CMTA
Charcot-Marie-Tooth Association

THE CMTA REPORT

SPRING 2021

A SPECIAL REPORT:
HARNESSING THE POWER OF STAR

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ACCELERATING RESEARCH EMPOWERING PATIENTS

THE CMTA REPORT

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A MESSAGE FROM THE CEO

Harnessing the power of STAR

Dear Friends,

As the CMTA approaches its fifth decade of research and service to the CMT community, we thought the time was right to sum up—and celebrate—STAR, our Strategy to Accelerate Research. In the past few years STAR has lived up to its name as never before. Our portfolio of research means that virtually every person with CMT—no matter the type—is affected by at least one of our 50 current projects, and there are more in the pipeline.

It has been 30 years since a CMTA Advisory Board member, Dr. James Lupski, MD, PhD, first identified the gene that caused CMT1A. Before that, diagnosis depended on family history, clinical examination of nerve and muscle function, electrodiagnostic testing and sometimes nerve biopsy.

In the following years the genetic causes of CMT1A, HNPP, CMT1B, CMT1D and CMT1X were also pinpointed. The work continued but it was relatively slow going until 2008 when the CMTA conceived and implemented STAR based on the lessons of venture capitalism described on the next page.

STAR focused first on gathering the top experts and researchers in the field, then building an amazing testing machine with the tests, animal models and stem cells needed to proceed. Related to our portfolio approach, we tested potential treatments on animal models we developed and worked with our partners to translate those to other types where possible. You'll read more about our cross-type initiatives on page 6.

Thanks to the CMTA's testing tools, models and experts, pharmaceutical companies have contacted us in ever-growing numbers to test their drugs and technologies on CMT. Some companies use the traditional "small molecule" approach, while others are leaders in the latest genetic and neurological technologies such as CRISPR, gene therapy, gene silencing and axon and muscle regeneration.

In recent years, the acceleration promised by STAR has gained even more momentum, like a snowball rolling downhill. Since 2012, CMTA-funded initiatives have resulted in the discovery of 46 of the 100 genes currently known to cause CMT. It's an ongoing process and you'll read more in these pages about our current work on gene discovery.

You'll also read about the CMTA's extensive and ongoing gene therapy efforts, which now cover CMT1A, CMT1X, CMT2A, CMT2D, CMT2E, CMT2F, CMT2K, CMT4A and CMT4C, utilizing a number of different technologies, including AAV delivery, gene silencing, gene replacement and genome editing using CRISPR-Cas9 and antisense oligonucleotides (ASOs).

The CMTA continues to lead the way in CMT research and today we are working in partnership with the Inherited Neuropathy Consortium (INC) and our Centers of Excellence to get ready for clinical trials. This means recruiting large numbers of patients, studying the evolution of CMT in them and developing outcome measures and biomarkers to measure a given drug's effectiveness quickly and conclusively.

I hope this issue of *The CMTA Report* answers all your questions about STAR research. If you'd like to go deeper, please visit cmtausa.org/our-research. And if you still have questions after that, please feel free to contact me or Jeana Sweeney, the CMTA's director of development. As always, our aim is to keep you up-to-date and as hopeful about the future of our research as we are.

Best,

Amy Gray

CMTA Chief Executive Officer

BUILDING AND PAYING FOR A STAR

When CMTA Board Chair Gilles Bouchard started getting involved with the organization 11 years ago, he found the world of CMT research depressing: Some great researchers were working on CMT, but because there were no pharmaceutical companies involved, the research wasn't being translated to treatments.

HOW DID WE GET FROM THERE TO WHERE WE ARE TODAY? Board members decided to apply a business approach to the problem, starting with analyzing the challenges. The ones they identified are still valid today. The first is that developing drugs takes a lot of time, in many cases more than a decade, and a lot of money, often over a billion dollars. It's also very risky—more than 90 percent of the drugs that enter clinical trials fail. CMT is an even riskier investment for pharmaceutical companies because there hasn't yet been a successful clinical trial. And because CMT is a slowly progressive disease, it takes a long time and a lot of patients to run a clinical trial. That's what kept a lot of potential players on the fence, and that's what the CMTA Board decided to address.

The core strategy for STAR from day one was figuring out how to attract partners to work on CMT. The CMTA didn't (and doesn't) have the billions of dollars needed to develop drugs, so the focus was (and is) on attracting the top players, top labs and top technologies. By working with researchers from the pharmaceutical industry and academia, the CMTA is determined to cross the "Valley of Death" that often lies between research and successful innovation.

Five elements proved particularly important:

- The first one was to enlist key opinion leaders (KOLs) to the cause.
- The second one was providing a preclinical testing infrastructure so that companies could test their products quickly, inexpensively and reliably.
- The third one was establishing a clinical trial infrastructure, complete with patients, their natural histories and biomarkers to measure the effects of a given treatment.
- Fourth, more and more companies are looking for innovation that they can license and take to market. All of the investments the CMTA has made over the years—in the labs and in new developments—are now starting to draw a lot of interest from pharmaceutical companies.
- The final factor was facilitating access to the CMTA community so partners can understand how CMT affects patients.

MAKING CMT ATTRACTIVE TO PARTNERS

Gilles Bouchard has led the CMTA Board since 2016

The strategy is working even better than anticipated, resulting last year in:

- **$2.5 million invested** in research ($17 million since 2008)
- **19 joint preclinical treatment studies** with leading pharmaceutical and biotech companies developing treatments for CMT
- **32 total alliance partners** from top biotech, pharma and gene therapy labs around the world
- **50 active research projects** and studies and eight more projects approved in recent months
- **More than 30 of the leading CMT scientists and gene therapy experts** from around the globe working with our STAR Advisory Board
- **Research tools for biotech companies** to use in testing potential therapies for types CMT1, CMT2, CMT4 and CMTX
- **Investments in the discovery of new genes** that cause CMT

Gilles attributes that success to the fact that STAR is supported almost 100 percent by the CMT community. That's why the CMTA had a really good year in 2020, despite the pandemic.

One of the reasons the community supports the CMTA is that its financials are considered best-in-class, with an overhead of just below 13 percent. Charity Navigator gave the CMTA a four-star rating and Guidestar gave it a Platinum Seal of Transparency, both the highest rankings awarded by the two organizations. People know that when they donate to the CMTA the money will be used in the most efficient and transparent way possible.

The Board of Directors is also incredibly supportive, providing some 20 percent of the CMTA's revenues. Overall, the organization is already seeing bigger investments—where initially the CMTA might have written a five- or six-figure check, the companies coming in can write seven- or eight-figure checks. Just as in the venture capital world, the seed money that the CMTA put in is now leading to much bigger investments.

CROSS-TYPE INITIATIVES

While there are many genetic causes of CMT, certain advancements are common to virtually all types. Those commonalities include the development of gene therapies, improving genetic diagnostics and extending it to currently unclassified types of CMT, providing the biomarkers that enable and stimulate clinical trials, preventing axon degeneration and developing inhibitors.

Nerves are bundles of many nerve fibers, most of them wrapped in myelin. Myelin is an insulating and protective coating, formed by Schwann cells, which also makes nerve impulses much faster (from 1 to >50 meters/second). Myelin problems cause demyelinating CMTs (CMT1). Problems with nerve fibers, or axons, cause axonal CMT (CMT2). Type 4s can be either.

Mutations in more than 100 different genes cause CMT neuropathies. The mutations have diverse cellular functions, resulting in many disease mechanisms.

Mutations in genes expressed by Schwann cells mostly cause demyelinating CMT, though eventually this damages the axons as well. Mutations in genes expressed in nerve cells and their axons mostly cause axonal types of CMT.

GENE THERAPY

Gene therapy involves the introduction of genetic material (DNA or RNA) into the cells and tissues of an individual instead of drugs or surgery.

There are several approaches to gene therapy: replacing a faulty (missing or mutated) gene that causes a disease with a healthy copy of the gene; deactivating or "silencing" a mutated gene that is functioning improperly; or editing part of a mutated toxic gene using a "cut and paste" method.

How does gene therapy work? Essentially, a virus, or "vector," delivers the therapeutic gene to the target cell and inserts the genetic material. Once the healthy gene enters the cell, it restores proper functioning.

Gene therapies have to address the disease mechanism. That means that for CMT neuropathies caused by loss of function (mostly CMT 4 and X) mechanisms, we can deliver the healthy gene to restore the function (gene replacement). For CMT neuropathies with a toxic gain of function (mostly CMT 1 and 2) mechanism, we can either silence (reduce) the toxic gene or try to repair (edit) the mutation.

The CMTA sponsors gene therapy development for many types of CMT, including CMT1A, CMT1X, CMT2A, CMT2D, CMT2E, CMT2F, CMT2K, CMT4A and CMT4C, utilizing a number of different technologies, including AAV delivery, gene silencing, gene replacement, genome editing using CRISPR-Cas9 and antisense oligonucleotides (ASOs).

EFFICIENT, EFFECTIVE BIOMARKERS CRITICAL FOR CLINICAL TRIALS

Because clinical trials involve a large investment of both time and funding, many conversations with CMT pharmaceutical partners about potential therapies focus on how to design clinical trials that will quickly address a new medication's efficacy.

These companies want to see measures that can evaluate signs of success, ideally within three to six months of starting the clinical trial. A measure that works only after a year or two simply takes too long for them to make that investment. Consequently, **one of the most urgent needs in the CMT field is to find better ways to assess the dysfunction of the peripheral nerves in patients with CMT.**

The CMTA was an early supporter of INC's development of neuropathy scores for adults. They went on to develop pediatric and infant neuropathy assessments. But since CMT is a slowly progressive disease, these neuropathy scores by themselves are not sensitive enough to changes and therefore not really adequate to serve in a clinical trial as a measure of whether the neuropathy has improved.

Biomarker efforts extend across types and include a number of different studies. In London, neurologist Dr. Mary Reilly developed a biomarker that uses magnetic resonance imaging (MRI) to measure the amount of muscle mass in calves. As CMT progresses, there is a gradual replacement of some of the muscle with fat. MRI was not identified with CMTA support, but we are supporting extension of 1A studies to other types.

Dr. Reilly and Dr. Alexander Rossor also found that blood samples can be used to measure a protein called neurofilament light that is released from CMT nerves. Since the focus of several CMT1A therapies is reducing the expression of the PMP22 gene that causes neuropathy, the collaboration of Dr. Michael Shy at the University of Iowa and Dr. John Svaren at the University of Wisconsin has turned to the analysis of both blood samples and skin biopsies.

There are nerves present in the skin, so the affected Schwann cells—the cells in the peripheral nervous system that produce the myelin sheath around neuronal axons—can be assessed by sensitive gene detection methods to determine the level of PMP22.

