Highlights and Learnings of Alliance Partnerships

The CMTA's research is done in teams drawn from academic labs and clinical centers sponsored by the CMTA (the STAR Alliance). One of the Alliance's first initiatives was to develop a toolbox of cell and animal models for Alliance partners to use in their research. The toolbox has been crucial in recruiting partners and in 2022 drew 12 Alliance partners to invest more than $2 million in 28 studies.

- Most companies do not have the time and knowledge (or the funding) to put a CMT testing infrastructure in place. Without the infrastructure provided by the CMTA, they probably wouldn't explore CMT therapy opportunities.
- Company projects are often adapted from treatments for other neurodegenerative diseases, increasing the possibility they'll be effective against CMT. Company approaches to CMT cover the span of therapy modalities: Small molecule, biologic and genetic therapy approaches are all represented. The Alliance approach is intentionally "therapy agnostic," which allows us to partner across the spectrum.
- We regularly get requests for relatively rapid and valid tests in a dish that would show whether a potential therapy should advance to animal testing. The CMTA is investing in the development of additional in vitro models to add to the toolbox, removing yet more barriers for companies that want to test a therapy's effectiveness against CMT.
- Many companies want to see effectiveness across a number of CMT types and commission studies in multiple models. The CMTA's broad capability makes this approach possible.
- Companies deciding whether to enter the field of CMT look at several criteria: 1) Is the mechanism of their therapy's action in the disease understood? 2) Can a clinical trial be successfully done? 3) Can the therapy be used safely and effectively over time? This is especially important in non-lethal but chronic diseases such as CMT. The CMTA's STAR efforts are helping to meet these criteria, from basic science and discovery to clinical trial readiness.
- Most Alliance partners are well-financed and/or publicly traded companies, but the toolbox can also be used by early-stage companies, university projects and foundations that need know-how, early-stage investment or access to resources.
- Company discussions and collaborations have shown that muscle therapies used in conjunction with CMT therapies to slow disease progression are a viable commercial option, and a broadly applicable approach for many CMTs.

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FUELING CMT RESEARCH WORLDWIDE

CMTA'S STAR LEADS THE WAY

Today, we are proud to share that the CMTA's Strategy to Accelerate Research (STAR) stands as the largest philanthropic funder of CMT research worldwide. Our commitment to advancing research is unwavering.

Just as the CMTA is the driving force behind CMT research, the patient community is the driving force behind the CMTA. Community members and their friends and families are the reason we thrive and will ultimately change the future of CMT.

With the support of our community, the CMTA has invested $23.8 million in 60 research projects covering more than 90 percent of all CMT subtypes since STAR was founded in 2008. We have also developed critical research tools that have attracted more than 40 partners to our STAR Alliance.

The pace of research can feel frustratingly slow, and we haven't yet reached our ultimate goal of a cure for CMT. But we've achieved a number of key milestones on the road to a world without CMT, and we are determined to continue driving progress with your support.

MAJOR MILESTONES

CRITICAL INFRASTRUCTURE

- In 2001, Dr. Michael Shy and the CMTA established the North American CMT Database to provide researchers with ready access to families categorized by their types and subtypes.
- In 2011, the CMTA established Centers of Excellence to help ensure that CMT patients receive the best possible evaluation and care and that their information is collected for possible recruitment into clinical trials. This network has now grown to 52 centers in 5 countries.
- With CMTA support, the global Inherited Neuropathy Consortium (INC) has expanded to 20 sites and recruited over 7,000 patients to the clinical registry and natural history studies, which will support upcoming clinical trials.
- In 1991 we identified the gene that causes 1A. Today 129 genes and 163 subtypes have been identified. In the last four years, CMTA support has directly contributed to 25 of these discoveries.

