WINTER 2022/2023

THE CMTA REPORT

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SPECIAL CMTA-STAR RESEARCH EDITION

CONTENTS

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Carrie Johnsen, currently enrolled in the Pharnext clinical trial for CMT1A, said she is incredibly grateful to the CMTA and STAR. "It is very reassuring knowing all the work that is being done to advance our knowledge and understanding of CMT and to ultimately find a treatment and a cure," she added.

EVERY DONATION HELPS ENSURE A BRIGHTER FUTURE FOR ALL OUR CHILDREN.
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"Everything you can imagine is real."
- Pablo Picasso

Dear Friends,

In 2008, the CMTA imagined a world in which researchers across the globe worked together to find a cure for CMT. Removing the silos that separated the researchers in those early days, the CMTA brought them together under the banner of our Strategy to Accelerate Research (STAR) and coordinated and funded their work.

Since then, with the support of our community, much of what we imagined has become real. As you'll read in this issue of *The CMTA Report*, tools and techniques that once seemed like science fiction are in everyday use. Gene editing and gene replacement are being developed for multiple forms of CMT and work on the biomarkers needed for clinical trials is proceeding rapidly. As you'll read on p. 34, several clinical trials are in late stages—PXT3003 to treat CMTA1A, AT-007 to treat a newly discovered type of CMT caused by a deficiency of the SORD gene and gene therapy for giant axonal neuropathy (GAN), which shares many commonalities with CTM2.

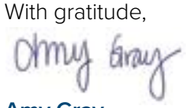
Members of our active and engaged patient community are our secret weapon in the fight against CMT. Carrie Johnsen is one such member. After enrolling in our Patients as Partners in Research initiative, she was accepted into Pharnext's PXT3003 trial. The study is a prime example of how the patient community and the research community are working together with the CMTA's support and coordination.

Carrie imagines a world where disease-modifying therapies slow the progression of CMT and says, "It is very reassuring knowing all the work that is being done to advance our knowledge and understanding of CMT and to ultimately find a treatment and a cure."

With 50 active research projects, 40 Alliance partners and virtually every type of CMT covered by an active research project, STAR is working the way its founders intended. Fueled by our incredible community, what was once unimaginable is now real.

Although we have made huge strides in the search for a cure for CMT, more needs to be done. That's why we are asking you to donate today—and make our shared dream a reality.

With gratitude,



Amy Gray
Chief Executive Officer

Jeana Sweeney
Chief Engagement and Gift Officer

CMTA**STAR** AND OUR **STAR PARTNERS**

When the CMTA launched STAR in 2008, we could not have imagined how far we'd come in under 15 years. Just a few researchers were working in the field, and just a few causative genes for CMT had been identified.

STARPOWER

ACCELERATING RESEARCH EMPOWERING PATIENTS

Since then, it has become clear that STAR is working the way its founders intended, resulting in:

- $18.5 million invested in STAR
- More than 50 projects and studies with leading academic labs, pharmaceutical and biotech companies developing treatments for CMT
- 40 plus STAR Alliance partners from top biotech, pharma, universities and gene therapy labs around the world
- More than 30 of the leading CMT scientists and gene therapy experts from around the globe on our STAR Advisory Board
- Research tools for Alliance partners to use in testing potential therapies for types CMT1, CMT2, CMT4 and CMTX
- Investments in the discovery of new genes that cause CMT
- A newly appointed chief research officer, Katherine Forsey, PhD, to handle the explosive growth in the CMTA's research portfolio

RESEARCH TOOLBOX

A crucial element in the advancement of CMT research and treatments has been the creation of a “toolbox” of cellular and animal models for the evaluation of therapy candidates along with the know-how to use these models. The CMTA purposefully set out to make or acquire the tools needed and developed benchmarks for using them. This preclinical testing capability has been assembled via close collaboration with an expert network of service providers and is currently being used by a number of STAR Alliance partners to advance research across a range of CMT sub-types. The maintenance, development and growth of the toolbox is key to attracting pharmaceutical, biotechnology and research organizations to work on and invest in CMT.

Because CMTA-STAR is a complex web of interconnecting organizations and individuals, understanding it requires an understanding of their roles and how they fit together.

THE CMTA-STAR ALLIANCE PARTNERSHIP NETWORK

The CMTA works with a consortium of pharmaceutical, biotechnology and contract research service industries, along with nonprofit research organizations, university research laboratories and the National Institutes of Health (NIH). In the last five years, the number of Alliance partners has skyrocketed from five to more than 40.

This unique network enables efficient testing of novel treatments for CMT. The CMTA works with STAR Advisory Board members and specialist consultants to support and advise companies that want their candidate treatments tested in CMT models.

Utilizing decades of experience in study design, the CMTA ensures that potential treatments are tested in the right way, on the right models, and provides support with interpreting results.

Through this network, the CMTA provides access to full safety and toxicology services and advice to help navigate complex regulatory and approval pathways, ensuring those bringing forward treatments can take the steps required to establish clinical trials and eventual roll-out to the patient community.

THE INHERITED NEUROPATHY CONSORTIUM (INC)

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 patient care. Funded primarily by National Institutes of Health (NIH), with supplemental funding from the CMTA and the Muscular Dystrophy Association, INC plays a key role in developing the infrastructure necessary to evaluate CMT therapies and conduct clinical trials. Several members of the CMTA’s Clinical Expert Board lead INC sites, working at the forefront of patient care and leading the roll-out of clinical trials to test new CMT treatments.

Over the past few years, INC has carried out studies; identified multiple genetic causes of CMT; begun testing possible biomarkers for CMT; enrolled thousands of patients in its studies; trained young scientists in CMT research; and created a website that provides information about CMT to patients, families and researchers. INC’s future goals include conducting further natural history studies to enable clinical trials, continuing the search for biological features (biomarkers) of disease; continuing to identify novel genetic causes and modifiers of CMT and continuing to provide information to patients, their families, doctors and researchers.

THE RARE DISEASES CLINICAL RESEARCH NETWORK (RDCRN)

RDCRN is an NIH-funded research network of 20 active consortia, each focused on a group of rare disorders. The network fosters collaborative research among scientists to better understand how particular rare diseases progress and to develop improved approaches for diagnosis and treatment.

THE CMTA CENTERS OF EXCELLENCE

The CMTA's four dozen COEs exist at the intersection of research and treatment. The COEs provide comprehensive care to children, adults and families affected by CMT. Almost half are also affiliated with INC, collecting and recording genetic and physical assessment information from patients in order to build comprehensive natural history study datasets, which are essential to CMT research and the establishment of clinical trials.

PATIENT ADVOCACY PARTNERSHIPS

The CMTA also works in partnership with other research funders and patient advocacy groups. To give just one example, the CMTA and the Muscular Dystrophy Association (MDA) co-funded a three-year, $276,430 research grant to Dr. Kleopas Kleopa, professor and senior consulting neurologist at the Cyprus Institute of Neurology and Genetics, Cyprus School of Molecular Medicine, in Nicosia, Cyprus. A world-renowned expert on gene replacement therapy for CMT1X, Kleopa is using the funding for critical, proof-of-concept studies to test whether delivery of the Cx32 gene using an adeno-associated virus (AAV) vector can improve symptoms in a mouse model of CMT1X.

THE STAR ADVISORY BOARD

The CMTA's STAR Advisory Board comprises a Scientific Advisory Board (SAB), a Therapy Expert Board (TEB) and a Clinical Expert Board (CEB).

The SAB provides input for ongoing or proposed projects, evaluating the scientific status of current CMTA-funded research and identifying the scientific basis of target strategies for each CMT subtype. It also reviews research proposals for scientific background and the soundness of the research strategy and measures the progress of research teams, recommending changes in research strategies as needed.

The TEB evaluates the translational quality (how quickly and efficiently discoveries can be moved into practice) of ongoing and proposed projects. Members review the pharmacological approach of disease area project team efforts, the potential to form strategic alliances with pharmaceutical partners and the preclinical strategy, particularly its contribution to clinical testing approaches. The TEB may also take an active role in managing and monitoring strategic alliances.

The CEB provides expert guidance and support to the CMTA's Alliance partners, helping to ensure the success of clinical trials by providing the natural history and clinical expertise to design, develop and enable clinical trials; collaborating with scientists in the development of clinical biomarkers and ensuring the adequate recruitment of carefully evaluated patients and experienced investigators to conduct these trials.