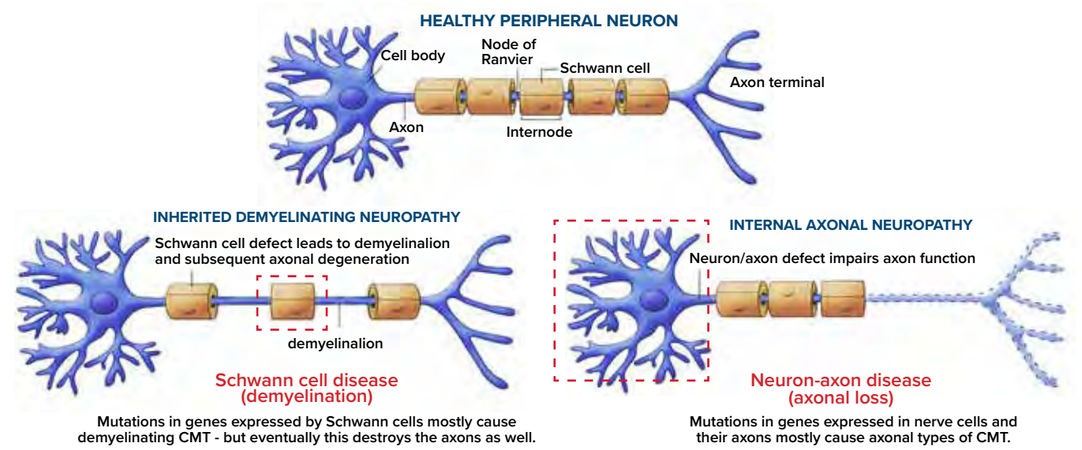
GENE DISCOVERY

Gene discovery is another area the CMTA is pursuing. Fewer than 50 percent of CMT Type 2 patients know their gene. If the gene isn't known, there can be no therapy development and the patient is likely to be forced into an ongoing "diagnostic odyssey."

The CMTA supports the most important genomic initiative by the INC and the GENESIS project, which in 2020 discovered the most common recessive CMT2 gene–SORD neuropathy, which may be treatable with already-approved drugs. The majority of CMT genes have been discovered in the past decade in this effort.

THE CAUSES OF CMT

Mutations in more than 100 different genes cause CMT neuropathies.
They have diverse cellular functions, resulting in many disease mechanisms.



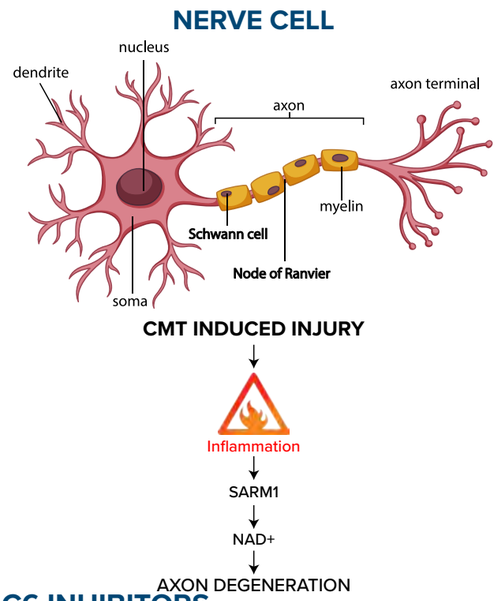
In some CMT types the mutation has a toxic effect (gain of function) and in other types the mutation results in loss of function.

AXON DEGENERATION

There are several genes involved in axon degeneration. Most notable is one called SARM1. The SARM1 gene codes for a protein that functions as an enzyme, affecting the levels of an important metabolite (NAD+) necessary for certain chemical processes in the body. So, what does this mean for a patient dealing with loss of neuromuscular functioning?

All nerve cells have axons whose proper functioning is essential in signaling muscles to contract. **Axons are vulnerable to degeneration due to several destructive injury-induced triggers.** In some types of neuropathy, a disease-induced (CMT) injury to the nerves causes inflammation, activating SARM1, which reduces the levels of axonal NAD+, and causes axonal degeneration.

Inhibiting the activation of SARM1 has the potential of preventing this cascade of events from happening. Several companies are working to develop compounds that inhibit SARM1, and it is thought that this will prove to be a successful therapeutic for blocking injury-induced axonal degeneration pathways.



HDAC6 INHIBITORS

While the many genes associated with CMT make it unlikely that a single treatment will work for all forms of the disease, preclinical studies with HDAC6 inhibitors, which have been shown to reduce motor and sensory deficits, have demonstrated promising results in several mouse models of CMT. Based on these promising results, scientists believe that HDAC6 inhibitors might be beneficial in treating a wide array of neurodegenerative conditions including demyelinating (Type 1 and 4) and axonal (Type 2) CMTs.

The CMTA recently granted Dr. Robert Burgess, a member of the CMTA's Scientific Advisory Board, $45,000 for a study using mouse models of several forms of CMT to determine which types may be candidates for treatment with HDAC6 inhibitors and whether HDAC6 inhibitors may be of therapeutic benefit across a variety of CMT types. The latter will help determine whether patients with genetically undiagnosed cases of CMT are likely to benefit from this therapeutic strategy, or whether only select forms of CMT may respond to this treatment.

CMTA FUNDS STUDY USING TWO ALREADY-APPROVED DRUGS TO TREAT CMT1B

The CMTA awarded researchers $138,110 in January for a study looking at whether two drugs currently approved for hypertension and erectile dysfunction can be used to prevent CMT1B.

CMT1B is caused by mutations in myelin protein zero (P0), the predominant gene product of Schwann cells. Previous work established that the accumulation of mutant MPZ protein in CMT1B causes activation of the unfolded protein response (UPR).

While other approaches to resolve the UPR are in testing (and clinical trials for CMT1A), the Feltri/Wrabetz Laboratory at SUNY Buffalo has developed a strategy to promote elimination of the mutant protein by raising levels of a key signaling molecule known as cGMP to activate the proteasome.

Based on positive results obtained in a short, two-week pilot trial using sildenafil in the S63del CMT1B mouse model, the grant will fund testing of two other drugs with more optimal pharmacology for treating the CMT1B S63del mouse model. Investigators will use short-term studies of the two drugs to establish optimal dosing and then perform a longer efficacy trial. This approach will also tested for its applicability to CMT1A.

Reviewers called the proposal "outstanding" and said that based on "very exciting" preliminary data, it has considerable translational potential.

INC EXPLAINED

The Inherited Neuropathy Consortium (INC) is an integrated group of academic medical centers, patient support organizations and clinical research resources dedicated to conducting clinical research in different forms of CMT and improving the care of patients. Funded primarily by the National Institutes of Health (NIH), with supplemental funding from the Charcot-Marie-Tooth Association and the Muscular Dystrophy Association, the INC plays a key role in developing the infrastructure necessary to evaluate CMT therapies.

Since 2008, INC members have identified many new mutations in genes that cause CMT, discovered new genes that cause CMT, illuminated the molecular pathogenesis of CMT, performed translational studies with animal models of CMT that may lead to new therapies, developed management strategies and standards of care for people with CMT, published strategies for genetic testing for inherited neuropathies, developed biomarkers, participated in three clinical trials of ascorbic acid for CMT1A and developed clinical observation assessments that have enabled natural history studies and will facilitate clinical trials.

Led by University of Iowa neurologist and CMTA Board Member Michael Shy, MD, the INC is part of the Rare Diseases Clinical Research Network (RDCRN), a group of scientists, clinicians, patients, families and patient advocates that studies a wide range of rare diseases. The RDCRN is supported by multiple NIH Institutes and Centers and led by NIH's National Center for Advancing Translational Sciences (NCATS) and the NCATS Office of Rare Diseases Research.

Originally, the INC consisted of six sites. With supplemental funding from the Muscular Dystrophy Association (MDA) and the Charcot-Marie-Tooth Association, that number has now expanded to more than 23 sites internationally.

The NIH granted the INC $7.2 million in renewed funding in October 2019 for continued clinical research on different forms of inherited peripheral neuropathies and improving the care of patients.

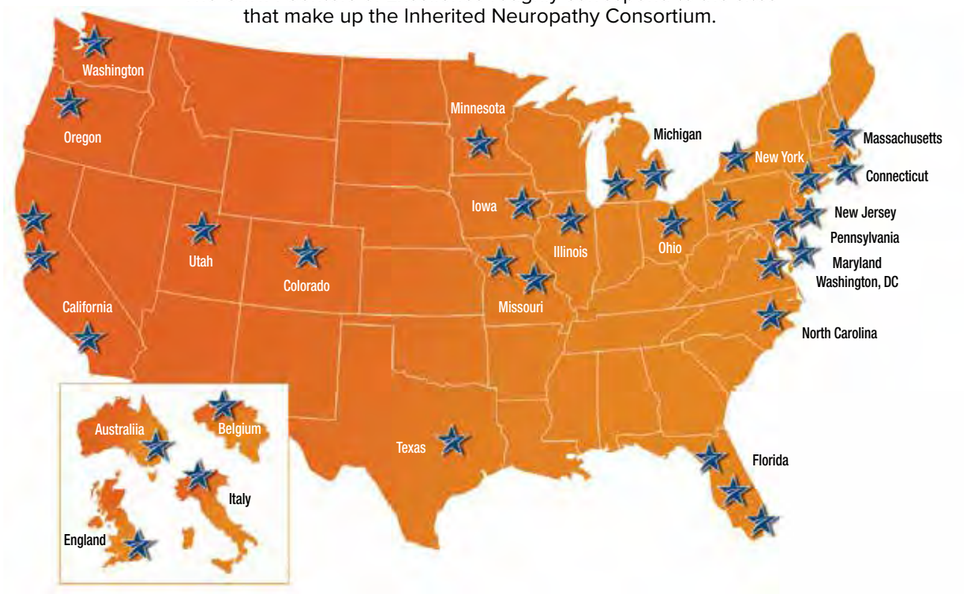
The grants were aimed at fostering collaborative research among scientists to better understand how rare diseases progress and to develop improved approaches for diagnosis and treatment.

According to Dr. Shy, professor of neurology and director of the CMT Clinic at the University of Iowa Hospitals & Clinics, the funding means that Iowa "will continue to pioneer natural history studies and develop clinical and biomarker outcome instruments for patients with multiple genetic forms of inherited peripheral neuropathies. We will also be able to continue our efforts to identify novel genetic causes of CMT and continue to train the next generation of young investigators in our field."

In addition to seeking new and better treatments for patients with inherited neuropathies, the consortium also provides up-to-date information to help patients manage their diseases and assists in connecting patients with support groups, expert doctors and clinical research opportunities.

THE CMTA CENTERS OF EXCELLENCE

The CMTA Centers of Excellence roughly correspond to the sites that make up the Inherited Neuropathy Consortium.



