. This work also provides a template for others to use, demonstrating the power of seeking out patient-lived experience when trying to educate the community about the impact and experience of a disease.

"This synthesized everything we wanted to do for these patients," he said. "It wasn't just shining a light on muscle as a fulcrum to treat this disease. It also speaks to the fortitude of patients who muscle through this disease and persevere. It's a noble commitment that biopharmaceutical companies make when they enter this field. And, just as we were so inspired by everyone we worked with and their desire to live their best lives, we hope others will be just as inspired and ultimately introduce new innovations and ideas that will benefit their humanity."

"It wasn't just ***shining*** a ***light*** on muscle as a fulcrum to treat this disease. It also speaks to the ***fortitude*** of patients who muscle through this disease and ***persevere***."

Ajay Sampat, M.D., holds a pen as part of the *Make Muscle Matter* campaign.

# Evy Reviers

***Evy Reviers' father*** was diagnosed with ALS when he was only 18 years old. He and her mother were already expecting a child. No one thought there might be time for a second baby. But then, against all odds, Reviers joined the family nine years after he learned of his disease. Reviers said, given the aggressive course of ALS disease, her father's condition shaped her childhood—and inspired her to become an advocate once she grew up.

"I never knew my father in a healthy condition. I saw how this disease can take such a toll on families," she said. "I started volunteering with the ALS organization my parents started in Belgium when I was young. Even after he was gone, I made it my commitment to keep working until a cure was found for ALS."

Today, Reviers is the founder of an umbrella advocacy organization that brings together patient groups from across the whole of Europe, the European Organization for Professionals and Patients with ALS (EUpALS). She said she was inspired to start the organization by Blum.

"I could see, working in Europe, that not all countries had the same access to information, nor access to treatments that were on the market," she said. "There were big gaps in communication and access in different places—and having one organization to connect different groups in different countries could help fill those gaps. [Blum] saw those same gaps and motivated me to start EUpALS. He told me that if anyone can do it, it was me."

Now, several years after starting the organization in 2017, Reviers remains as committed to the cause as ever. Under her leadership, the organization has been involved with international patient advocacy panels at Cytokinetics.

"Cytokinetics was our first industry partner. I appreciated how we worked together in full transparency, but also with friendship and collaboration," she said. "We've always appreciated how open the company is. Their patient panels, where they communicate about their strategy, has been very important to helping advocacy groups understand how industry partnerships can work."

She said that EUpALS' mission remains to free the world of ALS. But she is equally committed to finding ways to support equal rights for patients across all of Europe.

"This isn't just about equal rights for eligibility in clinical trials—it's about care, financials, and support resources. Where you are from should not determine how you are treated if you have this disease," she said. "This is one of the most important things we are doing with our advocacy—and, working together, we can make important changes that will benefit everyone."

This isn't just about equal rights for eligibility in clinical trials—it's about care, financials, and support resources. Where you are from should not determine how you are treated if you have this disease.

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# The Courage of One's Convictions

While COURAGE-ALS, ultimately, did not meet its endpoints—it has provided a wealth of lessons about how ALS clinical trials should be conducted in the future


COREY REICH

*With promising Phase 2 clinical trial results—and* a 5-star patient-centric trial design rating from I AM ALS—Cytokinetics began enrolling PWALS into the COURAGE-ALS trial in 2021. The company planned a year-long global trial with 555 participants spanning 16 countries, with two interim analyses; the first to test for futility, or signs that the trial was failing to meet its endpoints, and the second to test for futility and possibly increasing the number of participants enrolled to increase the study's statistical power. Dr. Shefner, who was acting as a principal investigator for the trial, said, after seeing a trend in the previous trial's data that suggested the drug was more beneficial for PWALS with more rapidly progressing disease, Cytokinetics decided to alter the trial's inclusion criteria to enhance the ability to detect the drug's effects.

"We intended to recruit a slightly higher percentage of more rapidly progressive early onset patients," said Dr. Shefner. "Participants needed to have a vital capacity of greater than or equal to 65%, symptoms for 24 months or less, and an ALSFRS-R score of 44 or less. The goal was to eliminate people, even those with early onset, who hadn't shown at least some signs of clinical progression."