PATIENT PARTICIPATION IS KEY

The CMTA's most important partners are undoubtedly our patients, who literally provide their blood, sweat and tears to CMT research. Clinical trials are the penultimate step on the road to drug approval and preparations are in full swing. This means recruiting large numbers of patients, studying the evolution of their CMT (natural history) and developing outcome measures and biomarkers to measure a given drug's effectiveness quickly and conclusively.

Recruiting participants is crucial, and the CMTA is well-positioned to facilitate patient involvement. The RDCRN INC Patient Registry makes it possible for researchers to develop new treatments, create new studies and work to improve the lives of everyone with CMT. Enrollees in the patient registry are contacted with opportunities to participate in clinical trials for their types and other studies such as a longitudinal study of individuals with CMT to see how it changes over time.

Recognizing the ever-increasing role that patients play in research, the CMTA established Patients as Partners in Research in 2019. Participants complete surveys about their symptoms and experiences with CMT, participate in focus groups with the CMTA and our strategic partners in the biotechnology and pharmaceutical fields, enroll in CMTA-funded research studies with the CMTA's clinical and scientific partners and join clinical trials. For a list of open trials, visit cmtausa.org/patient-partners.

CMT&ME GIVES PATIENTS ANOTHER OPPORTUNITY TO PARTICIPATE IN RESEARCH.

Conducted on an app and sponsored by the French company Pharnext, the aim of the CMT&ME study is to collect real-time data directly from patients about what it is like to live with CMT. The study also seeks 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.

MORE ROLES FOR PATIENTS

GENE DISCOVERY

While some 95 percent of CMT patients with a demyelinating type can get a genetic confirmation, 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 more than 100 undiscovered disease-causing genes.

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 mutation. CMT is caused by mutations in DNA, which is responsible for coding—or instructing—the creation of proteins involved in 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 an underlying genetic mutation.

Genetic tests for CMT often identify only a variant of unknown significance, or VUS, which can be very frustrating for CMT patients. CMTA researchers have begun adding VUS findings to a massive international database, stripped of all identifying information, and then studying that database to see if any of them are actually connected to CMT diagnoses.

"I am so proud to be part of a large Dutch family. Three generations of my relatives met together last spring to contribute a large pool of genetic data that led to the discovery of the genetic variant that caused CMT in our family. In doing so, we built a relationship with a passionate team of researchers, and we felt more like participants, rather than bystanders, in genetic research that affects us so personally. I would encourage large families to collaborate and participate in CMT research. Your help will be life-changing!" – Distant Cousin Project participant

THE DISTANT COUSIN PROJECT

Effective treatments for genetically caused rare diseases are within sight: Gene therapy has already been successfully used for other diseases such as spinal muscular atrophy. That makes the effort to identify disease-causing, or culprit, genes more important than ever.

Dr. Stephan Zuchner's team at the University of Miami recently identified a heretofore unknown CMT gene—SORD1—which immediately led to the identification of a potential treatment—an already approved drug used to treat diabetes.

Half of individuals with Type 2 have not had their culprit gene identified, and it is impossible to "fix" a gene and difficult to treat a genetic disease without knowing which gene needs to be fixed or treated. Thus, the focus is on identification. The Distant Cousin Project aims to speed up the rate at which Type 2 CMT culprit genes are identified.

Intuitively, it might seem like having one's genome and the genomes of family members with the same disease sequenced should lead to a discovery of the culprit. To some extent, that's true. The problem is that researchers can readily identify hundreds of potential culprit genes (variations of unknown significance), and people share too much DNA with close relatives to narrow the genes down to just a few possibilities. However, by locating a distant cousin with the same causal gene, the number of potential culprits can be reduced to one or two.

For example, fourth cousins share about only about one-fifth of one percent of their DNA. If two of these cousins share the same culprit gene, there is a very good chance that researchers can locate it.

The Distant Cousin Project is paying for sequencing of the first 10 sets of eligible families with an unidentified form of CMT. The genomes will be sequenced as part of Dr. Zuchner's research studies at University of Miami and analyzed by the Genesis Project database.

One culprit gene has already been identified in this way: ITPR3. Two large families from Wisconsin and Sydney, Australia, were the key to this discovery.

The success of the Distant Cousin Project will depend on the efforts of CMT patients who have an unidentified culprit gene. Eligible families include those in which:

- The cause of CMT is unclear despite genetic testing.
- One parent is affected with CMT.
- There is a distant cousin, or other distant relative on that parent's side, who also has an unidentified form of CMT. This is the most difficult part of the challenge.
- If the patient and their cousin have not yet been to a CMTA Center of Excellence, a COE physician will ideally confirm the CMT diagnosis.

Several sequencing slots are still available for any interested family. Patients who meet these criteria should contact study coordinator Lisa Abreu directly at l.abreu@med.miami.edu. Consent for both the patient and distant family member will be necessary, followed by a family history and a blood draw, either at the patient's doctor's office or at home.

CONDUCTING CLINICAL TRIALS

The CMTA's drug development pipeline is filled with projects in various stages of the Food and Drug Administration's drug approval process. Some are in the early stages—the discovery/concept phase, which begins in the laboratory. Some are in the pre-clinical phase in which drugs and devices undergo laboratory and animal testing to answer basic questions about safety.

Clinical trials start with completion of the FDA's Investigational New Drug (IND) process, which requires researchers (or developers) 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 about a treatment.

Before a clinical trial begins, researchers review existing information about the treatment, 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 of people who receive a placebo, 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 start with early, small-scale Phase I studies lasting several months and involving 20 to 100 volunteers with the disease. Phase I studies are designed to assess safety and dosage. Approximately 70 percent of drugs move on to the next phase.

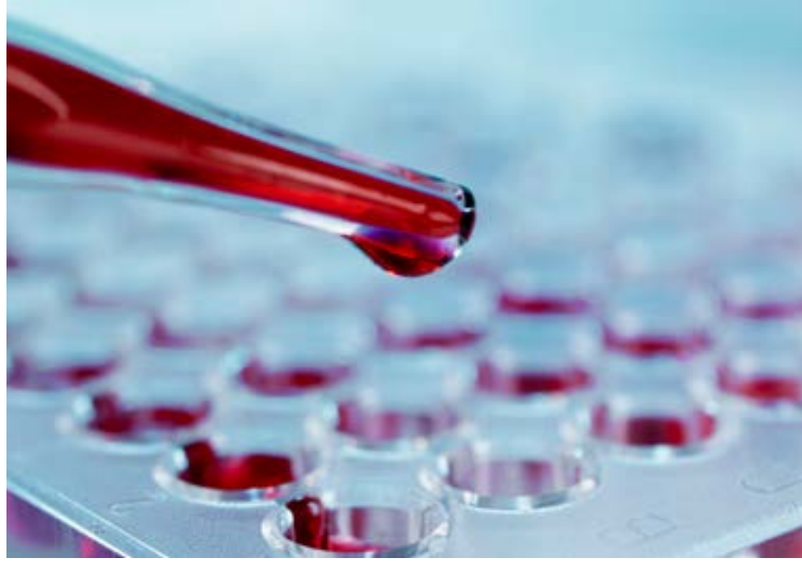
Phase II studies have up to several hundred people with the disease/condition and can last from several months to two years. Their purpose is to examine the drug or device's efficacy and side effects. Some 33 percent of drugs move on to the next phase.

Phase III 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 III studies, which last from one to four years, with 25 to 30 percent of drugs moving on to Phase IV.

Several thousand volunteers with the disease take part in the Phase IV study, which looks at the drug's safety and efficacy. In rare diseases like CMT, where the patient population is smaller, fewer volunteers may be needed for clinical trials. 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 decide 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.

On occasion, the FDA requires additional studies. If the NDA doesn't contain sufficient data for the FDA to determine a drug's safety and effectiveness, it may organize a meeting of one of its Advisory Committees to get independent, expert advice and to permit the public to make comments. Frequent communication can lead to earlier drug approval and access by patients.



BIOMARKERS KEY TO CLINICAL TRIALS

Because clinical trials involve a large investment of both time and funding, they need to be designed to measure a new medication's efficacy as quickly as possible.

Pharmaceutical partners want to see measures that can evaluate signs of success 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.