MARKING 38 YEARS OF GROWTH

ACCELERATING RESEARCH. EMPOWERING PATIENTS.

2020

Gene therapy projects in progress for 1A, 1X, 2A, 2E, 2F, 4C, and 4A with world-class labs and four biotech partners. SORD discovered. Working with Pharnext on biomarkers for its 2021 1A trial.

2019

Passage Bio commits to CMT2A gene therapy CRISPR project with top lab at UC (associated with 2020 Nobel prize laureate), CMTA partner InFlectis BioScience completes Phase 1 clinical trial for Sephin (1A and 1B potential). Renewed support for the INC.

2018

Gene therapy summit. New gene therapy projects and SAB members. Multi-year, multi-partner initiative to test drugs developed to slow axon degeneration in many CMT models.

2017

In collaboration with Ionis, the CMTA announces a major breakthrough in CMT1A research.

2016

The CMTA establishes Camp Footprint - the first camp in the US for children living with CMT.

2013

Dr. John Svaren, from the University of Wisconsin, creates state-of-the-art cell lines employing genome editing technology, while other scientists in the CMTA network develop and utilize human stem cells in CMT research.

2012

The CMTA establishes 11 Centers of Excellence to help ensure CMT patients receive the best possible evaluation and care, and their information is collected for possible recruitment into clinical trials.

2011

CMTA board member Elizabeth Ouellette organizes the first CMT Awareness Week. Her effort sparks an international movement and becomes an annual month-long celebration to spread awareness about CMT.

2010

The CMTA brings together globally recognized CMT specialists for a CMT Type 2 research symposium in San Diego, CA.

2009

Less than one year after STAR is set into motion, the first CMT1A cell line is grown. CMT1A drug discovery begins using high throughput screening at the National Institutes of Health.

2008

In a vote of confidence for the CMTA's new research initiative, two CMTA families make large contributions and kick start fundraising campaigns to support the **Strategy to Accelerate Research (STAR).**

2006

Joining forces with the MDA, the CMTA funds the first-ever ascorbic acid clinical trials.

2003

CMT advocate and volunteer Bob Budde becomes the liaison for CMTA support groups.

2001

In conjunction with Wayne State University, Dr. Michael Shy and the CMTA establish the North American CMT Database.

1995

The CMTA Board of Directors begins awarding $35,000 fellowship grants to CMT researchers.

1991

Dr. James Lupski, MD, PhD, identifies the gene that causes CMT1A.

1983

The CMTA's predecessor, the National Foundation for Peroneal Muscular Atrophy, meets for the first time.

The CMTA is Treatment-Driven and Partner-Focused

Research and Strategic Partnerships

Dr. John Svaren, Chair CMTA-STAR Scientific Advisory Board

To advance CMT research, the CMTA:

- Invested over $17M since 2008 and expects to spend $10M more to bring CMT drugs to market.
- Currently has over 50 active research projects with top labs around the world.
- Has a STAR Scientific Advisory Board with 30 of the best CMT scientists from around the world.
- Partners with more than 32 of the top pharmaceutical, biotech and service companies.
- Actively works with the patient community in the drug development process through the Patients as Partners in Research program.

Support for 80,000 Patients and Families

Youth Council established in 2019

The #1 trusted resource for information about CMT, the CMTA provides support through:

- An Advisory Board with 25 expert contributors
- 41 CMTA Centers of Excellence (COE)
- 70+ CMTA Branches
- Biannual Patient Family Conferences
- Camp Footprint for children living with CMT
- *The CMTA Report* and other publications
- The CMTA Emotional Support Group
- CMTA Virtual programs and Webinars
- In-person and online community engagement
- National CMT Awareness Month

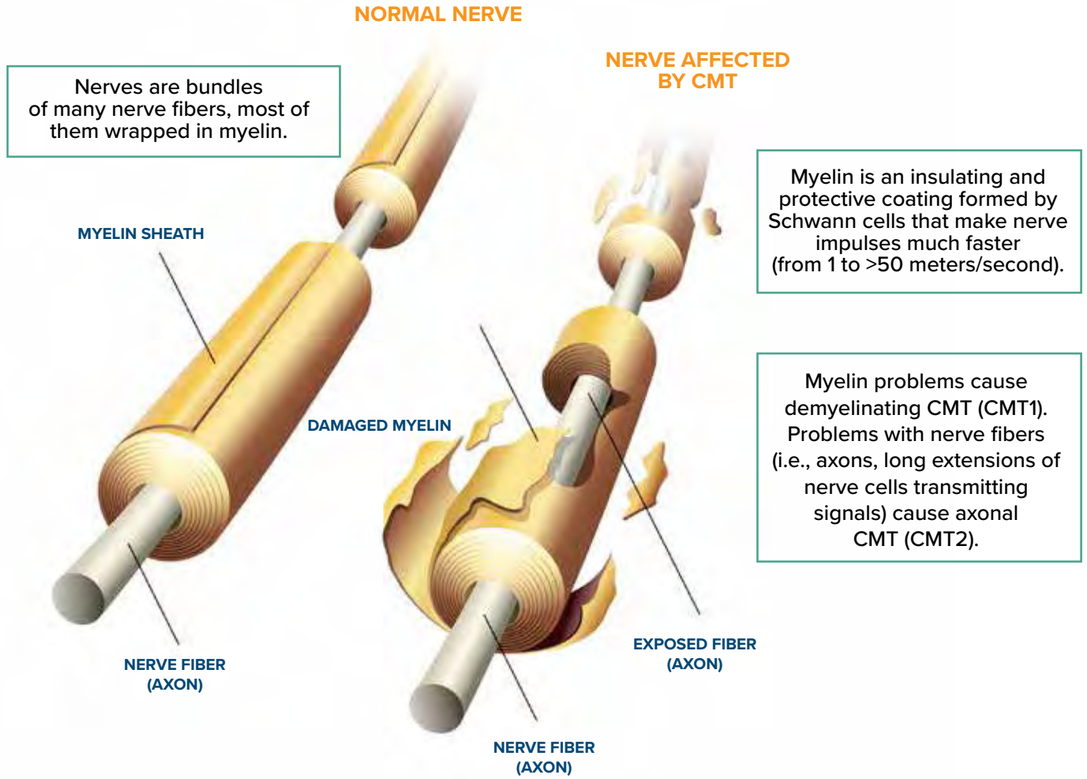
Active Fundraising and Stewardship of Donations

CYCLE 4 CMT successfully raised over $1,400,000 from 2014-2020

The CMTA is community powered:

- In addition to annual campaigns, the CMTA community supports our research and our programs through the national Walk 4 CMT campaign, fundraisers held by CMTA board members and grassroots events organized by CMTA community members.
- The CMTA makes efficient use of your donations - more than 87 percent of every dollar goes directly to support our mission.
- A 4-star rating by Charity Navigator two years in a row, the highest rating a non-profit can receive, and a 100 percent score for governance and transparency.

STAR'S PORTFOLIO FOR DEMYELINATING CMTs - 1A, 1B, 1X (AND SOME 4s)



Demyelinating forms of CMT affect the protective coating, or myelin, that insulates the "electrical wire" that is the nerve. Research specific to demyelinating forms of CMT—Types 1A, 1B, 1X and some Type 4s—includes some two dozen projects:

GENE THERAPY AND GENE EDITING PROJECTS

In collaboration with Ionis Pharmaceuticals, we are developing antisense oligonucleotides (ASOs), which have shown dramatic results in two rodent models of CMT1A.

CMTA-funded studies by Dr. Kleopas Kleopa of the Cyprus Institute of Neurology and Genetics have shown that gene therapy is feasible in rodent models of CMT1X and CMT4C, and the CMTA is actively supporting the efforts of several gene therapy companies to develop new CMT gene therapies. Pioneering CMTA-sponsored preclinical gene therapy studies have shown great promise in models of demyelinating CMT. This approach is now being extended to use RNA interference to decrease the PMP22 levels found in CMT1A and to optimize delivery to the affected Schwann cells in demyelinating CMT.

As the CMTA engages various partners to initiate gene therapy projects, it is important to keep in mind that we have a clear pathway for treatment of CMT2 type neuropathies that affect motor neurons. The recently approved AAV treatment for spinal muscular atrophy lays the technological groundwork for similar treatments for CMT2A and others. However, for CMT1A, it is not yet clear if AAV9 will be the optimal vehicle for Schwann cell delivery. Because of this, we are supporting a collaborative relationship to build on Dr. Kleopa's success in fixing Schwann cell deficits in preclinical trials for CMT1X and CMT4C. The partnership of Dr. Kleopa with an eminent gene therapy expert, Dr. Steven Gray, and an expert in Schwann cell specific gene expression, Dr. John Svaren, will address these challenges by trying multiple AAV subtypes and optimizing the vector engineering so that we can build in the necessary safety factors and optimal administration of AAV vector so that we can efficiently target Schwann cells and move to clinical trials for CMT1A. These collaborative efforts will provide the basis of future partnerships as we engage in parallel testing of several strategies to determine which vector designs are most effective.

We are currently collaborating with one company to use CRISPR (genome editing) to treat demyelinating CMT, and additional collaborations with leading labs are underway.

SMALL MOLECULE AND BIOLOGICAL THERAPY PROJECTS

In partnership with InFlectis BioScience, we are developing agents to restore myelin protein balance for CMT1A and CMT1B. Phase 1 clinical trials have concluded, and InFlectis is gearing up for Phase 2 trials.

The progression of all types of CMT occurs as the longest axons are compromised in a process called axon degeneration. We are working with partners to develop molecules that regulate the triggers of axon degeneration. We are currently testing the applicability of this approach in multiple models of CMT, collaborating with a number of companies to show that candidate drugs can promote axon survival, preserve nerve function and prolong patient mobility in demyelinating Type 1 CMT disorders.

We are supporting work done by Dr. Maurizio D'Antonio of the San Raffaele Scientific Institute to test new drug classes for CMT1B, which are being developed for stress-related disorders such as stroke, Alzheimer's and retinal degeneration.

The CMTA has just approved two new projects to test small molecule therapies in preclinical models of CMT1A.

Most recently, the Board of Directors awarded the Feltri/Wrabetz Lab at the University at Buffalo $138,110 for a 12-month study that will test whether drugs already approved for hypertension and erectile dysfunction can stifle the unfolded protein response of CMT1B.

PREPARING FOR CLINICAL TRIALS

In partnership with the Inherited Neuropathy Consortium, we are building on their recent successes in development of novel biomarkers and outcome measures in CMT1A and supporting major efforts to extend development and testing of critical biomarkers for CMT1B and CMT1X to support upcoming clinical trials. Toward that end, the CMTA Board of Directors awarded $601,407 in January for a CMT1X biomarkers project that will evaluate 60 patients over two years, measuring progression using outcome measures and biomarkers.

