

A Window of Opportunity and an Extraordinary Commitment

Through both their personal contributions and the events they sponsor, members of the CMTA Board of Directors have always been generous supporters of the CMTA, and the current \$350K Board Challenge demonstrates their extraordinary commitment to funding research and the work of the CMTA. For the second year in a row, they are matching your contributions, dollar for dollar, up to that amount.

We have also held two very successful "Honor a Star. Be a STAR." galas. Among the honorees at the first gala in 2008 were the Chernega family for their generous gift to the STAR project, the Livney Family Foundation for their challenge grants, and Coach Joe Paterno



Sue Paterno and CMTA CEO Dave Hall look on at the 2nd Annual STAR Gala as "Joe Pa" tells our guests, "We can cure it. It will take a little money...."

for his work in making people more aware of the name Charcot-Marie-Tooth. At the second gala in April, Joe and Sue Paterno were honored for their "Lifetime of Achievement" and help in supporting the CMTA and other charities.



The CMTA Circle of Friends... Working Together for a Cure!

Though they are too numerous to mention here, we are also very grateful for the extraordinary commitment of everyone who has organized or joined a CMTA Circle of Friends, sponsored a swimmer or bike rider, or held a fundraiser to support the work of the CMTA.

With the leadership of our new CEO, David M. Hall, the scientific advances that have made STAR possible, and the dedicated effort of our members and supporters, we have a compelling window of opportunity to promote real change through a campaign of research, education, awareness, and clinical care. All we need is your commitment and your support.

"When it comes to improving our situation, we are our strongest advocates."

That's why a year ago the CMTA began a campaign to double its membership by offering everyone a year for free. You responded in record numbers, and the CMTA now has more than 4,000 members.

But for a disorder that affects an estimated 1 in 2500 people, doubling our membership is just a start. We have to continue building on our accomplishments.

That's especially true when it comes to creating awareness about CMT and educating patients and physicians. For the fourth year in a row, we have been the recipient of a Pennsylvania Department of Health grant in the amount of \$237,000. This grant has allowed us to publish and distribute a new booklet called "My Child Has CMT" to pediatricians, to host several patient/family conferences, and to produce radio and television ads throughout the state.



We have also been successful in placing stories about people with CMT in local newspapers across the country, but we need to do more, so on Rare Disease Day, we asked you to reach out to your political representatives and let them know about CMT and what they can do to help in their states or districts.

With the help of Board Member Elizabeth Ouellette, we were able to hold a patient-family conference in California, which we have since been able to make available to everyone on a 2-DVD set, and we've also added several other new publications including *CMT Facts VI* and a revised "What is CMT?" brochure (soon to be available in Spanish). For more, visit www.cmtausa.org/pubs.

Finally, we're very happy to report that our campaign to increase the number of CMTA support groups has met with success. Over the past year, we've added 23 groups, for a total of 43, and we hope to add many more in upcoming months.

To learn more about how you can get involved, please visit us on the web at www.cmtausa.org, call 1-800-606-2682, or email info@charcot-marie-tooth.org.

Meeting Our Goals: A Year of Progress at the CMTA

The mission of the CMTA is to generate the resources to find a cure, to create awareness and to improve the quality of life for those affected by Charcot-Marie-Tooth.

In our 25th anniversary year, we have taken impressive strides toward the development of treatments and a cure; we have increased the visibility and recognition of CMT; and we have continued to improve patients' lives by educating, informing and supporting them.

We are pleased to share this report of our accomplishments with you, and we hope you will take this and every opportunity to get involved and stay involved with the work of the CMTA.

Together, we can achieve our vision of a world without CMT.



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Strategy to Accelerate Research (STAR)[™] Enters Second Phase

We established our Strategy to Accelerate Research at the beginning of our 25th year, and we have since made amazing progress toward our goal of finding effective therapies for CMT1A and other common forms of CMT.



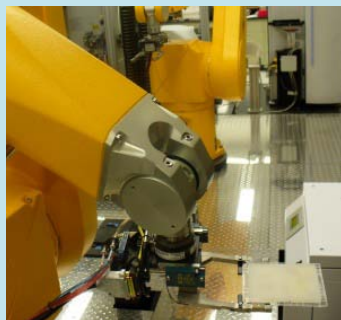
CMT1A is caused by a duplication on chromosome 17 that results in the overexpression of a peripheral myelin protein known as PMP22.