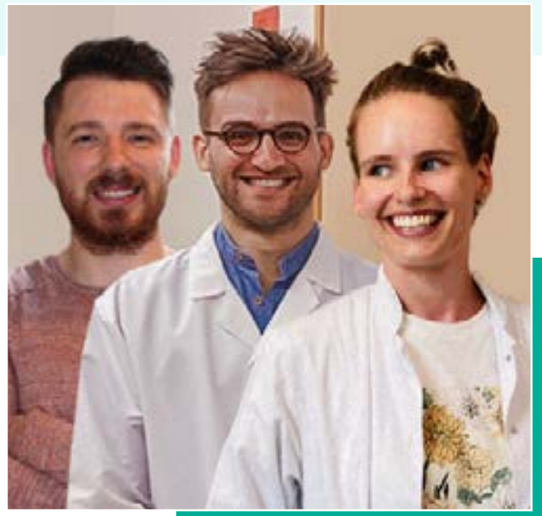
Therefore, one of the most urgent needs in the CMT field is to find better ways to assess the dysfunction of the peripheral nerves in patients with CMT. The CMTA was an early supporter of INC's development of neuropathy scores for adults. They went on to develop pediatric and infant neuropathy assessments. But since CMT progresses slowly, these neuropathy scores by themselves are not sensitive enough to measure changes in a short period of time and are inadequate to determine if neuropathy has improved.

Biomarker efforts extend across types and include a number of different studies (see pp. 21 to 30). In London, neurologist Dr. Mary Reilly and her team developed a biomarker that uses magnetic resonance imaging (MRI) to measure the amount of fat present in calf muscles. As CMT progresses, muscle is replaced with fat.

Dr. Reilly and Dr. Alexander Rossor also found that blood samples can be used to measure a protein called neurofilament light (NfL) that is released when nerves are damaged by CMT.

Dr. Michael Shy at the University of Iowa and Dr. John Svaren at the University of Wisconsin are using both blood samples and skin biopsies to develop biomarkers for CMT1A . Peripheral nerves are 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.

PATIENT-SCIENTISTS BRING PASSION, COMPASSION TO CMT RESEARCH



Call them the “patient-scientists”: Three of the young investigators who presented at the recent meeting of the Peripheral Nerve Society—Rob Prior, Wolfgang Pernice and Helena Pernice—know firsthand what it is to live with CMT. Having CMT is what drew all three of them to the field of peripheral neuropathy and the search for a cure. Their passion for the research is matched by their deep empathy for those who have the disease.

Helena, 28, and Wolfgang Pernice, 34, are sibling-scientists as well as patient-scientists. They grew up in Berlin, inspired by a father with CMT who traveled globally in his work for the European Union. As the children turned 14, their father took them on a trip to the destination of their choosing. Wolfgang chose China.

The two student guides who accompanied Wolfgang and his father to the Great Wall told them about a popular saying in China: “You aren’t a real man until you have climbed the Great Wall.” Wolfgang’s father was on crutches, so they took the gondola up instead of the steep path to the top. But once they reached the top, several steep and crowded staircases remained. They didn’t stop his father. Step by step, he pulled himself up the narrow staircase, completely blocking any traffic behind him.

Wolfgang couldn’t understand what the people squeezing by them were saying but suspected they were complaining about having to wait. As Wolfgang recounted, “Finally, with the last step, the magnificent view from atop the Great Wall opened up. Then, our guides looked at us and said: “You know what the folks in the staircase were saying? They said, ‘Look, that’s a real man!’”

Helena’s inspiration will be familiar to anyone with CMT–walking the dreaded balance beam in high school gym class. Other than that, being slower, tripping more often and walking differently from her friends didn’t really bother her too much. Her father had showed her that CMT wasn’t a barrier to her dreams.

Helena and Wolfgang didn’t set out to be CMT researchers. Helena was planning to go to art school in France, but on the eve of her departure, she switched to med school at Ludwig-Maximilian University in Munich, Germany. That was followed by a residency in the neurological department of Charité University in Berlin, after which she joined the Neuromuscular Research Group there. Today, she’s in the third year of her neurology residency, splitting her time equally between research and clinical work.

Wolfgang studied law for a year before transferring to the biology program at Imperial College London. He moved to New York City to get his PhD at Columbia University and today is an associate research scientist at the H. Houston Merritt Clinical Research Center at Columbia. There, he leads projects aimed at overcoming some critical roadblocks in genetic diagnostics and translational medicine for inherited neuropathies like CMT.

The Pernice family's gene has never been identified, and Helena said that the lack of a causative gene left her with many unanswered questions. So she and Wolfgang divided up responsibilities: He threw himself into the world of basic science and genetics while she decided to work on the patient side, eventually starting the first CMT clinic in Berlin. She also started her first projects on CMT, including her first project with Wolfgang. "Starting to work in clinical research made me realize how incredibly important it is for patients to get involved, because any result depends on the number of patients that take part in the study. Luckily, more and more I get the chance to work together with patient organizations, which is just the most amazing way to get connected and spread the word."

In her first years as a doctor, Helena said, she sometimes struggled with the responsibility for other peoples' lives. But when she started to work with CMT patients who had gone through the same experiences as her family, she was thrilled that she could understand them and answer their questions.

Even though clinical research can be slow, there is no better time than now for finding treatments for CMT, Helena said, citing gene therapy and other new therapeutic options "popping up everywhere."

Most importantly, she said, the patients drive the research—anyone with CMT has the potential to help in the fight against CMT by participating in studies, raising awareness of the disease, sharing data and strengthening the community. As she meets more and more patients and researchers, she has come to believe "The question is not if we find a cure, but when."

Wolfgang first got involved with CMT research when he arrived at Columbia and convinced a professor to help him find his family's gene. As for many CMTers, it turned out to be tricky. As he explained, "The basic strategy to identify new disease genes and mutations is to compare groups of patients to healthy individuals to find the common genetic denominator among all those with CMT: If all the patients but none of the healthy folks have mutations in a certain gene, that's probably it. But in rare diseases, such as CMT, groups of patients tend to be very small. That means that typically, in CMT cases where we return the diagnostic test as unsuccessful to patients, that's not because we didn't find anything. It's usually because we found too many candidate variants, among which we cannot identify the truly pathogenic mutation. So, in many cases, all we can do is wait until we find more patients that can help us see the genetic puzzle more clearly."

Today, Wolfgang's group at Columbia is trying to solve this problem by maximizing the study of a small amount of patient data. Working with Drs. Mike Shy and Steven Scherer in the United States and Helena and her mentor Katrin Hahn in Germany, they are collecting small skin biopsies from CMT patients that are used to grow cells in the lab. Next, they apply cellular profiling—a battery of measurements, including microscopy and RNA-sequencing—and crunch the numbers through some of the newest AI algorithms to find subtle differences among the cells of CMT patients and healthy individuals. These "disease-associated phenotypes" allow investigators to proactively test whether a given candidate variant is responsible for the disease, rather than having to wait until more patients are found.

While Wolfgang is excited about strategies enabled by new technology, he said the more powerful factor is community.

"In the end, it's a numbers game," he explained. "The more patients' genetic data we can compare, the faster we will identify the remaining CMT disease genes. The more patient cell lines we can compare in the lab, the quicker we can spot common disease pathways that we can target in drug development. And the more patients track their disease progression by enrolling in natural history studies, the better positioned we will be as promising new therapeutic approaches reach the stage for clinical trials."

Wolfgang finds the inherited peripheral neuropathy community friendly, supportive and collaborative, thanks in large part to leaders like Dr. Mike Shy, Dr. Mary Reilly, Dr. Steven Scherer and Dr. Stephan Zuchner. "I am really fortunate to be part of a new generation of researchers and clinicians that were trained by them," he said, adding, "Together, we are setting the stage for a new wave of CMT research, based on new, cutting-edge technologies and expanding communities, including through new international forums such as the European CMT Federation (ECMTF). I think we stand at the cusp of significant breakthroughs on both the diagnostic and the therapeutic front for CMT. And as more patients become partners in research, I think the next few years will be very exciting!"

Born and raised in Ireland, Rob Prior, 30, knew from the age of 16 that he wanted to get involved in CMT research. He watched as CMT1X robbed his mother, aunts and cousins of their mobility. "It's hard watching the people you love lose part of themselves year after year and watching their struggle become ever more burdensome while knowing this is the path that you are on," he says.

From his family's own initial misdiagnosis, he had an appreciation of what patients who don't have a genetic diagnosis go through—and the solace of putting an exact name on the disease and subtype.

Rob completed a BSc in biological and biomedical sciences at Maynooth University and a MSc in regenerative medicine at the National University of Ireland in Galway. He then worked for a year as a lab demonstrator as he looked for CMT-related PhD positions around the world, because there were no CMT labs in Ireland. He eventually found Prof. Ludo Van Den Bosch from VIB-KU Leuven, Belgium. They hit it off, and Rob started work on his PhD there. But a project he was supposed to work on was scrapped due to issues with the mouse model, a foretaste of the research roller coaster.

