

Breakthroughs to a cure



The CMTA's Strategy to
Accelerate Research



ON THE COVER

There are 2.8 million compelling reasons why the Charcot-Marie-Tooth Association (CMTA) is driving so hard to find treatments for CMT. Cover girl Lily Sander, 9, is one of them. Three years ago, Lily couldn't walk or stand without leg braces. After surgery to straighten her feet, she now rides horses, roller blades and does gymnastics. In 2016, Lily and 31 friends and classmates completed a half-mile Spartan Race, raising tens of thousands of dollars for CMT research in the process. Our goal is to break through for Lily and others like her.

2.8 million
reasons to care

Fast Facts About CMT

- Charcot-Marie-Tooth is one of the most commonly inherited neuromuscular diseases often passed down from parent to child.
- CMT affects the long (peripheral) nerves that go to the feet and hands of approximately one in 2,500 people worldwide. As the nerves degrade and die, the muscles around them atrophy.
- CMT causes foot-drop, foot bone abnormalities, muscle wasting, fatigue, problems with balance and hand function, occasional lower leg and forearm muscle cramping, loss of some normal reflexes and scoliosis (curvature of the spine). It can also affect breathing. In rare cases it can be life-threatening.
- CMT is progressive, meaning it gets worse over time. There is no way to predict how far or how fast the disease will progress, and the severity varies widely from person to person, even within the same family.



Amy Gray, Chief Executive Officer

A breakthrough is defined as a sudden, dramatic and important discovery or development. In truth, breakthroughs are most often the result of relentless hard work and determination. That's what drove the CMTA's Strategy to Accelerate Research (STAR) to where it is today: on the precipice of delivering treatments for CMT, the progressive neuromuscular disease that affects more than 2.8 million people worldwide.

Thanks to CMTA-funded research, we have identified promising therapeutic approaches for CMT1A. Studies in two rodent models of CMT1A not only stopped progression of the disease, but also showed improvement of some symptoms.



Gilles Bouchard, Chairman of the Board

It's a huge breakthrough, but we need another breakthrough to get from drugs and therapies that work in animals to ones that work in people. We also need to develop other potential drugs and therapies. To deliver the first treatments for CMT, we need funding for clinical trials and further drug development. And, while the 1A project is furthest along the path to drug delivery, projects addressing 90% of all cases of CMT, including types 1B, 1X, 2A, 2E and 4, are also delivering promising results using cutting-edge techniques like antisense oligonucleotides and gene therapies.

The CMTA has worked hard to accelerate breakthroughs in the past decade, committing \$8 million to bring together world-class academic and industry researchers, and using innovative and efficient research methods to prepare for drug delivery.

As detailed on p. 5, the CMTA's drug discovery program is working exactly as planned, attracting new pharmaceutical partners every year.

But challenges remain. The safety and efficacy of these drugs must be validated. Key metrics must be developed to quickly demonstrate their efficacy in humans. Conducting clinical trials is expensive. That's why we're asking you to help the CMTA once more as we reach for our next breakthrough: translating the research and promising test results to a treatment that will slow, stop or even reverse the progression of CMT. We're asking you to invest in Breakthroughs, which will target these final challenges.

We don't have to tell you what a drug treatment for CMT will mean. You undoubtedly have your own living example—maybe a child, like Lily, who will fulfill her dream of becoming an Olympic gymnast or a grandfather who will be able to cast off his braces and walk on the beach with a grandchild who will never know the ravages of CMT. We simply ask you to think of that person as you consider your investment in Breakthroughs.

Sincerely,

Amy Gray, Chief Executive Officer

Gilles Bouchard, Chairman of the Board

the

campaign

STAR started





with CMT1A, but it didn't end there...

STAR, the CMTA's research program, is based on the concept that when the CMTA puts top researchers together with pharmaceutical partners that have relevant expertise and assets—and attracts donors willing to fund their research—scientific breakthroughs follow. In the 10 years since the CMTA laid out STAR's parameters, the concept has proved successful time and time again. The CMTA now has more than half a dozen partnerships with pharmaceutical companies and has funded more than 70 projects.