The primary endpoint for COURAGE-ALS was change in ALSFRS-R score from baseline, with secondary endpoints of a combined assessment of function and survival, forced vital capacity (FVC) metrics, ALSAQ-40 scores (an ALS specific quality of life measure), and

hand grip strength as measured with handheld dynamometry. In addition, a variety of innovative exploratory endpoints were included such as time to durable medical equipment, hospitalization rates, and changes in the different sub-domains of the ALSFRS-R score in order to make COURAGE-ALS a very robust trial. The goal was to shed light on multiple outcome indicators in hopes of showing that the therapy would help improve function for PWALS.

At the first interim analysis, which occurred 12 weeks following the randomized treatment of at least one-third of the planned participants, the Data Monitoring Committee (DMC), an independent group of experts monitoring patient safety and treatment efficacy, made the recommendation the trial should continue. At the second interim analysis, however, when nearly 40% of trial participants had received 24 weeks of randomized treatment, something had clearly changed. Dr. Shefner said he and his team were astonished to learn that the drug was not showing benefit.

The goal was to shed light on multiple outcome indicators in hopes of showing that the therapy would help improve function for PWALS.

***Right:*** **Robert Blum speaks to the crowd at the 2023 International Symposium on ALS/MND in Basel, Switzerland.**

**THE DMC RECOMMENDED THE** trial be discontinued due to futility, as the trial, if continued, would be unlikely to achieve statistical significance in its primary or first secondary endpoint. Dr. Shefner said the decision was gut-wrenching.

"The previous trials all seemed to show a pharmacologic signal. FORTITUDE-ALS was a large trial, well powered, and looked like it was having an effect," he said. "I've been doing this long enough that you never know what a trial will end up showing, but I absolutely believed we would see something here. I didn't know how big the signal would be, or whether it would be statistically significant or big enough to move forward, but the idea of not seeing anything whatsoever—and that the patients on *reldesemtiv* seemed to be doing worse than those on placebo—was completely shocking to me."

When Blum received word of the results of the interim analysis, he said he, too, was stunned.

> The idea of not ***seeing*** anything whatsoever—and that the ***patients*** on ***reldesemtiv*** seemed to be doing worse than those on placebo—was completely ***shocking*** to me.

"It was the worst day of our professional lives when we learned we came up empty after so many years of work. We spent countless hours on *tirasemtiv* and *reldesemtiv*, providing high integrity science, research, and development. We had many patients who were dedicated to our cause. Yet, we had no ability to demonstrate that this could lead to a medicine," he said. "At the end of the day, I felt like we let [the community] down. Because the results from COURAGE-ALS were unequivocal. There was no signal for efficacy—and that was consistent across all endpoints we measured."

Yet, as Dr. Cudkowicz said, while the COURAGE-ALS trial failed to meet its endpoints, it is far from a failure.

"It is hugely disappointing for something not to work," she said. "But Robert H. Rubin, M.D., an expert in infectious diseases, was the person who taught me about clinical trials. And I remember him telling me that a trial only fails if you learn nothing from it. And we learned a lot from COURAGE-ALS."

***Above:*** **Chuck Schretzman, with his wife Stacy, lived an active life as a West Point graduate and active-duty serviceman in the U.S. Army. He is facing his ALS diagnosis the same way he has faced all challenges in his life: head on.**

# Lessons Learned

**WHEN ASKED ABOUT THE** most important lessons learned from COURAGE-ALS, leaders at Cytokinetics, as well as their partners in the ALS community, highlighted a variety of teachings that can help guide ALS therapy development in the future.

## Emphasizing Good Science

Dr. Cudkowicz said that the company's focus on doing good science early on provided critical intelligence to other researchers and biopharmaceutical companies that are also working to understand ALS.

"They did a series of small Phase 1a studies, which focus specifically on dosing requirements. And I think the fact they stayed in the Phase 2 space for so long is important even though COURAGE-ALS did not meet its endpoints," she said. "Those studies demonstrated that *reldesemtiv* hit its intended target and they were at the right dose. We now know that a fast skeletal muscle troponin activator is not going to work for ALS. But we can take what we learned from these studies to help us identify future targets for ALS therapies."

## The Patient Comes First

Dr. Rudnicki said, despite a disappointing Phase 3 result, she is heartened that the team was able to show that you can do good science and still minimize patient burden. Many thought they would not be able to get the data they needed with so few clinic visits.