After defending his PhD—"Modeling CMT1A and Investigating HDAC Inhibitors as a Therapeutic Strategy"—last summer, Rob started a postdoctoral research position in Germany. He said his experience in CMT research has been "simultaneously invigorating and dejecting." On the one hand, he's had the amazing opportunity to investigate therapies for CMT and model the disease in a preclinical setting. At the same time, he said, "It is difficult to see your body deteriorate by the disease you are trying to cure."

In the current scientific era, Rob said, "If you work smart and hard enough, you may be able to position yourself to find a therapy. But science is a slow process and that is hard for patients and the non-scientific community to grasp."

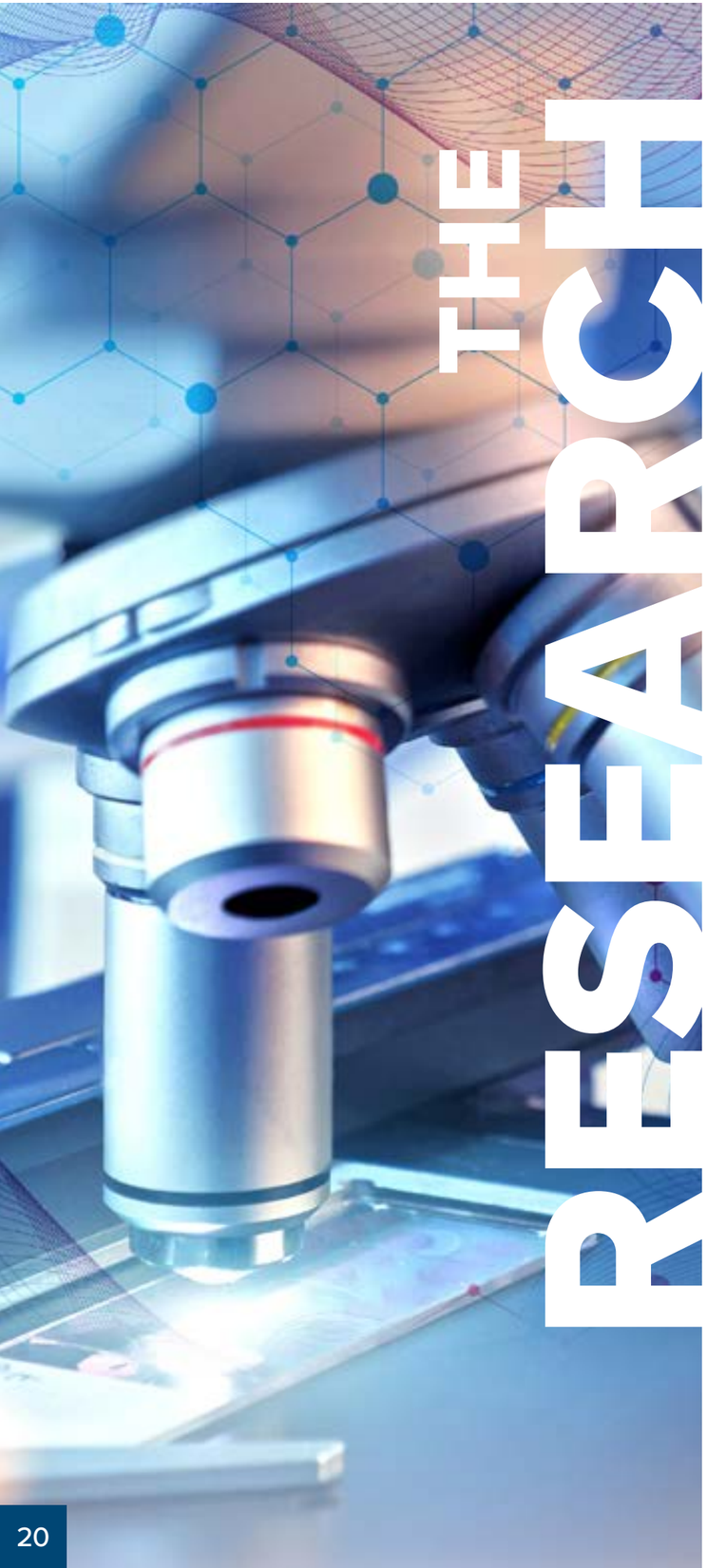
Rob still believes that a cure will be found for certain subtypes. For others, he said, "We will find effective treatments to mitigate the disease progression and even reverse certain clinical features." Eventually, "We will get there."

Until then, he recommends that patients adopt a dedicated fitness program. He's been doing resistance training and daily stretching since the age of 15 and says it has helped tremendously. Maintain the muscles you have by resistance training and avoid long periods of inactivity, but be smart and don't destroy your body, he advised. Diet is also key, he emphasized, as CMT severity correlates with being excessively under- or overweight.

Above all, he said, "Don't use your disease as an excuse not to do things. Use it as a motivation." He urged his fellow patients to "Get involved in the CMT work. Understand the disease. Volunteer in patient organizations, donate to research or, even better, get involved in the research if you can. Understand that science takes time though."

"The more patients' genetic data we can compare, the faster we will identify the remaining CMT disease genes. The more patient cell lines we can compare in the lab, the quicker we can spot common disease pathways that we can target in drug development."

-Wolfgang Pernice



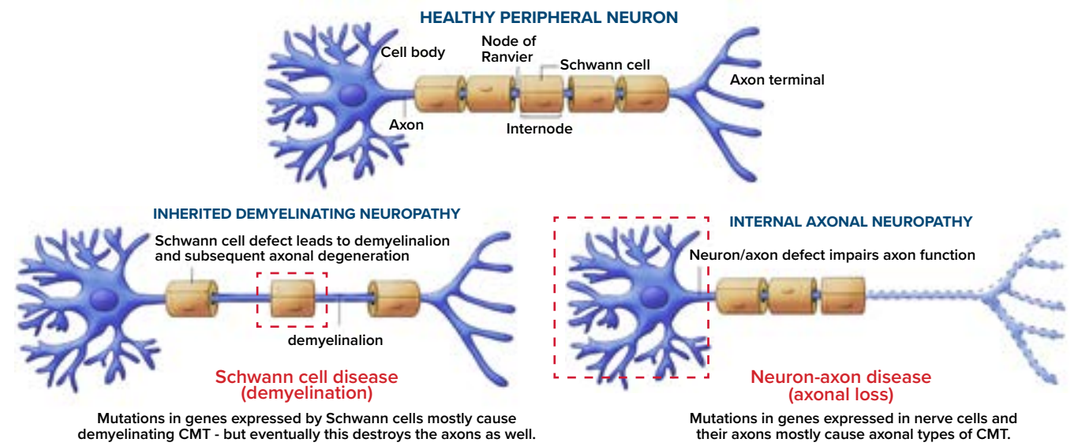
THE RESEARCH

Nerves are bundles of many nerve fibers, most of them wrapped in myelin. Myelin is a protective coating, formed by Schwann cells, that surrounds the nerve and speeds nerve impulses from 1 meter per second to more than 50 meters per second.

Myelin problems cause demyelinating CMT (CMT1). Problems with nerve fibers, or axons, cause axonal CMT (CMT2). Type 4s can be either. The CMTA's current sponsored-research portfolio contains three major categories—cross-type initiatives, demyelinating initiatives and axonal initiatives.

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.