What makes STAR unique is that it brings the world's top CMT researchers out of their silos to collaborate with each other, share results and discuss strategies. The CMTA holds those researchers accountable for achieving their stated goals—if they don't meet them, the funding goes elsewhere. STAR initially started with a focus on CMT1A, but it didn't end there. The CMTA has added projects over the years as the science and the funding for different subtypes has come together, always emphasizing the translational value of the work—how fast and effectively the research could be translated from basic medical research to treatments for CMT.

While the STAR Advisory Board is responsible for setting the research agenda, the CMTA is a patient-led organization and patients also have a voice. More than once, their ability to fund a project put it on the STAR agenda.

“Unlike my friends, I can't do things like run around or go to the beach. I look forward to the day a cure is found and all my daily struggles of having CMT go away!”

Julia Beron



CMTA—funded researchers have identified
promising drug candidates for


CMT1A

One of them has not only stopped progression of the disease, but also showed improvement of some symptoms. The promise of symptom alleviation and the possibility of symptom reversal is real.

After creating the Strategy to Accelerate Research (STAR), CMTA decided to focus its first efforts on CMT1A because researchers had already developed the basic building blocks needed. Animal models and cell lines—critical assets for drug development—already existed. The fact that CMT1A is the most prevalent form of CMT also played a role in the decision. With almost \$4,000,000 committed to funding 1A since 2008, STAR has:

- Attracted strong alliances with pharmaceutical partners, including flagship partner Sanofi-Genzyme.
- Launched partnerships that are in advanced stages of developing drugs to treat CMT1A. One treatment stops the progression of CMT1A in two models of the disease.
- Collaborated with the National Institutes of Health (NIH) and pharmaceutical companies to develop the first drug-screening tests using CRISPR/Cas9 and genome editing.
- Conducted the first large-scale drug screen for CMT1A at the NIH.
- Conducted multiple screenings of drugs from the libraries of three different pharmaceutical partners. More than 2 million compounds have been screened.
- Identified candidate biomarkers for CMT clinical trials, allowing potential new drug treatment results to be measured faster and with fewer patients.
- Developed stem cell lines from CMT1A patients which will be used to validate promising compounds.

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A close-up photograph of a hand holding a clear glass test tube. The test tube is partially filled with a vibrant green liquid. The hand is positioned in the center-left of the frame, with fingers wrapped around the tube. The background is a blurred white lab coat, suggesting a laboratory setting. The overall lighting is bright and clean.

“Patient groups like the CMTA bring funding, expertise in disease biology and advice on meaningful intervention approaches and the National Center for Advancing Translational Sciences brings expertise in therapeutic development. The result is a more patient-relevant and efficient route to new treatments—true translational innovation.”

CHRISTOPHER P. AUSTIN, MD, DIRECTOR,
National Center for Advancing Translational Sciences
at the National Institutes of Health

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“A treatment would mean hope for patients like Tessa, that until now has only been a dream.”

DR. SHY, CMTA CLINICAL ADVISORY BOARD CHAIRPERSON,
CLINICAL DIRECTOR AT THE CMTA CENTER OF EXCELLENCE IN IOWA



The Transformation Project

In 2012, the STAR Advisory Board (SAB) decided that because testing on animal models does not always translate to humans, human cell lines were needed to further validate candidate drugs. The project transformed human skin and blood cells from CMT patients into stem cells, and from there, into neurons (nerve cells) and Schwann cells (which make myelin). With more than \$114,000 in funding dedicated to this effort, STAR developed CMT1A and CMT2A cell lines for investigative use and made them available to researchers around the world.

CMT2A

In 2010, the CMTA’s scientific and medical experts turned their attention to CMT2A. Researchers and the Board of Directors approved a plan to grow CMT2A cell lines and animal models. With almost \$1,500,000 in funding dedicated to 2A since 2011, STAR has:

- Created two new rat models of CMT2A that are available for testing.
- Created stem cell models of CMT2A that are being used to identify how MFN2 mutations cause neuropathy.
- Created the first drug screen for CMT2A.

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CMT1X

By 2013, the SAB had identified key researchers and projects for CMT1X. With more than \$130,000 in funding dedicated to 1X since 2013, STAR has:

- Proved that drugs could be used to reduce inflammation that worsens CMT in a mouse with CMT1X.
- Initiated a gene therapy approach to treat advanced symptoms of CMT1X.