"The big takeaway, for me, is that you can design a trial and make it easier for participants to take part in it," she said. "We have learned that you can do remote visits. You can do remote assessments. You can get the data

***Right:*** **Robert Blum spends his time at conferences like the annual International Symposium on ALS/MND speaking with PWALS, researchers and other industry partners. He understands that it's strong partnerships that will ultimately bring the ALS community effective treatments.**

> Not only were we able to make things ***easier*** for ***patients***, but we were also able to draw a ***broader participant*** group. That's something that will ***benefit*** future trials.

you need. And the patients appreciate that. When participants were interviewed about the trial, they were asked about the home visits and whether it influenced their decision to participate. They told us it was much less fatiguing and less stressful than trying to find their way every month to the clinic."

This, she added, is even more important when you think about trying to expand access to investigational medicines to more PWALS.

"After we learned COURAGE-ALS was negative, I met a young woman whose father participated in the trial. They lived in the middle of nowhere in Canada and she told me that her father would never have had the opportunity to participate if they had to visit the clinic every month, because it was 8 hours away," she said. "Not only were we able to make things easier for patients, but we were also able to draw a broader participant group. That's something that will benefit future trials."


*Above:* Organizations pursuing ALS treatments must emphasize good science—and work with other stakeholders in the space so they can build from the strong development foundation that already exists.

*Right:* Mary Pomerantz, Senior Director, Patient Advocacy and Engagement at Cytokinetics.

Our ALS partners have always been so ***fierce***, vulnerable, and authentic. They've ***always*** been ***willing*** to say and do the hard things.

Working with PWALS also underscored the importance of open label extension, managed access, and extended access programs. These critical programs will help PWALS maintain hope and resolve in the face of an unrelenting disease.

"We heard loud and clear, not only from our patient advisory council, but other patients living with ALS, that these kinds of programs are super important to the community," said Pomerantz. "It's no small effort to make them happen—but they provide access to investigational medicines that many patients may never be able to get otherwise."

## Make It Happen

Pomerantz said the urgency felt within the greater ALS community to come up with new therapies has helped her become a better advocate—and to take on a more "make it happen" mindset in all that she does. This is one of Cytokinetics' core values. It calls for employees to navigate ambiguity, demonstrate courage, take calculated risks, and be tenacious. Pomerantz said she's learned all of that from working with patient advocates in the ALS community.

"I've now seen firsthand that we can apply a team-thinking and patient-thinking approach to solve problems and find ways forward," she said. "Our ALS partners have always been so fierce, vulnerable, and authentic. They've always been willing to say and do the hard things. They've taught me how important it is to be resilient and to keep fighting. I approach my work differently now."

The entire ALS team at Cytokinetics were inspired by this value—and use it to guide work in every development program.

## Building an Ecosystem

By working with various community players, from early on in the drug development process, Cytokinetics fostered relationships that helped to grow an ecosystem that will continue to support growth and forward momentum, even as the company steps away to pursue different priorities.

"There are many studies that fail to achieve their primary objectives," said Jordan. "But by working across the greater community, whether it was working closely with patient advocacy groups or getting scientific advice early in the process from HTA bodies, will help those who come after us to make sure there are fewer barriers to testing new therapies and then getting the effective ones into the hands of patients more expeditiously."

## We > Me

Cytokinetics has grown considerably since it started developing therapies for ALS. Yet, despite that growth, the team that worked to develop *reldesemtiv* remained strong and cohesive even in the face of disappointment and adversity.

"We worked with the same vision, regardless of our business function," said Allegra. "And we

shared the same sense of commitment and passion. We were proud to be part of something so meaningful and that came through in our work."

This coalesced into yet another one of Cytokinetics core values. Today, the company prides itself on knowing that it is stronger when it works as a team, rising together as one. It is that mindset—and the transparency, collaboration, and feedback that goes with it—that will bring about tomorrow's best-in-class therapies.

## The Value of Commitment

Weiser said while it is not uncommon for a biopharmaceutical company to be aligned with the advocacy community as its investigational medicine goes through development, Cytokinetics, from the very beginning, signaled its long-term commitment to advocacy and research partners.

"Far too often, with other companies, when the drug fails, they pull their funding," she said. "That's the typical approach, which I suppose makes some sense from the business perspective. But we have always tried to find a balance between doing what's right for the patients and what's right for our business. And that's meant continuing to show up."

Gschwind added that the company has always been inspired by Blum and his leadership.