CROSS-TYPE INITIATIVES

BIOMARKERS AND OUTCOME MEASURES

John Svaren, PhD;
Davide Pareyson, MD;
Steve Scherer, MD, PhD;
Mary Reilly, MD;
Michael Shy, MD

Biomarkers, which are used to evaluate the efficacy of potential therapies, are particularly important for slowly progressive diseases like CMT. Multiple labs are attacking the problem, including the Svaren lab at the University of Wisconsin; the Pareyson lab at the University of Rochester; the Scherer lab at the University of Pennsylvania; the Reilly lab at University College London; and the Shy lab at the University of Iowa. The identification of plasma neurofilament light (NfL) levels as a biomarker to measure axon degeneration was a major advance, but new and complementary protein biomarkers are needed. Drs. Shy and Svaren and partner Sanofi-Genzyme recently collaborated to identify potential Schwann cell-specific proteins that are elevated in blood samples from individuals with CMT1A and CMT2A. They identified NfL and a new protein biomarker, TMPRSS5, also known as spine-sin, that is highly expressed in the Schwann cells of CMT1A peripheral nerves. The group also identified other candidate Schwann cell proteins that are elevated in CMT1B plasma. Another independent biomarker initiative identified plasma microRNAs thought to be released from muscles and originally identified as "myomirs," which are elevated in the plasma of individuals with muscular dystrophy. Myomirs were elevated in the plasma of CMT1A patients, and even higher elevations were seen in CMT1X, CMT1B and CMT2A patients. The elevation of myomirs correlates to the degree of muscle degeneration seen in calf muscle as measured by the QS MRI protocol (see below). The team also adapted its skin biopsy Nanostring platform to test for treatment-responsive changes early in the course of a clinical trial. For CMT1B, the team assessed a pathogenic pathway involving the unfolded protein response (UPR) and incorporated several measures of UPR in the Nanostring assay. They found elevation of several UPR-associated transcripts in CMT1B patient skin samples. With support from the CMTA, the team is extending microRNA, transcript and protein biomarker analysis to larger

cohorts of CMT1X, CMT1B, CMT2A and CMT2F, enabling them to compare biomarker levels to other assessments of neuropathy, including the QS MRI protocol.

MRI DEVELOPMENT

Mary Reilly, MD

In another project involving biomarkers, the Reilly group at University College London developed the Queen Square (QS) Neuromuscular MRI protocol, which measures calf muscle fat using a non-invasive MRI scan. In CMT patients, the nerves become damaged over time and eventually lose their connection to the muscles. Fat then accumulates inside the muscles. Increased fat correlates to increased disease severity. Working with CMT1A patients from the United States and the United Kingdom, the group found that calf muscle fat in 1A patients increased significantly during a 12-month period. There were no significant changes in the control group.

The team is now working with five centers in the United States, the United Kingdom and Italy on a CMT1A study to compare the QS MRI protocol with multiple other clinical measures and novel blood and skin biomarkers. Further studies have shown the QS MRI protocol can measure change over 12 months in CMT1B, CMT1X and CMT2A. Additional studies in these subtypes will compare the QS MRI protocol with multiple other clinical measures and novel blood and skin biomarkers.

GENETIC DELETION OF SARM1

Rob Burgess, PhD

The Burgess group at the Jackson Laboratory investigated whether SARM1 inhibition could be used to treat CMT types other than CMT2A (see the Milbrandt report about the Type 2 project p. 28). The team bred a mouse knockout of SARM1 (a mouse with the SARM1 gene deleted) in three different CMT mouse models—HSN2C, CMT4J and CMT1X, and measured the effect on CMT symptoms. While there was no change in CMT symptoms in any of these models, the work contributes to a greater understanding of the disease process. Switching off the SARM1 pathway may not be enough to reduce CMT symptoms, or axons may be preserved anatomically but they may not be functional. Additional models of CMT—CMT2D, CMT2E and CMT2S—will be tested with this approach. While SARM1 inhibition may be effective for CMT2A, it may not be a magic bullet for all forms of CMT. Work will continue to determine which forms might benefit from SARM1 inhibition approaches.

AXONAL DEGENERATION IN LATE-ONSET CMT1B

Maurizio D'Antonio, PhD

Myelin protein zero (MPZ or P0) is critical for myelin formation and maintenance. It is expressed by Schwann cells, which play an essential role in the development, maintenance, function and regeneration of peripheral nerves. Many mutations in MPZ are associated with the demyelinating neuropathy CMT1B. Surprisingly, the myelin protein zero mutation P0T124M causes axonal neuropathy (CMT2J) with little to no myelin damage. The D'Antonio laboratory at the San Raffaele Scientific Institute created targeted knock-in P0T124M mutant mice (a mouse that has the P0T124M mutation added). Like CMT2J patients, these mice develop defects in their axons (axonopathy) between 2 and 12 months of age. They show axonal damage with little myelin modification. The team detected metabolic changes that could lead to axonal degeneration and alterations in areas of the cell system involved in communication between Schwann cells and axons. Schwann cells in the CMT2J mice cannot provide axons with sufficient support, leading to reduced energy production and axonopathy. The creation and validation of the new P0T124M mouse model faithfully reproduces the human neuropathy and represents a unique tool for identifying the molecular basis for Schwann cell support of axons, which is key to the development of new therapeutic strategies.

ADVANCED DIAGNOSTIC CAPABILITIES

Stephan Zuchner, MD, PhD

Working with CMT researchers and clinicians worldwide, the Zuchner lab at the University of Miami is spearheading CMT gene discovery by combining genetic data (panels, exomes and genomes) from patients into a common database for use by qualified researchers. In recent years, this this data-sharing strategy has led to the discovery of more than 25 new CMT genes, including the SORD gene, which constitutes the most common recessive form of CMT2.

The discovery of the SORD gene led to the development of a new therapeutic approach, which is now being tested in a Phase III clinical trial, just two years after the gene's discovery. The GENESIS database and analysis platform now contain more than 2,500 CMT datasets from over 30 countries. Any researcher can upload patient datasets anshare them with colleagues. The Zuchner lab built new advanced analysis methods into this database, such as machine learning. Their combined efforts have led to a stream of new CMT gene discoveries, including the ITPR3 gene, a newly confirmed CMT1 gene; the FICD gene; the CADM3 gene; and expanded phenotypes of the ATP1A1 gene. Patients with access to their genome data from clinical testing are free to contact the Zuchner laboratory to add their data. Those who don't yet know their type are encouraged to seek genetic testing and help researchers fill out the CMT puzzle. The team's long-term goal is a database of 10,000 CMT genomes available for research studies.

DEMYELINATING INITIATIVES

Mutations in genes expressed by Schwann cells mostly cause demyelinating CMT. The CMTA's portfolio of sponsored demyelinating projects includes the following:

NIACIN TREATMENT FOR CMT4B

Alessandra Bolino, PhD

The Bolino laboratory at IRCCS Ospedale San Raffaele is assessing the efficacy of niacin as a treatment for some forms of CMT. Using an extended-release formulation, the team hopes to treat demyelinating neuropathies that are characterized by the presence of abnormal myelin (CMT4B1, CMT4B2, CMT4C, CMT4H and HNPP). Early data from animal studies with the CMT4B1 mouse model show daily oral niacin treatment restores the expression profile of nerve cell mRNA, which is required for protein production in cells, improves nerve structure and function and protects nerve fibers from degeneration. Following these promising results, further studies are being conducted to explore the effect of this treatment on nerve cell myelination and myelin thickness.

ACTIVATING PROTEIN DEGRADATION TO TREAT CMT1B

Jordan Verplank, PhD

In the mouse model of CMT1B, protein breakdown by the Ubiquitin Proteasome System, also known as simply the proteasome, is slowed down in peripheral nerve cells. This causes a buildup of potentially toxic proteins that may contribute to disease progression. Animal and cellular models of other CMT neuropathies also show impairment of the proteasome and reduction in protein breakdown. The Verplank laboratory at the University at Buffalo seeks to activate and restore the effective functioning of the proteasome using phosphorylation—the attachment of a phosphate group. They have shown that phosphorylation increases the proteasome's ability to degrade proteins and are exploring whether this approach may be an effective treatment for CMT. The team treated the CMT1B mouse model with the proteasome-activating drugs sildenafil, tatalafil and CYR-119, which are known to be well-tolerated in humans. Results for all three drugs showed restoration of the proteasome, myelin thickness and nerve conduction. Activating protein degradation with these drugs may also be effective in other types of CMT in which the proteasome is impaired.

GENE THERAPY FOR CMT1A, CMT1X AND CMT4C

Kleopas Kleopa, MD, FAAN

The Kleopa laboratory at the Cyprus Institute of Neurology and Genetics is working to identify suitable targets for gene therapy, focusing on connexin mutations in CMT1X, which have been shown to cause demyelinating neuropathy. Mutations in the gene coding for the gap junction beta-1 protein (GJB1), also known as connexin 32 (Cx32), are associated with CMT1X. Replacing the mutated gene could prevent neuropathy. The team tested different AAV vector delivery methods of getting the gene therapy into the target cells. They selected vectors with established safety profiles that are already approved for use in clinical trials in other diseases. In tests with mouse models of CMT1X with both early and later stages of neuropathy, results showed a therapeutic benefit using various outcome evaluation methods.