Clinical outcome assessments (COAs) are measures that have been developed to evaluate the clinical severity and progression of CMT over time. Biomarkers are chemicals in the body that reside in fluids like blood and tissues. Biomarkers are more sensitive than COAs, meaning that they measure changes over shorter periods of time, and therefore can more quickly and precisely measure whether a treatment or drug had a positive impact on the neuropathy.

COAs used in the CMT1X study will include:

The CMT Neuropathy Score (CMTNS) and the Examination Score (CMTES)—These measures are based on patients' symptoms, physical findings and electrophysiology. Measures include assessment of sensory symptoms as well as motor skills and strength of the arms, hands and legs.

The CMT Health Index *(CMT-HI)—*This is a patient-reported measure to assess therapeutic benefit in CMT clinical trials, but it may also be used to measure overall CMT patient health. This measure is unique because it measures patients' perspectives on their mobility, foot and ankle strength, hand and finger function, and a series of related symptoms (pain, fatigue, numbness, hearing, etc.).

Lucas (left), a passionate footballer, was diagnosed with CMT1A at the age of 8, the only one in his family to carry the gene.

The CMT Functional Outcome Measure—This is a newer, performance-based measure that assesses the functional ability of adults with CMT. Performance measures include strength in hands and feet, lower and upper limb functioning (hand and finger dexterity), balance and mobility.

Biomarkers used in the CMT1X study will include:
MRI, the assessment of muscle, has been shown to a sensitive measure of progression in CMT1A, and this will be extended to CMT1X.

Skin Biopsies—Research shows that CMT affects expression of genes in the nerves found in skin, which can be used to measure response to treatment.

Neurofilament Light Chain—
Blood plasma levels of the protein neurofilament light chain have been shown to be a marker of axonal damage as levels are elevated in CMT patients and correlate with disease severity.

A LOOK AT 1A STAR BIOTECH ALLIANCE PARTNERS:

THE CMTA HAS ESTABLISHED A UNIQUE CAPABILITY TO DEVELOP AND TEST NEW THERAPIES DIRECTLY WITH COMPANIES. THIS ALLOWS ANY COMPANY INTERESTED IN POSITIONING A THERAPY FOR CMT TO ACCESS THE INFRASTRUCTURE NEEDED TO EVALUATE THE THERAPY WITHOUT COMMITTING SIGNIFICANT TIME AND MONEY UP FRONT.

The CMTA has acquired and characterized best-in-class mouse and rat models of CMT1A so we know when to test a drug, for how long and what signifiers of improvement need to be measured. Currently, six models are well characterized and available, representing four different types of CMT. Expert contract research organizations have been engaged to perform the testing under CMTA direction, and our agreement structure lowers common barriers to entry such as confidentiality, retention of intellectual property and long-term financial commitment.

In addition to the validated CMT animal models, the CMTA and the New York Stem Cell Foundation (NYSCF) have put together a collection of patient-derived stem cell lines for CMT, including CMT1A. These cell lines give companies the ability to test therapies on patients' own genes, the first step to enabling a personalized medicine strategy.

A number of companies are engaged in testing for CMT1A with us. Of the four CMT types currently in preclinical testing, CMT1A has attracted the highest interest due to its prominence in the CMT patient population. All therapy modalities are represented in the current portfolio of alliance activity, from small molecules to biologicals to genetic modifiers.

Sanofi was our first alliance partner for CMT1A and in 2020 evaluated small molecules that came from this joint program as potential new alliance partners have expressed interest in acquiring them. In addition, Sanofi has asked the CMTA to lead testing of a new small-molecule approach that has been advancing for a different but related disease area. In 2020, Sanofi restructured, closing its neuroscience unit in Boston.

Ionis Pharmaceuticals was the first partner to demonstrate that a genetic modifier of the PMP22 gene (anti-sense oligonucleotides or ASOs) could effectively repair CMT1A defects in animal models of the disease. Since then, Ionis has been working to solve a generally understood limitation of its technology–the delivery of the ASOs to the target Schwann cells. They have acquired from us CMT1A stem cell lines in the NYSCF repository for use in testing different approaches to enhance ASOs delivery. We are awaiting results from this work, which would allow its CMT1A effort to advance if successful.

Regenacy owns a drug candidate that has been in human testing for a different disease but may have value in treating CMT. Regenacy accessed our testing resource to evaluate the candidate in several CMT types, including CMT1A. The results of the evaluations were mixed, and Regenacy is evaluating which efforts merit further study via an external collaboration to test activity in cell-based models of CMT.

Confidential Partner A owns a drug candidate derived from a program at a major pharmaceutical company. Based on known evidence of the drug target's possible role in CMT disorders, the company pursued evaluation in both Type 1 (CMT1A) and Type 2 CMT animal models. We provided partial evidence of effect in CMT1A, and very detailed data that the drug's effect was primarily on sensory, not motor, nerves. From this data, the company concluded that the benefit of using this drug class in CMT therapy was not sufficiently compelling and the effort was terminated.

Confidential Partner B: The testing resource is "therapy agnostic" and can be used to evaluate gene therapy approaches as well as ASOs, biologicals and small molecules. Our first alliance partner in this area has been evaluating the delivery of its gene modifying system, packaged inside an AAV virus, to nerves in CMT1A animals. The gene localization studies are still in progress, and if delivery is sufficiently effective, this will be followed in 2021 by a complete series of preclinical efficacy studies to determine if the approach can correct the CMT1A defect and restore normal function in the animals.

Confidential Partner C is developing a novel biological approach to treat CMT and asked for our help in evaluating its candidate in both Type 1 (CMT1A) and Type 2 models. These studies showed promising results in both models, and together we are pursuing studies to determine the site of action of the candidate therapeutic, which may not be directly in the nerve but at the junction of nerve and muscle. Additional studies are being discussed that would examine further biomarker elevation in both models and assess the survival of peripheral nerve in the completed studies.

InFlectis BioScience, a French startup company, is working to develop a new approach to CMT1B and CMT1A. Sponsored research studies have been performed in the CMTA STAR consortium to assess drug effects in both animal models and InFlectis is currently raising funds for clinical trial testing of the molecule in patients.

Pharnext, a French company, is developing a combination of several known drugs for the treatment of CMT1A, which when given together may be effective at slowing progression of the disease. The small molecule combination showed benefit in early clinical trials, and regulatory authorities have asked the company for an additional, expanded trial using the highest proposed dose combination. The company has raised additional funds for this clinical trial extension, and is currently continuing to dose patients. Results are expected in the second quarter of 2021.

The CMTA has supported Pharnext with patient advocacy efforts and is providing biomarkers in preparation for Phase III clinical trials.

DEMYELINATING TYPES

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
1A	Pharnext	Small Molecule	Discovery → Research Tools → Preclinical → Phase1 → Phase2 → P3
	Acceleron*	Biological	Discovery → Research Tools → Preclinical → Phase1 → P2
	InFlectis BioScience	Small Molecule	Discovery → Research Tools → Preclinical → P1/P2
	Cyprus + University of Wisconsin + University of Texas, SW	Gene Therapy	Discovery → Research Tools → Preclinical
	Ionis	Gene Therapy	Discovery → Research Tools → Preclinical
	National Institutes of Health*	Assays/Small Molecule	Discovery → Research Tools → Preclinical
	Regenacy Pharmaceuticals*	Small Molecule	Discovery → Research Tools → Preclinical
	Sanofi*	Small Molecule/Biomarkers	Discovery → Research Tools → Preclinical
	STAR Biotech Partner A*	Small Molecule	Discovery → Research Tools → Preclinical
	STAR Biotech Partner B*	Small Molecule	Discovery → Research Tools → Preclinical
	STAR Biotech Partner C	Gene Therapy	Discovery → Research Tools → Preclinical
	STAR Partner D	Biological	Discovery → Research Tools → Preclinical
	University of Wisconsin	Small Molecule	Discovery → Research Tools → Preclinical
	University of Wisconsin	Target Validation	Discovery → Research Tools → Preclinical
	Jackson Laboratory	SARM1/Target Validation	Discovery → Research Tools → Preclinical
	Jackson Laboratory	HDAC6/Target Validation	Discovery → Research Tools → Preclinical
	University of Rochester, NY	Biomarkers (Wearables)	Discovery → Research Tools → Preclinical
	University at Buffalo, NY	Small Molecule	Discovery → Research Tools → Preclinical
	University of Wisconsin + Memorial Sloan Kettering	Target Discovery	Discovery

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
1B	Acceleron*	Biological	Discovery → Research Tools → Preclinical → Phase1 → P2
	InFlectis BioScience	Small Molecule	Discovery → Research Tools → Preclinical → P1/P2
	National Institutes of Health*	Assays/Small Molecule	Discovery → Research Tools → Preclinical
	San Raffaele Scientific Institute	Small Molecule	Discovery → Research Tools → Preclinical
	University at Buffalo, NY	Small Molecule	Discovery → Research Tools → Preclinical
	Universities of Iowa and Wisconsin	Biomarkers	Discovery → Research Tools → Preclinical
	University of Wisconsin	Target Validation	Discovery → Research Tools → Preclinical
	University of Iowa	Target Validation	Discovery → Research Tools → Preclinical
	University at Buffalo, NY	Animal Model/Target Validation	Discovery → Research Tools → Laboratory
	University at Buffalo, NY	Target Discovery	Discovery

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
1X	Acceleron*	Biological	Discovery → Research Tools → Preclinical → Phase1 → P2
	Cyprus Institute	Gene Therapy	Discovery → Research Tools → Preclinical
	University of Pennsylvania	Target Validation	Discovery → Research Tools → Preclinical
	Jackson Laboratory	SARM1/Target Validation	Discovery → Research Tools → Preclinical
	Universities of Iowa & Wisconsin	Biomarkers	Discovery → Research Tools → Preclinical
	University of Illinois (Chicago)	Animal Model	Discovery → Research Tools → Laboratory
	Jackson Laboratory	Animal Model	Discovery → Research Tools → Laboratory

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE
4	4A – University of Texas South Western	Gene Therapy	Discovery → Research Tools → Preclinical
	4B – San Raffaele Scientific Institute	Small Molecule	Discovery → Research Tools → Preclinical
	4C – Cyprus Institute	Gene Therapy	Discovery → Research Tools → Preclinical
	4J – Neurogene	Gene Therapy	Discovery → Research Tools → Preclinical
	4A – Envigo	Preclinical Testing Partner	Discovery → Research Tools → Research Tools/Preclinical

* Project concluded

DEVELOPING AND CHARACTERIZING NEW MOUSE MODELS OF CMT1X

Mouse and rat models are invaluable in disease research because models can be developed to mimic the exact same genetic trends seen in patients. They can also be used for gene therapy testing, axonal degeneration assessment and testing various therapeutics.