CMT2E

Strong research, coupled with proper funding launched an initiative to deliver treatments for CMT2E. With two key supporters, two key researchers, and more than \$625,000 in funding dedicated to 2E, STAR has:

- Supported the development of the best mouse model of CMT2E.
- Developed both mouse and human stem cell models of CMT2E, which are being developed for drug screening.
- Initiated the testing of compounds on nerve cells derived from the animal and patient models.

CMT4C

In 2014, the time was right to address the recessive types of CMT. The SAB mapped out a pathway to address CMT type 4C and once key researchers were identified, work began in 2016. Early funding allows STAR to explore the gene therapy approach that was shown to be successful in CMT1X.

CMT1B...One Person Can Start a Movement

In 2013, a donor approached the CMTA, interested in the state of CMT1B research. At the time, there was no coordinated effort to identify novel treatments for CMT1B. Knowing that this donor had the capacity to make a significant investment in STAR, the CMTA assembled its Advisory Board to map out a strategy for drug delivery for CMT1B. The donor generously donated \$500,000 of the \$1.5 million needed for the project, then another family learned about the strategy and donated \$500,000 to the initiative. The CMTA community met the first donor's challenge, raising the final \$500,000 needed for the research. Since 2013, STAR has:

- Conducted an assessment of the range of mutations within 1B.
- Identified many different mutations within 1B, developing a better understanding of the unfolded protein response (UPR) and how CMT1B works.
- Developed a mouse model of CMT1B to represent the variations of CMT1B patients (early to late onset).

While the CMTA is currently focused on these seven research initiatives, the knowledge gained from each project is likely to inform projects involving other types.

The CMTA continues to compress the timeline for finding a treatment—and eventually a cure—for CMT. Our development of a toolkit of assays (tests), animal models and CMT cell lines has earned the CMTA a sterling reputation in the pharmaceutical and biotechnology industries, leading top pharmaceutical companies to seek partnerships with us. Those partnerships will be particularly important as we move forward with clinical trials, always the riskiest and most expensive part of drug delivery.

In the next three years, the CMTA will need \$10 million to maintain the quickened pace of its research. With these funds, the CMTA will be able to:

- Accelerate the development of drugs currently being tested that are viewed most promising to treat CMT.
- Discover and develop new drugs to treat CMT.
- Conduct clinical trials on drug candidates already identified to treat CMT, poising them for Food and Drug Administration approval.
- Conduct clinical trials on new drugs identified to treat CMT.
- Continue to search for other treatments for 1A, 1B, 2A, 2E, 1X, 4C, and other types of CMT.
- Attract more partnerships in the pharmaceutical and biotechnology industries to support CMT drug development and clinical trial efforts.
- Continue to pursue every promising avenue toward a cure until we reach our goal of ending CMT.

Why Give to the Charcot-Marie-Tooth Association (CMTA)?

EXPERTISE: The CMTA has recruited the best and brightest CMT researchers in the field to work on the STAR Advisory Board. These researchers help set the agenda and strategies to develop treatments for CMT.

EFFICIENCY: The CMTA is a gold star rated charity of Guidestar, an agency that monitors non-profits. Approximately 80 cents of every dollar of the Association's revenue goes to vital research, community education and support programs.

RESULTS: Thanks to wise investments by the CMTA in research, education and support programs, there are promising treatments on the horizon, all while providing more resources for people living with CMT today.



Breakthroughs means the hope of a cure for children like Ava and the comfort that future generations may never know the difficulties of living with CMT.

Our vision of a world without CMT is taking shape. With your financial help, the CMTA can continue to leverage the breakthroughs made by STAR, targeting the more than 90 genes known to cause CMT and systematically working to eliminate them. We look forward to the day when all CMTers can stand straight and tall, casting aside their braces, walkers and wheelchairs to move easily through life. Please help us continue to deliver breakthroughs for all people living with CMT. With your support, one day soon, CMT will join smallpox, polio, rubella, malaria and a host of other diseases that are now largely or completely eradicated.

be the
breakthrough
in their lives



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