"[Blum's] personal value set is doing the right thing for patients—and the greater community," she said. "That involved continuing our financial support where we could and phasing it down over time. It was about being open and transparent about the trial and what we learned. We pulled together the investigators from COURAGE-ALS to go over the results with them in advance of their being presented at the International Symposium on ALS/MND. We continued our sponsorship of that meeting and held a symposium with a panel discussion to discuss the challenges and what might be ahead for ALS development in the future."

Fisher said he hopes that commitment in the face of setbacks is what others will take away from Cytokinetics experience with *tirasemtiv* and *reldesemtiv*.

"We want to see that same level of resolve and commitment from everyone who is working with ALS," he said. "Unfortunately, ALS has one of the worst track records in the pharmaceutical development space. Neurodegenerative diseases, in general, have a very high failure rate in terms of clinical trials. If you are going to wade into these waters, we need you to be resilient because you probably won't get it right the first time around. What Cytokinetics modeled was a true commitment to being part of the ALS community. And if every company were like Cytokinetics, we would be powering tremendous partnerships, not just in support of the ALS community, but in support of developing drugs that can help that community."

## It's Not a Competition

Dr. Hardiman said Cytokinetics' openness to partnering not only with clinical researchers and patient advocacy organizations, but other biopharmaceutical companies as well, is also something that other organizations should emulate.

"[Cytokinetics] understands that we are all working to solve the same problem," she said. "And, in areas that are not of direct commercial concern, they have always been willing to brainstorm with other companies. They were also instrumental in helping to fund a number of studies and surveys with a number of different industry partners."

**MOMENTS THAT MATTER**

# Stacy Rudnicki, M.D., Vice President, Clinical Research and Therapeutic Area Lead, Neuromuscular

As a neuromuscular specialist leading the ALS MDA Center of Excellence at the University of Arkansas Medical Center, Dr. Rudnicki said she quickly appreciated the tenacity and hope she saw in PWALS, as well as their families.

"At the time, they had very little expectations, since there were no treatments available at the time, so anything you could do to help by addressing malnutrition or breathing problems was just so appreciated," she said. "Despite the fact that there were initially no drugs available, it was remarkably rewarding work."

But, she said, after diagnosing patients for years, she became more inspired to get involved with therapy development.

"ALS, even today, is an old-fashioned diagnosis. It's obtaining a medical history, doing an examination, and, basically, ruling out everything else. When you finally got to the ALS diagnosis, you would have a lengthy discussion about it with the patient and their families about what it was and what to expect," she said. "Over time, it just got harder and harder for me emotionally. Having to tell people, over and over again, how little we could do for them became personal on some level. When you work in the ALS clinic, you get to know not just the patients, but their families. I wanted to move to a place where I could offer these incredible people more hope. I ended up going to Cytokinetics, where I could use my knowledge about patients, the greater ALS community, and clinical trials, with the hope that I could change something on a bigger scale."

# Setting the Standard

**CYTOKINETICS WAS INVOLVED WITH ALS** interventional trials from 2009 until 2023. The company conducted trials in both the U.S. and abroad, recruiting more than 2,000 PWALS for it trials. Cytokinetics developed robust new clinical trial protocols that are both innovative and patient friendly.

Blum credits an "all-stakeholder" approach to successfully reducing the PWALS burden across trials. The company worked hard to connect with PWALS, caregivers, clinicians, researchers, regulatory agencies, payers, and HTAs. And, had COURAGE-ALS been successful, it would have paved the way for the company to bring *reldesemtiv* to PWALS faster.

Blum added that this same comprehensive strategy also benefitted Cytokinetics' marketing, medical affairs, and health economics and outcomes research (HEOR) efforts—as well as all other key business functions. By being proactive—and always being guided by PWALS—the company was able to make important advances that other organizations can now build upon.

"Many companies become a bit of a slave to process, positioning themselves ultimately for the commercial benefit of the business," he said. "But our nature was to look at things from a more unconventional perspective, which was all about ensuring that patients can actually access and benefit from our medicine."