Over the years, the CMTA has funded the development and usage of multiple models for CMT1A and CMT1B. Continued development of new genetically engineered mouse models for CMT1X is ongoing in many labs and is critical because CMT1X is more heterogeneous (> 400 variants identified) than other forms of CMT. It is therefore essential that multiple mouse models are developed to model the genetic variability found in CMT1X patients.

Additionally, further work is being done to characterize new CMT1X mouse models as they are developed. This means that each model (representing a specific mutation) is analyzed to characterize every aspect of the progression and severity of CMT1X. Some of the characterizations include age of onset, quantifying changes in axonal loss, nerve conduction, demyelination patterns over time and performance of various motor skills.

Both development of new models and characterization of each model are critical to support the development of new drugs to treat CMT and, ultimately, to find a cure.

STAR ALLIANCE PARTNERS

32+ Research Partners
50+ Research Projects
$17M+ in Research Funding

STAR
Strategy To Accelerate Research

1ATIMELINE

CMTA Roadmap to Success

STAR
Strategy To Accelerate Research

2008

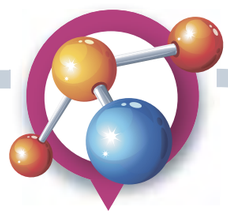
Strategy to Accelerate Research (STAR) project launched

2009

Inherited Neuropathy Consortium (INC) launched

2010

Development of first drug screening assays in partnership with the NIH



2011

First NIH funding for small molecule screening project

2012

First drug screen published; first stem cell project initiated; CMT Pediatric Scale published

2013

First clinical trial in USA published (Lewis et al., JAMA Neurology); partnership with Sanofi initiated

2014

First use of genome editing to create drug screen; rodent models incorporated into testing platform; Ionis alliance initiated

2015

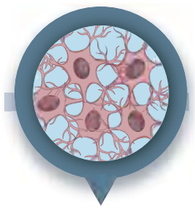
InFlectis and CMTA Board Member Dr. Lawrence Wrabetz publish successful CMT1B studies, later developed for CMT1A clinical trials; over 2.3 million compounds screened in partnership with the NIH and Sanofi; human stem cells made in NYSCF alliance

2016

Biomarker studies with Sanofi initiated

2018

Ionis-CMTA partnership leads to breakthrough proof-of-principle of PMP22 effect on disease phenotype; the INC develops patient-centric clinical scales



2019

Stem cell studies published, first gene modifier and skin biopsy assay (treatment-responsive for CMT1A); CMT Health Index (CMT-HI) and CMT Functional Outcome Scale (CMT FOM) published

2020

Sanofi partnership identifies novel blood biomarker; natural history study published (>1000 patients); gene therapy project with three major institutions launched; CMTA engaged in pre-clinical testing or clinical planning with a record 10 biotech partners

PHARNEXT ANNOUNCES

PHASE 3 CLINICAL TRIALS FOR 1A

Recruiting for 1A Clinical Trials Underway

Pharnext announced Phase III clinical trials for its PXT3003 drug for CMT1A February 21. The international, multi-center, randomized, double-blind, placebo-controlled study is designed to evaluate PXT3003 versus placebo in male and non-pregnant female subjects with genetically confirmed CMT1A of mild-to-moderate severity, aged 16 to 65 years.

PXT3003 is a novel, fixed-dose synergistic combination of baclofen, naltrexone and sorbitol formulated as an oral solution. The three individual components of PXT3003 were selected to downregulate the overexpression of PMP22 protein, leading to improvement of neuronal signaling in dysfunctional peripheral nerves.

Pharnext is an advanced clinical-stage biopharmaceutical company pioneering new approaches to developing innovative drug combinations based on big genomics data and artificial intelligence. The CMTA is collaborating with Pharnext on a project aimed at identifying and validating potential treatment-responsive CMT1A biomarkers that could be further explored in future clinical studies. The current clinical trial will be conducted in approximately 48 sites worldwide. Genetically confirmed CMT1A subjects will be screened and randomized in a 1:1 ratio to receive either oral PXT3003 or a matching placebo daily for 15 months. A total of approximately 350 subjects will be enrolled.

Visits will take place at screening, baseline (day 1), and months 3, 6, 9, 12, and 15. Randomization will occur at the baseline (day 1) visit. Telephone contacts will take place at weeks 2 or 3, month 1 and 2, and then monthly between subsequent in-person visits. A safety follow-up visit will be conducted at month 16.

Subjects will receive in-clinic dosing of study medication at visits on day 1 and months 6, 12, and 15. Study medication will be dispensed for outpatient dosing on day 1 and months 3, 6, 9, and 12. During outpatient dosing, subjects must complete a study medication diary using an application on their tablet, phone or computer. The diary will be evaluated, along with returned unused study medication, as part of study drug compliance at visits at months 3, 6, 9, 12, and 15.

The primary outcome measure (mONLS) and the 10-Meter Walk Test (10mWT), along with the Columbia Suicide Severity Rating Scale (C-SSRS) will be evaluated at each post-screening visit. A safety follow-up visit will take place 30 days (month 16) after the active treatment period ends (month 15). A Data Safety and Monitoring Board (DSMB) will meet on a scheduled basis throughout the study to review safety data and will reconvene on an ad hoc basis as necessary.

Camper Doug celebrating virtual Camp Footprint

CLINICAL TRIALS – THE ROAD TO DRUG APPROVAL

The Food and Drug Administration's drug approval process involves five basic steps. The discovery/concept phase comes first, as research for a new drug or device begins in the laboratory. In Step 2, the pre-clinical phase, drugs and devices undergo laboratory and animal testing to answer basic questions about safety.

Clinical trials follow, then FDA review and finally FDA Post-Market Safety Monitoring. Clinical trials are simply studies, or trials, in humans. They occur only after researchers (or developers) complete the FDA's Investigational New Drug (IND) process, which requires them to submit animal study data and toxicity data, manufacturing information, clinical protocols (study plans) for studies to be conducted, data from any prior human research and information about the investigator.

While preclinical research answers basic questions about a drug's safety, clinical trials study the ways the drug will interact with the human body. They are designed to answer specific research questions related to a medical product and follow a specific study plan, or protocol, developed by the researcher or manufacturer.

Before a clinical trial begins, researchers review existing information about the drug, then decide who qualifies to participate (selection criteria), how many people will participate, how long the study will last, whether there will be a control group, how the drug will be given to patients and at what dosage, how to assess the results and how the data will be reviewed and analyzed. Clinical trials follow a standard progression, starting with early, small-scale Phase 1 studies lasting several months and involving 20 to 100 volunteers with the disease.

Phase 1 studies are designed to assess safety and dosage. Approximately 70 percent of drugs move on to the next phase. Phase 2 studies have up to several hundred people with the disease/condition and can last from several months to two years. Their purpose is to examine the drug or device's efficacy and side effects. Some 33 percent of drugs move on to the next phase.

Phase 3 trials look at the drug's efficacy and monitor subjects for adverse reactions. Some 300 to 3,000 volunteers with the disease participate in Phase 3 studies, which last from one to four years, with 25 to 30 percent of drugs moving on to Phase 4. Several thousand volunteers with the disease take part in the Phase 4 study, which looks at the drug's safety and efficacy.

Once the FDA receives a New Drug Application (NDA), the review team decides if it is complete. If not, the review team can refuse to file the NDA. If it is complete, the review team has six to 10 months to make a decision on whether to approve the drug.

If the FDA determines that a drug has proved safe and effective for its intended use, it works with the applicant to develop and refine prescribing information, or "labeling." Labeling accurately and objectively describes the basis for approval and how best to use the drug.

In many cases, issues remain to be resolved before the drug is approved for marketing. Sometimes the FDA requires the developer to address questions based on existing data. In other cases, the FDA requires additional studies. If the NDA doesn't contain sufficient data for the FDA to determine the safety and effectiveness of a drug, it may organize a meeting of one of its Advisory Committees to get independent, expert advice and to permit the public to make comments. These Advisory Committees include a patient representative who provides input from the patient perspective.

In cases involving serious conditions with unmet medical needs, the FDA can "fast track" the drug approval process in order to get important new drugs to patients sooner. Once a drug receives Fast Track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

THE CHALLENGE OF RARE DISEASES

Clinical trials for rare diseases like CMT, which affect fewer than 200,000 people in the United States, present additional challenges. Populations are small, limiting opportunity for study and replication. Genetic disorders like CMT are often characterized by a wide range of severity, clinical presentation and rate of progression. Rare diseases are often poorly understood and natural histories incompletely described. Diagnosis is often difficult, with years between presentation and diagnosis. Many rare diseases are serious or life-threatening, and many who have them have unmet medical needs. Regulatory and drug development precedent is often lacking, as are outcome assessment tools.

The FDA review team thoroughly examines all submitted data on the drug and makes a decision whether to approve it. The NDA's purpose is to demonstrate that a drug is safe and effective for its intended use in the population studied. Along with clinical results, developers must include proposed labeling, safety updates, drug abuse information, patent information, data from studies conducted outside the United States, Institutional Review Board compliance information and directions for use.

WHY WE GIVE: WE BELIEVE IN THE CMTA

TO BELIEVE IS TO HAVE CONFIDENCE, TO FEEL SURE AND TO TRUST.

By Missy and Seth Warfield

Here's why we are such believers:

We have been active with the CMTA for many, many years. We have watched it grow and fine-tune its organization and mission "to support the development of new drugs to treat CMT, to improve the quality of life for those with CMT and, ultimately, to find a cure."

We watched as the STAR (Strategy to Accelerate Research) alliance brought CMT researchers from around the world together to work in collaboration, not competition. We watched as those research scientists tackled the first few genes known to cause CMT, then kept working to discover CMT in more than 100 genes. We've seen the CMTA grow from searching for pharmaceutical companies, large and small, who would offer their "libraries" of developed drugs to test for efficacy in treating CMT. Now there are 32 committed "pharmas" and others "knocking on the CMTA's door."

Yes, we believe in the CMTA and its Charity Navigator 4-star (the best) rating for the high percentage of money raised that goes directly to CMT research and the transparency overall. Not every charity achieves that high rating.

Our reasons for giving to the CMTA go deep. Our family lives with CMT every day. Missy was diagnosed with CMT1A as a young teenager, having struggled running, jumping, twisting ankles and falling down for years. She was reason #1. Then, our two children were diagnosed with CMT as youngsters. Reasons #2 and #3. Years later, two of our six grandchildren were added to our CMT1A list. That's #4 and #5—three generations! We long for a cure.

What has the CMTA done to help us all? It has named Centers of Excellence across the United States and five more overseas. The 41 clinics have multidisciplinary teams of experts to evaluate and help those affected by CMT. Our family has been to several different CMT clinics, where we were helped with bracing, exercise and advice. Add the 72 CMTA branches—patient and family support groups, one started by us—to see how many people have been helped by the CMTA.