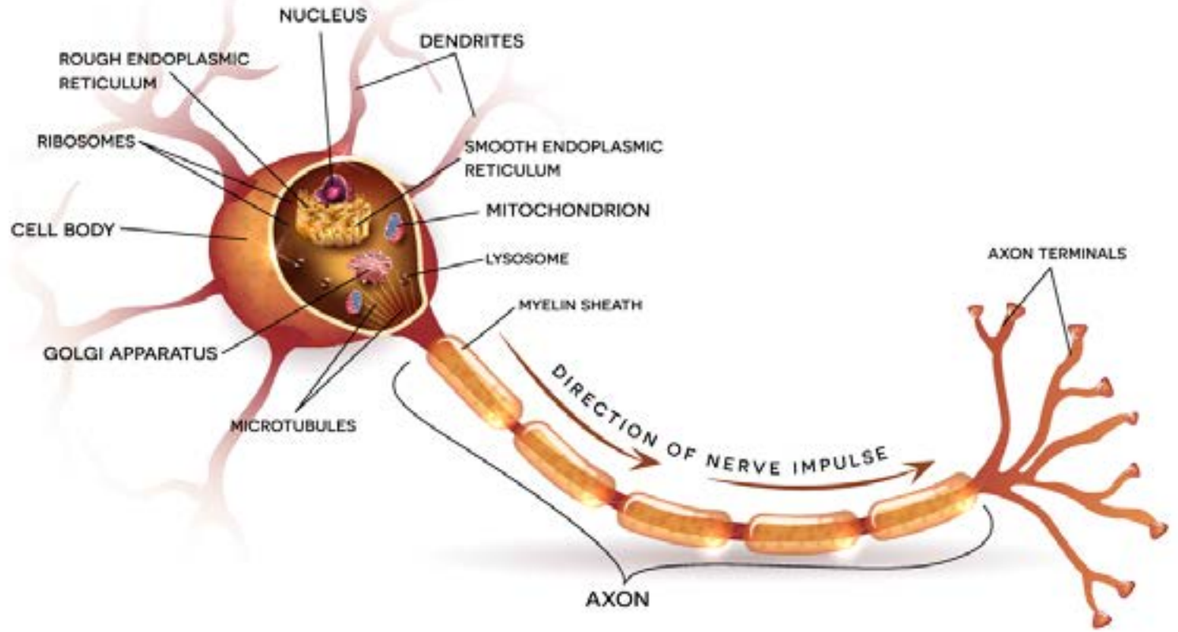
The team was also able to establish clinically relevant blood biomarkers that can be useful in future clinical trials. The team is now working in partnership with a gene therapy company to undertake the preparatory work necessary for clinical trials. The Kleopa laboratory is also developing gene therapy approaches for other CMT types, using a gene replacement therapy that is effective in improving peripheral nerve structure and function for CMT4C and a gene-silencing approach that corrects the functional, morphological, and inflammatory abnormalities of CMT1A without causing any apparent side effects.

ATASE INHIBITION OF CMT NEUROPATHY

Luigi Puglielli, MD, PhD

In several types of CMT, a toxic buildup of proteins in the cells results in peripheral neuropathy and disease progression. The cell's normal system of disposing of these toxic proteins is through the endoplasmic reticulum (ER), which is essentially the transportation and disposal system of the cell. The Puglielli laboratory at the University of Wisconsin identified and characterized novel small molecules, called acetyltransferase (ATase) inhibitors, that can control ER function.

They are testing whether these small molecules can increase the ER's ability to dispose of the toxic protein, reducing the toxic buildup and disease symptoms. The team tested one ATase inhibitor on mouse models of CMT1E, CMT1A and CMT1B, which are all associated with the formation of toxic protein buildup in the ER. Positive results were seen in the CMT1E and CMT1B models, with a reduction in the measurable symptoms of CMT, suggesting that ATase has the potential to delay and reduce the disease symptoms of certain forms of CMT.



TRANSFORMING DENTAL STEM CELLS TO SCHWANN CELLS

Esther Wolfs, MsC, PhD

Found in extracted wisdom teeth, dental pulp stem cells (DPSC) can differentiate into several different cell types depending on the signals they receive. The Wolfs laboratory at the Biomedical Research Institute (BIOMED) of Hasselt University pioneered a method to create Schwann cells from DPSCs. In 3D cultures, these Schwann cells are functionally myelinating and provide a good in vitro (in the dish) model for use in research. The team is developing a new in vitro model for CMT1A because in vitro testing is usually quicker and cheaper than in vivo (in the body) testing using animal models. Using a lentiviral vector transport mechanism and CRISPR/Cas9 gene editing technology, they caused DPSC-derived Schwann cells to overexpress PMP22, the causative gene for CMT1A. The team is also collecting DPSCs from CMT patients and using the same system to differentiate them into Schwann cells. They will compare these patient-derived models to the lab-created models of CMT1A.

SENSE TRIAL FOR HSN

Mary Reilly, MD

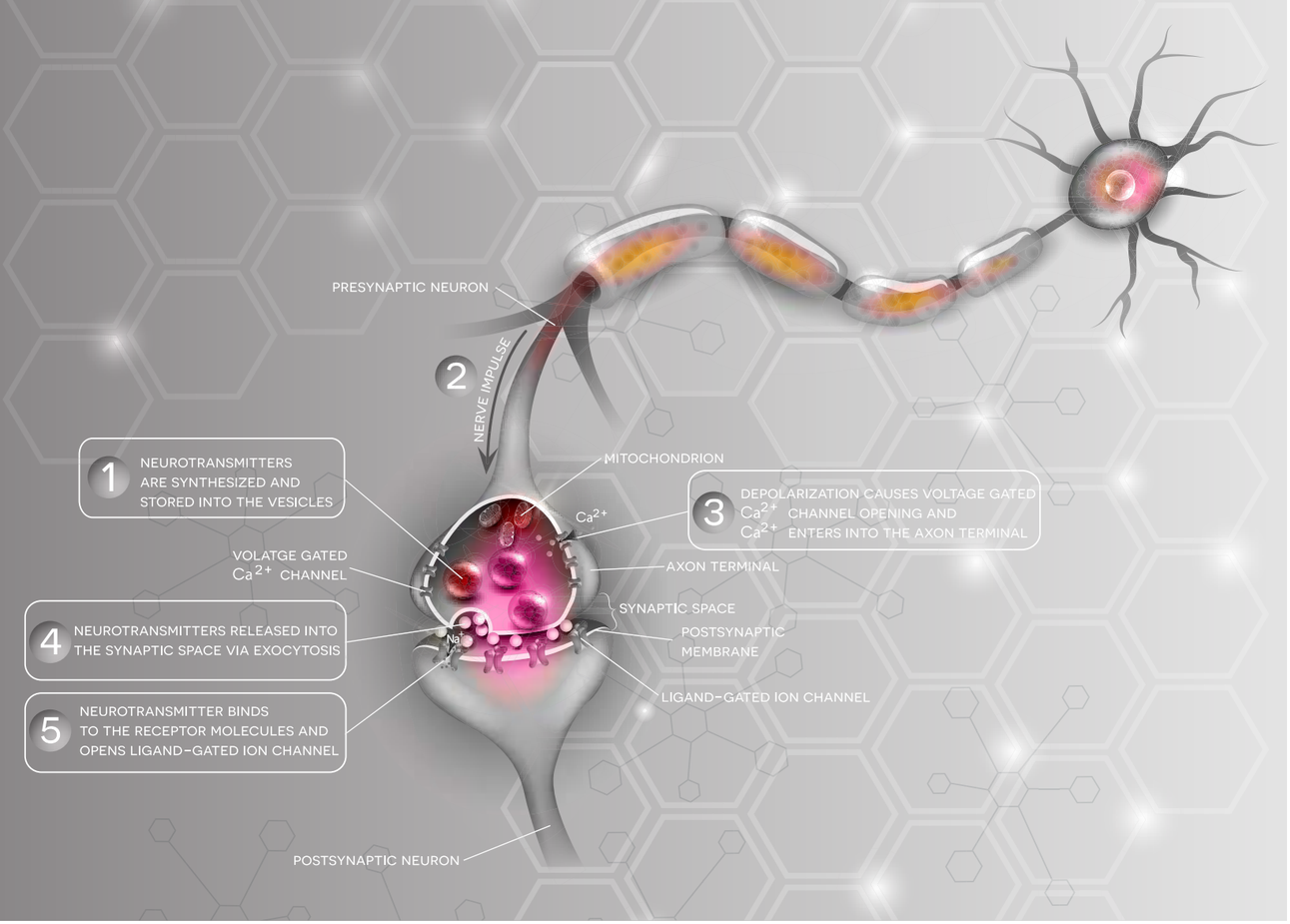
Hereditary Sensory Neuropathy (HSN) is a rare neuropathy with severe sensory and motor involvement for which there is currently no treatment. Genetic mutations cause HSN by a gain of function mechanism resulting in the production of toxic deoxysphingolipids (DSBs). Both HSN1 patients and the mouse model of the disease show elevated blood levels of DSBs. The SENSE (Hereditary Sensory Neuropathy Serine) trial is a CMTA-funded 12-month trial of

L-serine in HSN1 patients. HSN1 mice treated with L-serine showed reduced DSB levels and a mild improvement in symptoms.
A 10-week human trial of L-serine treatment in HSN1 patients led to a 75 percent reduction in plasma DSB levels.