***Above:*** **Cytokinetics team members, a representative of The ALS Network, and Ryan Farnsworth at the ALS Adds event in 2018. At this event, PWALS like Ryan discussed what their diagnosis had added to their lives.**


Elevated Community Relationships
Servant Leadership • Moral Intentions
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AFTERWORD

# Passing the Baton

With other industry players now working to bring new ALS therapies to market, it is important to build on the foundation Cytokinetics and the greater ALS community have built

*More than six months after Cytokinetics learned* COURAGE-ALS had failed to meet its endpoints, the company's *reldesemtiv* leadership team traveled to Basel, Switzerland, for the 2023 International Symposium on ALS/MND. Despite the negative trial results, there was no question that the company would fulfill its sponsorship commitment to the conference. Dr. Shefner would conduct a full post-mortem on the COURAGE-ALS results. The company would also host a symposium to talk about the future of ALS therapy development. And, most important, the Cytokinetics team would, once again, convene with the community that has meant so much to them over the past fifteen years. It was, Lee said "bittersweet."

"I had so many people come up to me at the meeting and tell me how sad they were because they couldn't imagine ALS research without Cytokinetics being involved," she said. "There were a lot of tears—from us and them. COURAGE-ALS not meeting its endpoints is the biggest disappointment I've had to deal with. But we know that there will be someone else out there who will have something that can help these patients. Someone who will roll up their sleeves, push forward, and be ready to go."


*Above:* **Members of the Cytokinetics *reldesemtiv* team at the 2023 International Symposium on ALS/MND in Basel, Switzerland.**

**AS DR. CUDKOWICZ SAID,** the unmet need in ALS is too great to try to "reinvent the wheel" with each trial. She is hopeful that others will learn from Cytokinetics' example, work with the greater ALS ecosystem, and forge ahead with a new therapy. The need is too great not to.

"Cytokinetics got to know ALS by actually talking to the people living with it," she said. "To move forward, we need to be open about knowledge sharing and efficiency. We need to include the patient voice to develop trials that patients will want to participate in—but will also want to tell other patients about. And we need, despite so many trials not meeting their endpoints, to keep going."

Cytokinetics demonstrated the power of joining forces to move the field ahead. Company employees showed commitment, consistency, and transparency—and were a true example of why persistence matters in a field littered with disappointments. And, most importantly, they showed other organizations what is possible when one shows up as a true partner in this space.

We need to ***match*** the resilience and perseverance that ***patients*** living with ALS demonstrate ***every day***.

That's why, at the end of the Cytokinetics Symposium at the 2023 International Symposium on ALS/MND, the greater ALS community had a surprise for the company. At the conclusion of the session's Q&A portion, Dr. Shefner called Blum to the podium to recognize Cytokinetics for "dedication and commitment to ALS therapeutic development and advances in patient care."

Blum said he was genuinely surprised—and incredibly moved by the recognition.

"It was a very emotional moment," he said. "I was caught very much by surprise. I didn't expect us to be recognized in that way. As far as I know, it's unprecedented for a company to be awarded something like this by the people we had hoped to serve with a potential new medicine. These are the leading lights and luminaries in the ALS community. The honor was truly humbling—but it was also gratifying. I felt so grateful to all of them, for welcoming us into their community, and providing so many valuable lessons that will help move the field forward."

Despite the fact that Cytokinetics is stepping away from ALS therapy development for now, Blum said what he hopes for most is that other biopharmaceutical companies will stand up and take its place. After all, PWALS show remarkable strength and resilience in the face of horrendous odds. It's time that the pharmaceutical industry does the same.

As Blum thanked ALS stakeholders after receiving the ALS/MND award, he said he is filled with gratitude for the experience of working with this community. And he looks now to others to continue the fight. He hopes, he said, they will move forward with a "clear-eyed vision of the why" to yield greater fulfillment and success.

"If anyone is to learn anything from us, I hope it will be discipline, high-integrity science, purpose-driven commitments, and perseverance," Blum said. "We need to match the resilience and perseverance that patients living with ALS demonstrate every day."

Yet, Blum also said that Cytokinetics hopes to one day champion a new ALS therapy even as the company now focuses on development of a hypertrophic cardiomyopathy therapy. He remains, as ever, dedicated to making it happen for the ALS community. He shared that same sentiment as he accepted the award from the ALS/MND community.

"We look ahead to taking all this inspiration and the collective learnings we've gathered for more than a decade back to our labs to continue our journey with the same high science, high integrity conviction that we've always brought to ALS drug discovery and development," he told the audience. "Please know that Cytokinetics is immensely grateful for the experience you've afforded us. We look to that science of gratitude to point us in a new direction. And we look forward to joining you further down the road in this fight against ALS."

# Acknowledgments

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