For the youngsters, the CMTA created Camp Footprint where "you're not the only one who cannot run very well," according to one grandchild. That is a place where those with fewer CMT issues can see those who must wear AFOs or braces or use wheelchairs or crutches and where they all know that they are loved and not alone.

So, we believe in the outreach of the CMTA and this is why we have led several challenge matches for CMT1A. These are difficult times: Nonprofits and those who need their help need all of us to believe. CMT is an "orphan" disease, a rare disease affecting barely 3 million people around the world and some 150,000 in the United States. Finding financial support to cure our "unusual" disease is tough when so many are dying of COVID-19 and so many others are facing food insecurity. But we believe in the CMTA. We hope for a cure and we believe in your decision to help. Please join us in our push to raise $1 million for CMT1A research by the end of this year. We will match all donations to our challenge up to $500,000.

We believe in you, too! Our challenge will come in two parts: one now to match $250,000 and another in the fall. The CMTA already has our good-faith gift of $250,000 for the first challenge. We believe that if all of us give—even a little—we can give CMT1A research the $1 million "shot in the arm" to find the cure. Donations to the CMT1A challenge can be made at: cmtausa.org/1Amatch

FILLING THE PIPELINE: THE CMTA | STAR FUNDING PROCESS

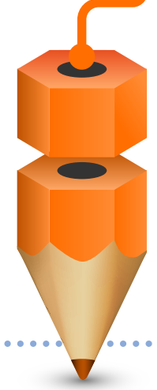
The CMTA Board does not accept unsolicited proposals, but it occasionally seeks out targeted proposals in specific disease areas, then employs a protocol aimed at reaching a funding recommendation within six weeks. Under that protocol, STAR Advisory Board members, including both Scientific Expert Board members and Therapeutic Expert Board members, conduct a first-level scientific review on translational projects brought to, or identified by, the CMTA. The initial pre-proposal is limited to three pages and must include specific aims.

STAR Advisory Board members then either reject the proposal or ask for a full proposal from the investigator, including a detailed budget. Applicants whose projects are green-lighted for a full proposal then have two weeks to submit it. All full proposals must include a research plan with preliminary data, budget, timelines and information about the investigative groups involved.

Once a full proposal is received, the Scientific Expert Board evaluates its scientific merit, and the Therapeutic Expert Board confirms that there is a therapeutic opportunity/asset that will benefit the CMTA's STAR therapy development mission. Each advisory board review is completed in two weeks or less, then both recommendations go to the CMTA Board of Directors.

Project proposals are scored in two stages, the first emphasizing scientific excellence and the completion of milestones and the second evaluating the translational and commercialization potential of the project. To read more about the scoring criterion, visit cmtausa.org/our-research/for-researchers/funding.

At the end of the sixth week, the CMTA Board of Directors either approves or rejects the project. When a proposal is funded, the CMTA documents, agrees and signs off on the research plan with the research investigator's institution.



YES, PLEASE PUT MY CONTRIBUTION TO USE IN THE FIGHT AGAINST THE PROGRESSIVE AND DEVASTATING EFFECTS OF CMT.

Please earmark my gift for STAR Research towards:

☐ Type 1A Dollar-for-Dollar Match ☐ Type 2 Dollar-for-Dollar Match ☐ STAR Research (All CMT Types)

YES! I want to make a donation in the amount of: ☐ $3500 ☐ $1000 ☐ $500 ☐ $250 ☐ $100 ☐ $50 ☐ Other: $_____

☐ Make My Gift a Monthly Donation. ☐ Please charge my credit card. ☐ Visa ☐ MasterCard ☐ American Express

☐ Check enclosed, payable to the Charcot-Marie-Tooth Association. Donate online at cmtausa.org/donate2star

To give the gift of stock, please call Jeana Sweeney, the CMTA Director of Development at 814-269-1319

Name_____Card #_____Exp. Date_____

Signature_____Address_____

City_____State_____Zip_____Phone_____

☐ Please send me CMTA updates via email. My email is: _____

Complete and mail to the CMTA, PO Box 105, Glenolden, PA 19036

Alexis was diagnosed with CMT2F at the age of 33. She mourns the loss of wearing heels, feeling "cute" and being able to work off pizza with an intense workout.

STAR'S PORTFOLIO FOR AXONAL CMTs - TYPE 2 (AND SOME 4s)

Axonal forms of CMT affect the "electrical wire" that is the nerve, which is surrounded by the protective insulator coating known as myelin. Research specific to axonal CMT—Types 2 and 4—includes some two dozen projects and the CMTA Board of Directors recently approved two new ones: a gene therapy study for CMT4A, which researchers have identified as an ideal candidate for this approach, and a study on CMT2A biomarkers.

GENE THERAPY AND GENE EDITING PROJECTS

The CMTA is supporting pilot studies of gene therapy in CMT mouse models following a gene therapy trial for one peripheral neuropathy (GAN) at the NIH.

We are partnering with Dr. James Wilson at the University of Pennsylvania and Passage Bio to use gene therapy to treat CMT2A.

We are funding work with two eminent experts, Drs. Bruce Conklin and Luke Judge of the Gladstone Institutes and UCSF Departments of Medicine and Pediatrics, to explore therapeutic application of genome editing technology (CRISPR) to CMT2A, CMT2E and CMT2F.

Most recently, the CMTA Board of Directors awarded $227,170 to two researchers who believe that CMT4A is an ideal candidate for potential gene therapy approaches. Noting the investigators' extensive expertise in gene therapy and viral vectors, reviewers from the CMTA's Scientific Advisory Board said the innovative project may lead to the development of clinically translatable gene replacement therapy for patients with GDAP1 (ganglio-side-induced differentiation associated protein 1) mutations.

The prevalence of CMT4A is estimated at 1,000 out of every 100,000 people living with CMT. Some of the patients already enrolled in the Inherited Neuropathy Consortium's natural history project have this type, making it a potentially attractive option for a biotech company to explore. One company has already expressed some interest.

Principal investigators Steven Gray, PhD, and Xin Chen, PhD, of the University of Texas Southwestern Medical Center hypothesize that broad central nervous system (CNS)-directed delivery of GDAP1 gene with adeno-associated viral 9 (AAV9) during early life can ameliorate CMT4A disease symptoms in GDAP1 mutant mice, using an approach amenable to human translation.

Reviewers from the CMTA's Scientific Advisory Board said the clear innovative aspect of the project may lead to the development of clinically translatable gene replacement therapy for patients with GDAP1 mutations, advancing the field of gene therapy for both CMT4A and CMT2K patients.

SMALL MOLECULE AND BIOLOGICAL THERAPY PROJECTS

CMTA partners are working on developing molecules that regulate recently identified biochemical triggers of axon degeneration.

CMT2E is caused mutations in the neurofilament light (NEFL) gene. The CMTA has a diverse portfolio of approaches for 2E.

First, we are funding Dr. Mario Saporta's work at the University of Miami using human stem cells to develop as-says and test additional libraries of drugs for treatment in CMT2E.

Second, we supported a screen of FDA-approved compounds in Dr. Ron Liem's lab at Columbia University.

Third, the CMTA is supporting a new project to bring gene therapy to CMT2E being conducted by Dr. Kathrin Meyer and a leading gene therapy group at Nationwide Children's Hospital in Cincinnati.

UNDIAGNOSED TYPE 2

Approximately 50 percent of CMT2 patients do not yet have a definitive genetic diagnosis. Dr. Stephan Züchner at the University of Miami is working to change that, spearheading an ambitious project to identify new disease-causing mutations in patients seen in COEs affiliated with the Inherited Neuropathy Consortium (see related story page 30).

PREPARING FOR CLINICAL TRIALS

In partnership with the INC, we are building on their recent successes in development of novel biomarkers and outcome measures in CMT1A and supporting major efforts to extend development and testing of critical biomarkers for CMT2A in order to support the efficient design of upcoming clinical trials.

The CMTA Board of Directors recently awarded $559,555 for a study on identifying disease biomarkers for CMT2A, complementing the Inherited Neuropathy Consortium's cross-sectional analysis and evaluation of impairment in those patients over time (longitudinal) in those patients (see related story page 32). Several academic centers and companies have reached out to the INC to develop clinical trials for CMT2A, which will likely be instituted within the next two to three years. However, disease biomarkers for CMT2A are needed to demonstrate biological effects of candidate therapies and to provide additional sensitive natural history data of disease progression.

Led by CMTA Board Members Drs. Michael Shy of the University of Iowa and John Svaren of the University of Wisconsin, the study will examine a number of different biomarkers, including: protein biomarkers identified in blood samples, such as neurofilament light, which can be used to measure axonal damage; RNA biomarkers identified from skin biopsies and MRI imaging of patients' legs because the accumulation of fat within muscles damaged by neuropathy can be measured very precisely.

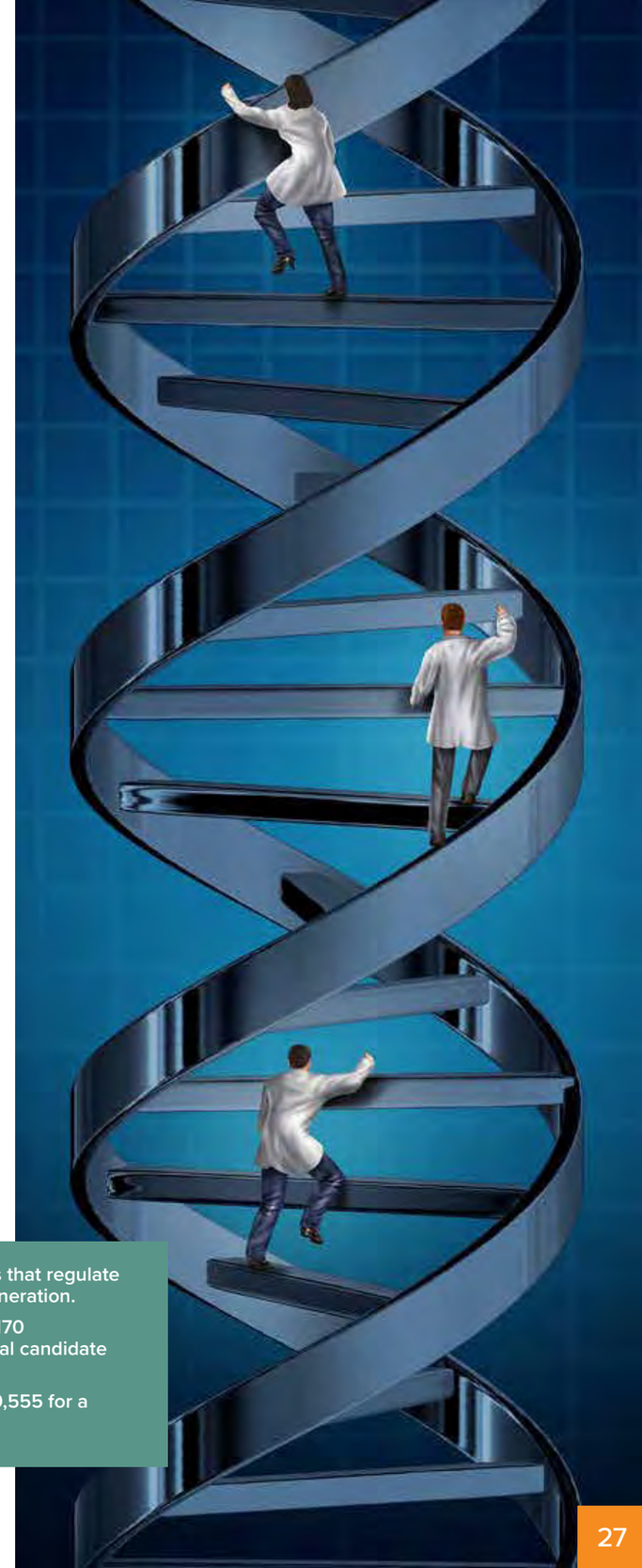
To bring this state-of-the-art program to CMT2A (as has already been done with CMT1A, and recently approved for 1B), study authors will evaluate 60 patients with CMT2A over two years to:

- Measure progression in a combination of clinical outcome assessments, including the Rasch modified CMT Examination Score (CMTES-R), CMT Functional Outcome Scale (CMT-FOM), and patient-reported CMT Health Index;
- Measure known biomarkers like neurofilament light and identify novel plasma biomarkers;
- Adapt a nanostring platform for skin biopsy analysis to help identify patients most able to benefit from a given therapy; and
- Take repeated MRI images over a 12-month period to identify increases in intramuscular fat accumulation (IMFA) of patients' lower limbs.

CMTA partners are working on developing molecules that regulate recently identified biochemical triggers of axon degeneration.

Last fall the CMTA Board of Directors awarded $227,170 to two researchers who believe that CMT4A is an ideal candidate for potential gene therapy approaches.

The CMTA Board of Directors recently awarded $559,555 for a study on identifying disease biomarkers for CMT2A.



AXONAL TYPES

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE: Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
2A	Passage Bio + University of Pennsylvania	Gene Therapy			Preclinical			
	Regenacy Pharmaceuticals*	Small Molecule			Preclinical			
	STAR Biotech Partner E	Small Molecule			Preclinical			
	STAR Biotech Partner A	Small Molecule			Preclinical			
	STAR Biotech Partner F	Peptide			Preclinical			
	Universities of Iowa & Wisconsin	Biomarkers			Preclinical			
	University of Iowa	Respiratory Study					P2	
	University of Pennsylvania	Animal Models		Laboratory				
	STAR Partner G	Small Molecule	Discovery					
	Gladstone Institute (UCSF)	Gene Therapy (CRISPR)	Discovery					
	Washington University	Small Molecule	Research Interest					

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE: Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
2D	Jackson Laboratory	SARM1/Target Validation			Preclinical			
	Jackson Laboratory	HDAC6/Target Validation			Preclinical			

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE: Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
2E	Regenacy Pharmaceuticals*	Small Molecule			Preclinical			
	STAR Biotech Partner D	Biological			Preclinical			
	Nationwide Children's Hospital + Ohio State University	Gene Therapy			Preclinical			
	Columbia University	Small Molecule			Preclinical			
	University of Miami	Small Molecule			Preclinical			
	Gladstone Institute (UCSF)	Gene Therapy (CRISPR)			Preclinical			
	Jackson Laboratory	SARM1/Target Validation			Preclinical			
	Jackson Laboratory	HDAC6/Target Validation			Preclinical			
	Columbia University	Animal Model		Laboratory				

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE: Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
2S	Jackson Laboratory	SARM1/Target Validation			Preclinical			
	Jackson Laboratory	HDAC6/Target Validation			Preclinical			

	STAR ALLIANCE PARTNERS	THERAPY TYPE	DRUG DEVELOPMENT STAGE: Discovery	Research Tools	Preclinical	Phase1	Phase2	Phase3
ALL TYPES	Psychogenics + Cleveland Clinic + Charles River	Preclinical Testing Partners			Preclinical			
	Inherited Neuropathy Consortium	Research & Clinical Tools			Preclinical			
	New York Stem Cell Foundation	Stem Cell Lines		Laboratory				
	University of Miami	Gene Identification	Discovery					
	Jackson Laboratory	Animal Models		Laboratory				

Kenneth is a martial arts instructor for children and adults with special needs. He has CMT1X.

THE CMTA'S TYPE 2 GENE DISCOVERY INITIATIVES

Dr. Stephan Züchner

Some 95 percent of CMT patients with a demyelinating type can get a genetic confirmation of their CMT. In contrast, only about 35 to 50 percent of patients with an axonal CMT are able to obtain genetic confirmation. Scientists have already identified more than 100 genes that cause CMT and they believe there are still over 100 causes waiting to be discovered.

Why is knowing one's type so important? Developing successful treatments and a cure for CMT depends on being able to target therapies to a patient's particular CMT-causing genetic mutation.

CMT is caused by mutations in genes, which are responsible for coding—or instructing—certain processes within the peripheral nerves. Each unique type of CMT is caused by a disruption in normal cell function, and each disruption is caused by the underlying genetic mutation.

THE SORD GENE DISCOVERY

In 2019, with CMTA support, Dr. Stephan Züchner and his team at the University of Miami discovered an autosomal recessive mutation in the SORD gene that causes an axonal type of CMT (Type 2). More than 3,000 patients in the United States have this mutation.

SORD, or SORD1, is responsible for coding an enzyme that converts sorbitol, a type of sugar, to fructose, another type of sugar, in a two-step process. It does this via the same pathway that is implicated in diabetic neuropathy. In diabetes, this pathway is disrupted, leading to the loss of sorbitol being converted into fructose, increasing intracellular sorbitol levels and decreasing intracellular fructose levels.

The CMT-causing mutation in the SORD1 gene causes the same loss of sorbitol conversion as diabetic neuropathy. Dr. Züchner is designing a study to investigate the candidate diabetic neuropathy therapy as a potential SORD-CMT treatment.

THE VUS INITIATIVE

Genetic tests for CMT often identify only a variant of unknown or uncertain significance—or VUS. Because of this, the CMTA is focused on studying VUS findings from CMT genetic tests. It can be very frustrating for CMT patients when their much-anticipated result does not identify the underlying responsible mutation and instead returns only a VUS finding.

VUS findings are common and CMTA researchers have begun adding them to a massive international database, stripped of any and all identifying information, and then studying that database in-depth to see if any of these VUS findings are actually connected to CMT diagnoses. This is what led to the discovery of the SORD1 gene mutation causing CMT.

Drs. Cortese, Scherer, Züchner and others studied over 1,100 database entries and identified 48 CMT patients whose genetic test results failed to identify an underlying genetic cause for their CMT, but who all had the same recessive SORD1 gene mutation, found with either whole exome sequencing (WES) or whole genome sequencing (WGS), and who all had similar clinical findings consistent with an axonal CMT.

From there, Dr. Züchner and his fellow CMTA-supported scientists were able to determine that the VUS finding in the SORD1 gene was indeed responsible for causing the associated CMT

THE MODIFIER GENES INITIATIVE

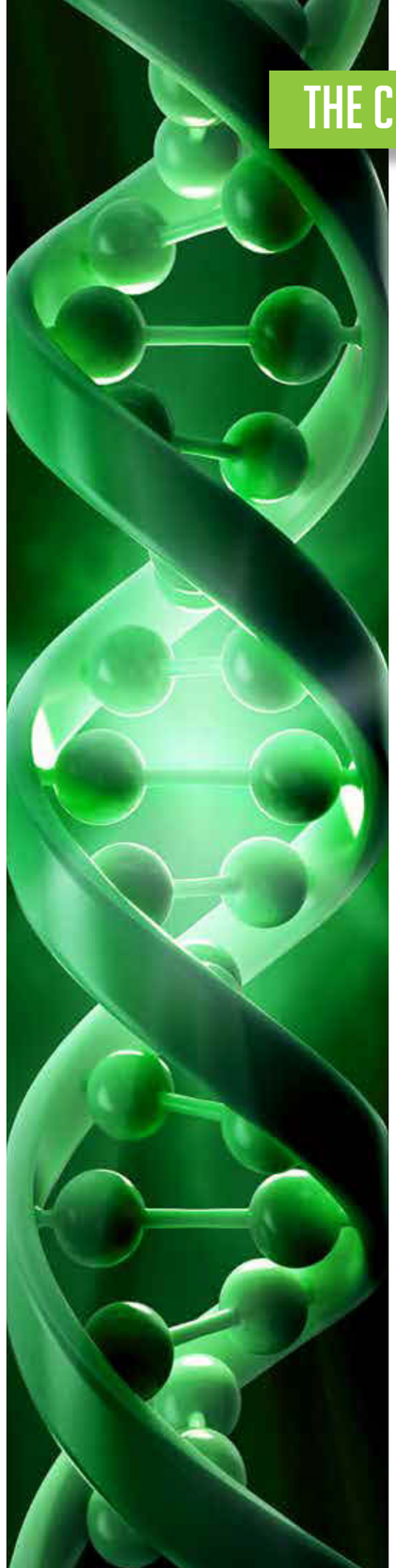
The CMTA is also pursuing an initiative to identify "modifier genes," which are secondary to the CMT-causing genetic mutation. The secondary genes are believed to play a role in symptom onset and/or disease severity.

CMT affects everyone differently, even within the same family. While some of the reasons for this are environmental, some might be due to modifier genes. SARM1, whose presence is required for axonal degeneration, is a modifier gene.

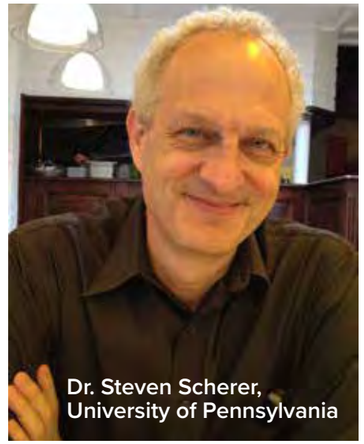
Scientists posit that if deleting SARM1 allows for the preservation of peripheral nerve axons, then a therapeutic approach that mimics a SARM1 deletion has the potential to be a successful treatment for axonal types of CMT. This discovery also demonstrates that targeting modifier genes like SARM1 may be more effective than targeting the underlying genetic mutation itself.

Scientists have already identified more than 100 genes that cause CMT and they believe there are still over 100 causes waiting to be discovered.