CRITICAL RESEARCH RESOURCES AND LEARNINGS

- New rodent models of CMT have emerged as crucial testing resources for potential therapies covering CMT1A, CMT2A, CMT1X, CMT2E and CMT1B. The CMTA has directly funded the creation of several best-in-class animal models, reducing the barriers faced by CMT researchers and pharmaceutical companies.
- Working with the New York Stem Cell Foundation, we established the first CMT biorepository in 2014. The stem cell lines and patient samples in the repository are an essential resource for academic and commercial researchers.
- We're pursuing multiple strategies to develop therapies for various CMT types. For instance, in CMT1A, we're investigating genetic therapies (ASO, RNAi, AAV gene therapy, and CRISPR-Cas9 genome editing) as well as drug-based approaches. Our collaborations with various companies encompass diverse methods, and we aim to identify the most effective CMT1A treatment through parallel clinical trials. Similar parallel approaches are being pursued for other major CMT types.

GENE THERAPIES

- Gene therapy has been shown to be an effective strategy in preclinical models of CMT1A, CMT1X, CMT4C and CMT4J. Company partnerships have been established to advance these therapies from the lab bench to the next stage of pre-clinical and regulatory testing in readiness for first-in-human clinical trials.
- Delivery of gene therapy reagents to motor neurons has culminated in an approved therapy for spinal muscular atrophy. Similar approaches for CMT4J and giant axonal neuropathy (GAN) have been successful in preclinical studies, and other efforts in CMT2A, CMT4A and CMT2E are underway.
- Delivery of gene therapy reagents to Schwann cells for demyelinating CMT remains a challenge, but AAV gene therapy studies have been successful in some preclinical models, with other advances reported for delivery of RNAi in demyelinating CMT. The CMTA recently funded a study that will investigate nanoparticles as a non-AAV delivery vehicle for gene therapy.
- Gene editing using CRISPR-Cas9 is in clinical trials for ATTR-associated neuropathy, and this technology may be applied to several types of CMT if effective delivery strategies for Schwann cells and motor neurons are found.

DRUG THERAPIES

- Several studies have highlighted the efficacy of lowering PMP22 gene expression in preclinical models of CMT1A, including the use of antisense oligonucleotides and RNA interference.
- Axon degeneration clearly plays a major role in the progression of CMT, and some candidate drug targets have emerged for testing.
- A novel type of CMT caused by SORD mutations led to rapid clinical trials using a drug developed for diabetic neuropathy.
- In a recent major advance, researchers have clarified the disease mechanisms in CMT2D, identifying treatment targets that will enable new types of therapy.
- The Food and Drug Administration is designating an increasing number of potential CMT treatments (and drug-repurposing efforts) as orphan drugs, an important step on the path to bringing treatments to the CMT community.

CLINICAL TRIALS

- One hurdle to clinical trials is CMT's relatively slow disease progression, which necessitates very long (and expensive) trials. CMTA-supported research on biomarkers—calf muscle MRI and blood and skin samples has provided several candidate predictors of therapeutic benefit to patients. Effective biomarkers can shorten the length of clinical trials and reduce the number of patients needed, lowering barriers to industry investment. Other important measures for evaluating functional outcomes (CMT-FOM), pediatric and infant assessments have been developed to support clinical trials. A vital prerequisite for clinical trials is the development of natural history studies for each type of CMT, and these have been completed and published or are currently in progress for most major types of CMT.
- A new clinical trial for one type of CMT (HSAN1) will provide a major test of calf muscle MRI as a clinical trial outcome measure and will open the door for its use in clinical trials in other forms of CMT.

Our efforts in CMT research are designed to have a wide-reaching impact across various CMT types:

The development of biomarkers for clinical trials holds promise for improving the assessment and treatment of most CMT variations.

Our gene therapy strategy targeting CMT1X is poised to indirectly benefit other types that affect Schwann cells, such as CMT1A, CMT4C, and CMT1B.

A crucial element in combating CMT progression lies in preventing the loss of nerve-muscle connections, or axons, which could prove to be a common strategy with benefits extending to many different CMT types. Through these multifaceted approaches, we aim to advance treatments and therapies that can positively impact the lives of all individuals affected by CMT, regardless of type.