Further studies on 18 HSN1 patients in the United States found insufficient measurable improvement in their CMT neuropathy score (CMTNS) after one year. However, the CMTNS improved in the L-serine group compared to the placebo group. The leaders of the human trial said the study was limited by both small patient numbers and a lack of proven sensitive outcome measures in HSN1 and recommended a larger study using more sensitive outcome measures. Dr. Mary Reilly's group at University College London carried out a 12-month natural history study of 35 HSN1 patients using a wide range of measurements to monitor their disease progression. The group found the Queens Square Neuromuscular MRI (QS MRI) protocol measuring calf fat was the most responsive outcome measure. This natural history study, which included further refinement of the QS MRI protocol, has allowed the group to plan the SENSE trial for HSN1 patients. The primary outcome measure of the SENSE trial will be the difference in lower limb muscle fat fraction measured by the QS MRI protocol over 12 months between L-serine and placebo-treated groups. The use of the QS MRI protocol as the primary outcome measure is a significant step forward for CMT research and paves the way for use of this new approach to be used in future trials of CMT treatments in all sub-types.

AXONAL INITIATIVES

Genome-editing technologies are poised to revolutionize the practice of modern medicine for the treatment of genetic diseases. Axonal forms of CMT are a prime target, as many are caused by the type of mutations that could be cured by switching off the disease-causing copy of the gene (mutant allele) while preserving the normal copy of the gene (wild-type allele).



SARM1 INHIBITION OF AXON DEGENERATION

Jeff Milbrandt, MD, PhD

Progression of all types of CMT is caused by the degeneration of nerve axons that connect to muscles. The Milbrandt lab at Washington University has identified and elucidated the SARM1 pathway of axon degeneration, providing potential targets for treatments that could enhance survival of these axons and reduce the symptoms of CMT. The lab developed a rat knockout of SARM1 (a rat that has had the SARM1 gene turned off), which was mated to the CMTA-developed CMT2A rat. The offspring have CMT2A, but no SARM1 pathway of axon degeneration, providing useful insights into how this pathway influences CMT2A symptoms. The offspring showed a dramatic reduction in neuropathy and CMT symptoms. Due to these promising results, several companies have formed to develop drugs to inhibit axon degeneration by targeting SARM1. It is anticipated these companies will initially develop drugs for chemotherapy-induced neuropathy, but their results will open the door to further testing of SARM1 inhibitors in CMT2A. The CMTA is also funding research to investigate SARM1 function in other types of CMT (see p. 22 for the Burgess lab's work on SARM1 inhibition).

GENE REPLACEMENT THERAPY FOR CMT4A

Xin Chen, PhD, and Steven Gray, PhD

The Chen and Gray laboratory at UT Southwestern is developing a gene replacement therapy for CMT4A based on the proposition that broad central nervous system delivery of the treatment in early life can reduce disease symptoms in animal models. Thus far, a gene therapy treatment using an AAV vector delivery method has been developed and successfully validated. Safety was demonstrated via standard toxicology screening, and the study animals will continue to be monitored for one year after treatment. CMT4A mouse models have also been treated with the gene therapy and are currently being assessed to measure treatment impact. If this CMT4A treatment proves effective, the lab is well-placed to design additional preclinical studies that, if successful, could eventually allow the translation of this approach into a human treatment.

GENE EDITING FOR TYPE 2S

Luke Judge, MD, PhD, and Bruce R. Conklin, PhD

Genome-editing technologies are poised to revolutionize the practice of modern medicine for the treatment of genetic diseases. Axonal forms of CMT are a prime target, as many are caused by the type of mutations that could be cured by switching off the disease-causing copy of the gene (mutant allele) while preserving the normal copy of the gene (wild-type allele). The Conklin and Judge laboratory at Gladstone Institutes UC San Francisco uses stem cells donated by CMT patients to test CRISPR gene-editing therapies in vitro (in the dish). Using this technology, the team validated gene editing reagents that are highly effective and specific for mutations in the genes causing CMT2A, CMT2E and CMT2F. For initial proof of concept, the team focused their in vitro studies on mutations that cause CMT2E. The disease markers produced by the CMT2E mutation can be measured by automated microscope imaging analysis to distinguish between healthy and CMT2E-affected nerve cells. In a recently published study, the team demonstrated that CRISPR gene editing efficiently and specifically switched off the CMT2E disease allele, reversing the disease markers in nerve cells created from patient-donated stem cells. The team is currently extending its studies to stem cells donated by several CMT2E patients who have different mutations of the NEFL gene. One of the team's major goals is to develop strategies to treat the majority of CMT2E patients, regardless of their specific mutations. The team is also collaborating with other research groups to test this approach in the CMT2E mouse model to evaluate methods to safely deliver the treatment to the spinal cord. This work is the first description of therapeutic gene editing for axonal CMT, and the first to demonstrate therapeutic gene editing in a stem cell model of any CMT type.

HDAC6 INHIBITORS AND NFL IN TYPE 2 MOUSE MODELS

Rob Burgess, PhD

The Burgess lab at the Jackson Laboratory examined mouse models of CMT to determine if elevated plasma NfL levels are an effective biomarker of disease severity and axon loss. NfL is a protein found in axons and released into the bloodstream when nerves are damaged through injury or in CMT neuropathy. After collecting and analyzing blood samples from several mouse models of CMT, the lab found that NfL was often elevated, and generally correlated with levels of axon degeneration seen in nerve biopsies. The lab also studied acetylation of proteins in mouse nerves, which often decreases with CMT, leading to axonal transport problems. Two important proteins in nerve cell axons were modified by the addition of acetyl groups (acetylation)—alpha-tubulin and Miro. In both cases, the acetylated forms of these proteins functioned more efficiently. Both tubulin and Miro are deacetylated by an enzyme called HDAC6. Inhibiting HDAC6 in several mouse models of CMT improves protein acetylation levels and makes the neuropathy milder. The Burgess laboratory is currently measuring levels of acetylated alpha-tubulin and Miro in several Type 2 mouse models of CMT to determine which models are most likely to benefit from treatment with HDAC6 inhibitors.

GENE THERAPY STRATEGIES FOR CMT2E

Anthony Brown, PhD

CMT2E is caused by mutations in the NEFL gene, which codes for the neurofilament light chain protein. Using two different mouse models of CMT2E, the Brown lab—in collaboration with the Burghes, Meyer and Arnold labs at Ohio State University—found that the neurofilaments were affected in different ways. The Brown team hypothesized that the mechanisms of CMT2E converge on an absence of neurofilaments in myelinated axons of peripheral nerves, leading to thinner axons and weakened nerve conduction. The primary goal of their research is to evaluate a "knockdown-and-replace" gene therapy strategy for restoring neurofilaments to diseased neurons in CMT2E, in which patients have one normal NfL allele (copy of the gene) and one mutant (disease-causing) allele. Researchers propose to knock down (switch off) both the normal and mutant NfL using RNA interference and simultaneously rescue (replace) them with normal NfL. This approach should be applicable to all CMT2E mutations, increasing the potential impact and number of patients who could be treated. The labs involved have complementary expertise

in neurofilament biology, mouse genetics, gene therapy, viral vectors, neurodegenerative disease and electrophysiological assessments of neuromuscular function. The team is currently screening lead candidates for therapeutic RNAs that reduce NfL expression and testing an AAV strategy to deliver NfL to neurons. This project will provide preclinical proof of principle of a gene therapy strategy to restore neurofilaments to diseased nerve cells.