- Less than 50 percent of CMT 2 patients know their gene.
- No known gene -> no therapy development.
- No known gene -> ongoing "diagnostic odyssey."
- CMTA supports the most important genomic initiative by the INC and the GENESIS project.
- In 2020, the most common axonal CMT was discovered - SORD neuropathy, which is likely treatable.



THE CMT2A GENE REPLACEMENT THERAPY INITIATIVE



Dr. Steven Scherer, University of Pennsylvania

With the CMTA's support, Dr. Steven Scherer at the University of Pennsylvania is building on the recent breakthrough treatment for spinal muscular atrophy (SMA), which involved treating the disease with a first-of-its-kind gene replacement therapy. Promising data from rat models suggests that the gene replacement technology developed at Ohio State University for SMA could be used to treat CMT2A and he has partnered with the inventors of the SMA treatment technology to investigate their gene replacement application for possible use in CMT2A.

CMT2A is caused by autosomal dominant mutations in the MFN2 gene. With dominant types of CMT, one copy of the associated gene has a mutation, and the other copy is normal. In the case of CMT2A, only one copy of the MFN2 gene has a mutation.
Dr. Scherer is working with colleagues at University of Pennsylvania and Passage Bio on a treatment that would reduce levels of the mutated copy of MFN2 and provide a second unmutated companion copy of the MFN2 gene to restore the function of this important gene.

THE CRISPR-CAS9 INITIATIVE

CRISPR-Cas9, often referred to as genome editing or genomic surgery, is different from gene replacement therapy. CRISPR-Cas9 technology uses induced pluripotent stem cells (iPSC), which can be reprogrammed (induced) to become any type of cell (pluripotent). The process typically starts with a patient providing a skin cell sample. From those skin cells, iPSC are developed and reprogrammed for use in that patient, reducing the chances of the patient's body rejecting the cells.

With support from the CMTA, Drs. Bruce Conklin and Luke Judge of the Gladstone Institutes and UCSF Departments of Medicine and Pediatrics are investigating the use of CRISPR for application to CMT2A, CMT2E and CMT2F. Working under the auspices of the Innovative Genomics Institute (headed by 2020 Nobel Prize winner Dr. Jennifer Doudna), the pair are investigating whether iPSC can be used to create a gene copy, MFN2 for example, free of the CMT-causing mutation.

Methods to modify DNA in the genome have been around for more than 30 years, but CRISPR technology has brought major improvements in the speed, cost, accuracy and efficiency of gene editing. CRISPR can make deletions in the genome and/or be engineered to insert new DNA sequences. The CRISPR system was adapted from a naturally occurring gene-editing system in bacteria that captures snippets of DNA from invading viruses and uses them to create DNA segments known as CRISPR arrays. The CRISPR arrays allow the bacteria to "remember" the viruses so that if they attack again, the bacteria can target their DNA. Remarkably, this bacterial defense system works in human cells to edit DNA and perhaps treat genetic diseases.

CMT2A RESEARCHERS ON THE WAY TO BEING TRIAL-READY

A large international study of patients with CMT2A demonstrated that researchers are "in a good position to perform clinical trials as candidate therapies become available."

Jeanne has CMT2A. She wants to educate people about CMT so they don't have to endure a 20-year journey to diagnosis like she did.

Published in BRAIN, A Journal of Neurology, in January, the study concluded that current clinical outcome measures, namely the CMT Examination Score v2 (CMTESv2) and the CMT Pediatric Scale (CMTPedS), along with the development of responsive biomarkers, put researchers on track to becoming trial-ready.

Led by Menelaos Pipis and Mary M. Reilly of the Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK, the cross-sectional and longitudinal study involved the largest CMT2A cohort reported to date (196 patients). Clinical information from patients was collected as a part of the ongoing Inherited Neuropathy Consortium (INC) natural history study of CMT. The study's aim was to provide guidance for interpreting mutations of uncertain significance in mitofusin-2 (MFN2), inform prognosis and also provide natural history data that will guide clinical trial design.

Pipis said the study, which was funded by the National Institutes of Health, the INC and the CMTA, among others, exemplifies the power of international multi-center collaborations.

It also illustrates the close relationship between the clinical and research functions at the CMTA's Centers of Excellence: Patients were evaluated at one of the 19 INC Centers between 2009 and 2019 and at Wayne State University between 1996 and 2009. Antecedent clinical data was collected retrospectively from patient history while longitudinal follow-up data (clinical history and examination with or without neurophysiological studies) was collected during annual visits.

CMT2A, the commonest axonal form of CMT, affects some 25 percent of CMT2 patients. It is caused by mutations in mitofusin-2 (MFN2). In comparison to CMT1A, the commonest form of CMT, CMT2A is associated with a more severe, motor-predominant phenotype that usually manifests earlier in life and carries a greater burden of disability. Additional symptoms include optic nerve atrophy in up to 9 percent of patients, vocal cord involvement and upper motor neuron dysfunction.

Earlier, smaller studies of CMT2A described the phenotypic spectrum, or physical characteristics, of the disease, but longitudinal natural history studies were lacking until now.

The study found that childhood onset of autosomal dominant CMT2A is the most predictive marker of significant disease severity, independent of disease duration. When compared to adult onset autosomal dominant CMT2A, childhood onset is associated with significantly higher lifetime rates of use of ankle-foot orthoses, full-time use of a wheelchair and dexterity difficulties. Patients with a childhood onset of symptoms had a similar disease duration compared to those whose symptoms started in adulthood, yet the former had a significantly higher CMT Examination Score (CMTESv2) and CMT Neuropathy Score (CMTNSv2) at initial assessment.

The longitudinal data revealed that over one year, the CMTESv2 increased significantly in autosomal dominant CMT2A. Over two years, both the CMTESv2 and the CMTESv2-R increased significantly, much more than the increase observed in CMT1A over the same duration.

Longitudinal changes in the pediatric CMT2A population (autosomal dominant and autosomal recessive CMT2A grouped together) were even more pronounced, increasing significantly both over one year and two years. In practical terms this means that the CMTESv2 and CMTPedS as bedside clinical assessment tools are sensitive enough to pick up significant progression of the disease over one and two years, despite CMT being a very slowly progressive disease. Therefore, the CMTESv2 /CMTPedS can be used as clinical outcome measures in future clinical trials as they will be able to identify if a trial therapy is effective or not, given that a sufficient number of patients are recruited for the trial.

The study's findings and the ongoing work in developing novel blood and skin biomarkers are significant milestones in the preparedness of the CMT community for clinical trials and could not have come at a better time for patients with CMT2A.

WONDERING HOW YOU CAN GET INVOLVED?

If reading about the CMTA's exciting research agenda has inspired you to get involved, there are lots of ways to do it.

Join the INC Patient Registry, which makes it possible for researchers to find new treatments, create new studies and work to improve the lives of everyone with CMT. Enrollees in the patient registry are contacted when there are opportunities to participate in clinical trials and other research studies such as 6601: Natural History Evaluation of Charcot-Marie-Tooth Disease.

INC 6601 is a longitudinal study of individuals with CMT to see how it changes over time. Participants are invited back on a yearly basis to determine how the changes are occurring. During the first visit, patients are assessed for eligibility, fill out consent forms and have minimal demographics and a treatment history taken. At each visit, your medications and medical history will be assessed, and you will be asked to have a neurological examination, have nerve conduction studies and fill out a questionnaire about your health.

Enrollment in the patient contact registry is being facilitated through INC-affiliated CMTA Centers of Excellence. We strongly encourage anyone who wants to be considered for clinical trials to visit a CMTA Center of Excellence where people with CMT can participate in clinical research.

Another great way to participate is to join our Patients as Partners in Research (PPR) initiative, which is enrolling the patient community in STAR's critical work of finding treatments and ultimately a cure for CMT.

Ways to get involved in PPR include completing surveys about your symptoms and experiences with CMT, participating in focus groups with the CMTA and our strategic partners in the biotechnology and pharmaceutical fields, enrolling in CMTA funded research studies with our clinical and scientific partners and joining clinical trials for which you may be eligible. For a list of open trials, visit cmtausa.org/patient-partners.

Finally, it's not too late to sign up for the CMT & ME digital app, which is not just an app, but an international research study being conducted on an app to determine the burden of disease in CMT. The French company Pharnext is sponsoring the study over two years in six countries: the US, UK, Germany, France, Italy and Spain. The aim of the study is to collect real-time data directly from patients, who describe what it is like to live with CMT. The study also aims to find out how treatment can improve patient quality of life and slow CMT progression.

The CMT&Me app collects real-world data using "bring your own device" (BYOD) technology—participants use their own smartphones to complete questionnaires or surveys at their convenience. The app immediately submits the information patients provide to a central database. A Scientific Advisory Board oversees the CMT&Me study, and includes clinicians who care for CMT patients, representatives from patient advocacy organizations (PAO) and experts in patient-reported outcomes (PRO) and data management.

IMPACT OF CMT ON WORK AND MENTAL HEALTH

More than 2000 patients from 6 countries, aged 18 or above, were asked to enter data about CMT, its management and its impact on their lives over at least two years via a smartphone app, CMT&Me.

IMPACT ON MENTAL HEALTH

1/3
Reported diagnosis of depression in addition to CMTIA*

Of these, **45%** use, or had previously used, anti-depressants*

IMPACT ON WORKING LIFE

74%
of salaried employees confirmed their working life was impacted by CMTIA*

36 days per year absent from work due to CMTIA*

To sign up or learn more, visit vitaccess.com/cmt-and-me

*Data from digital lifestyle study CMT&Me

ACCELERATING RESEARCH EMPOWERING PATIENTS

What Progress Have We Made?

The CMTA has invested over $17M in recent years and our strategy outlines investments of another $10M in the next few years to help bring CMT drugs to market.

- We currently have over 50 active research projects with the top labs around the world, all vetted through our advisory board, comprised of 30 of the top CMT scientists from across the globe.
- The CMTA now has partnership agreements with more than 30 academic, pharmaceutical, biotech and service companies across three continents. They are leaders in the latest genetic and neurological technologies (such as CRISPR, gene therapy, gene silencing, and axon and muscle regeneration). These partners are actively working with the CMTA to develop treatments for the 3 million patients living with CMT.
- The CMTA has a network of more than 40 CMT Centers of Excellence, 70 branches, and a partnership with the Inherited Neuropathy Consortium (INC). Through this network we are building patient registries and outcome measures for our pharmaceutical and biotech partners to aid in fast and effective clinical trials.

The CMTA was founded by a patient, and to this day is powered by a community of patients who are all rallying behind our mission. With the largest constituency of CMT families around the world, the CMTA actively works with the patient community in the drug development process to ensure patients are our partners every step of the way.

STAR IS THE **BRIGHTEST BEACON OF HOPE** IN ACHIEVING OUR VISION OF **A WORLD WITHOUT CMT.**

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