CMT2A ANIMAL MODELS SHOW PROGRESSIVE NEUROPATHY

Steven Scherer, MD, PhD

CMT2A, the most common inherited axonal neuropathy, is caused by mutations in the Mitofusin 2 (MFN2) gene. There are many different MFN2 mutations: Some cause a severe neuropathy, with an onset in early childhood and progression to wheelchair dependency by age 20. Other mutations cause an adult-onset neuropathy that is much milder. Because existing mouse models of CMT2A do not result in an obvious neuropathy, the CMTA funded the creation and analysis of two new rat models with two different CMT2A-causing mutations that are associated with severe, early-onset neuropathy.

Drs. Joel Li and Eunjoo Lancaster in the Scherer laboratory at the University of Pennsylvania analyzed the two new animal models, finding that both developed a progressive neuropathy, beginning at 16 weeks of age, with obvious electrophysiological and clinical evidence of progressive axonal loss. The new models provide the option to test new treatments either before the onset of neuropathy (a preventative trial) or after the onset of neuropathy (an interventional trial). The CMTA has made these rats available for use in preclinical testing of candidate treatments for CMT2A.

NEW ANIMAL MODELS OF CMT4A AND CMT2K

Steven Scherer, MD, PhD

The Scherer lab is also developing animal models of CMT4A and CMT2K. CMT4A, the most common recessively inherited axonal neuropathy, is caused by many different mutations in the GDAP1 gene. Other mutations in the GDAP1 gene cause CMT2K. Unfortunately, several existing mouse models of CMT4A do not result in an obvious neuropathy, and no animal model of CMT2K has been reported. Based on the Scherer laboratory's success in developing two new rat models of CMT2A, the CMTA funded the team to create rat models of CMT4A and CMT2K. If these new models are found to be authentic representations, they too will be made available for use in preclinical testing of candidate treatments. The provision of representative animal models for CMT4A,

CMT2K, and CMT2A increases the number of potential CMT treatments brought forward for testing by lowering the barriers to and costs of research and reducing the risk to investing biotechnology and pharmaceutical firms.

New animal models developed by the Scherer team provide the option to test new treatments either before the onset of neuropathy (a preventative trial) or after the onset of neuropathy (an interventional trial).

ALLIANCE PARTNERSHIP INITIATIVES

CMTA-sponsored research projects with university-based research teams like those described above represent just part of the CMTA's drive to accelerate research. Our Alliance partnership initiatives account for almost 40 percent of the CMTA's currently active research projects. Many of these initiatives are commercially sensitive and remain confidential. The partial list below shows our active, non-confidential Alliance partners, the service providers we work with to deliver research, and some of our Alliance partner alumni. With seven additional confidential CMTA Alliance partners actively engaged in research, the Alliance partner network is rapidly evolving, reflecting the nature of our work in this highly agile sector. Look for details on our Alliance partnership initiatives in a future issue of The CMTA Report.

CMTA Alliance Partners

- Applied Therapeutics
- HumanFirst Therapeutics
- InFlectis BioScience
- Ionis Pharmaceuticals
- Orthogonal Neuroscience
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- Shift Pharmaceuticals
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— Lennart
Biomedical Engineering student and foot drop patient

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THE FUTURE IS NOW: CLINICAL TRIALS

The CMTA has spent the last 15 years assembling the components needed for clinical trials, and those efforts are now coming to fruition. Late-stage clinical trials are underway and many more are expected in the coming years.

Three CMTA partners updated attendees at the CMTA's Patient & Research Summit Oct. 1 on their late-stage clinical trials for two drugs and one gene therapy.

Pharnext CEO David Horn Solomon, PhD, told the online audience that the French company expects a "readout," or results report, for its Phase III clinical trials for PXT3003 in the fourth quarter 2023.

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

The study enrolled 387 patients at 53 centers worldwide and continues to follow 123 patients who continue to improve after five years. "It's anecdotal," Solomon said, "but the fact that 123 patients globally continue to travel many hours to see their physician … and receive the medicine suggests to us … that the medicine must have some effect."

Noting that the FDA approved a fixed-dose combination of another dual-acting medicine for the motor neuron disease ALS on Sept. 29, Solomon said that the idea of fixed-dose combinations of existing medicines to treat rare neurologic disorders is back in favor with the agency.

Shoshana Shendelman, PhD, CEO and founder of Applied Therapeutics, updated the audience on its investigation of AT-007, a potential therapy for a newly discovered type of CMT caused by a deficiency of the SORD gene. Dr. Stephan Zuchner's team at the University of Miami found that the newly discovered type is caused by a mutated SORD (sorbitol dehydrogenase) gene that raises sorbitol levels so high they cause nerve damage. AT-007 prevents sorbitol from being formed in the body: In the pilot study, researchers found a 66 percent reduction in sorbitol levels within seven days.

Shendelman called the work "a really good example of how academic physicians and the Inherited Neuropathy Consortium and patient organizations like the CMTA have been able to work together to identify the genetic cause of a subtype of about 10 of genetic cause unknown."

The role sorbitol plays in neuronal degeneration had been studied for decades in the context of diabetic neuropathy, Shendelman said, giving researchers a chance to move very quickly. Just two years after the gene was discovered, the drug treatment for it is in clinical trials. "We're hopeful that a favorable safety trial and the urgency here will allow something like accelerated approval," she added.

Suyash Prasad, MD, chief medical officer and head of research and development at Taysha Gene Therapies, talked about his company's work with the eminent gene therapist Steven Gray, PhD, at UT Southwestern to develop an AAV-based gene therapy for giant axonal neuropathy (GAN), which shares many commonalities with CTM2.

Thus far, 14 patients have been dosed and 12 showed "highly relevant clinical benefit," Prasad said, and the company has manufactured enough of its gene therapy drug to treat 50 additional patients.

"So long as we know what the mutation is, what protein is missing and that the DNA that codes for the protein can be packaged, the GAN neuropathy approach can be translated to other forms of CMT," Prasad said.

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Thalidomide
Zalcitabine (ddC, Hivid)

Uncertain or minor risk:

5-Fluouracil
Adriamycin
Almitrine (not in US)
Chloroquine
Cytarabine (high dose)
Ethambutol
Etoposide (VP-16)
Gemcitabine
Griseofulvin
Hexamethylmelamine
Hydralazine
Ifosfamide
Infliximab
Isoniazid (INH)
Lansoprazole (Prevacid)
Mefloquine
Omeprazole (Prilosec)
Penicillamine
Phenytoin (Dilantin)
Podophyllin resin
Sertraline (Zoloft)
Statins
Tacrolimus (FK506, Prograf)
Zimeldine (not in US)
a-Interferon

Negligible or doubtful risk:

Allopurinol
Amitriptyline
Chloramphenicol
Chlorprothixene
Cimetidine
Clioquinol
Clofibrate
Cyclosporin A
Enalapril
Glutethimide
Lithium
Phenelzine
Propafenone
Sulfonamides
Sulfasalazine

The medications listed above are potentially toxic to CMT patients. Vincristine has been proven hazardous and should be avoided by all CMT patients, including those with no symptoms. Taxols also pose a high risk to people with CMT. The remainder of the medications listed above present varying degrees of potential risk for worsening CMT neuropathy. Before taking any medication or changing medication, all CMT patients should make sure the treating physician is fully aware of their medical condition.

WHAT IS **CMT?**

More than 3 million people worldwide have CMT. It is one of the most commonly inherited nerve disorders and affects the motor and sensory nerves.

CMT is slowly progressive, causing the loss of muscle function and/or sensation in the lower legs and feet, as well as hands and arms.

People in **all ethnic groups may be affected by CMT.**

CMT is genetic, but it can also develop as a new, spontaneous mutation.

CMT can vary greatly in severity, even within the same family.

CMT causes structural deformities such as high-arched or very flat feet, hammertoes, hand contractures, scoliosis (spinal curvature) and kyphosis (rounded back).

CMT can also cause foot drop, poor balance, cold extremities, cramps, nerve, muscle and joint pain, altered reflexes, fatigue, tremor, sleep apnea, hearing loss and breathing difficulties.

CMT rarely affects life expectancy.

Some medications are neurotoxic and pose a high risk to people with CMT, notably Vincristine and Taxols. See full list (at left) of medications that may pose a risk.

More than 100 different genetic causes of CMT have been identified.

Many types of CMT can be determined by genetic testing. Please consult with a genetic counselor (www.nsgc.org) or your physician for more information.

Although there are no drug treatments for CMT, a healthy diet, moderate exercise, physical and/or occupational therapy, leg braces or orthopedic surgery may help maintain mobility and function.

The CMTA-STAR research program and extensive partnerships with pharmaceutical companies are driving remarkable progress toward delivering treatments for CMT, bringing us closer to a world without CMT.

CMTAUSA.ORG