The first project of STAR was to develop a stable cell line for use in high-throughput screening (HTS), making sure that elements in the cell line that regulate PMP22 expression are as close as possible to the regulatory elements in Schwann cells that make myelin in nerves.

In April, this project was completed, and the CMT1A cell line developed by Ueli Suter at ETH Zurich using MSC80 cells (created from Schwann cells) was delivered to the high-throughput screening facility at the National Institutes of Health Chemical Genomics Center (NCGC).

“Immortalized” by fusing it with a cancer cell line so that it can be grown indefinitely, this cell line has also been genetically engineered by Professor Suter to turn on a protein called luciferase (the protein that makes fireflies glow) every time the PMP22 gene is expressed.

During the next phase of STAR, precise quantities of these cells will be injected into 1536-well plates like the one shown at right being held by a Kalypsys robot. Equally precise amounts of more than 350,000 compounds and drugs from the NCGC chemical compound library will then be added to each well, and the plates will be rapidly screened to detect any change in fluorescence. (Visit www.cmtastar.org/hts for a video and more on HTS.)



“HTS will enable us to identify compounds that reduce the overexpression of PMP22.”

Since the cells will glow in relation to the amount of PMP22 expressed, this high-throughput screening will enable us to identify compounds that reduce the expression of PMP22.

To accomplish this and future HTS work, the CMTA has established and funded a three-year post-doctoral fellowship at the NCGC. Sung Wook Jang, who holds a PhD in Cellular and Molecular Biology from the University of Wisconsin in Madison, has been appointed and began work in July.

Sung Wook is working closely with NCGC project leader Jim Inglese and his team of scientists to optimize the development of the candidate “chemical probes” for use in laboratory and clinical studies.

The success of this optimization depends, in part, on the work of two other scientists: Klaus-Armin Nave, Professor at the Max Planck Institute of Experimental Medicine in Gottingen, Germany, and John Svaren, Associate Professor at the Waisman Center of the University of Wisconsin.

Professor Nave is generating a laboratory model in which Schwann cells express the same luciferase reporter expressed by the MSC80-luciferase cell line. In this way, the regulatory effects of candidate medications from the HTS can be confirmed in an animal model.

The regulation of the mouse and rat PMP22 genes may be different than the regulation of the human PMP22 gene, however, and Professor Svaren, the leading expert on how myelin genes are regulated, is investigating the regulation of the human PMP22 gene to determine if our HTS can be further “tweaked” to optimize the probes.

All STAR projects are in process and on schedule to enable clinical trials of CMT1A patients within 4 years.



The NCGC Chemical Compound Library: Some of the 350,000 compounds stored here may become treatments for CMT.

Highlights from Additional Research Funded by the CMTA

Although STAR is taking a highly focused path to a treatment for CMT1A and represents an unprecedented funding challenge—\$10 million over 5 years—we have continued our commitment to funding research aimed at understanding and treating other forms of CMT, and we have awarded several three-year, \$100,000 grants.

One recipient, Dr. James Lupski, at Baylor College of Medicine, in his work entitled “Molecular therapy and management for CMT,” has shown that curcumin, a dietary supplement, may be useful in treating some forms of mutated proteins causing CMT. Dr. Lupski, who originally identified the gene causing CMT1A, has also done much to explain how such genetic coding errors occur in his work on DNA copy number variation, fork stalling, and template switching.

Dr. Stephan Zuchner, at the Miller School of Medicine, Miami Institute of Human Genomics, is working on “The function of Dynamin 2 mutations in peripheral neuropathies.” After studying 45 CMT families, it was determined that DNM2 mutations might be a relatively rare cause of CMT. However, they believe that finding the exact localization of the molecular defect in DNM2 related to CMT should facilitate the identification of drug targets.

Dr. Michael Garcia, at the University of Missouri, has just begun his project entitled, “Mechanisms of disease pathogenesis in neurofilament linked Charcot-Marie-Tooth.” He is developing mice who will express disease-linked NF-L mutations, which cause CMT type 2E.

Enrollment in the ascorbic acid clinical trial co-funded by the CMTA and the MDA also ended in April. Unlike other studies using lower doses of Vitamin C over shorter periods, this study, scheduled for completion in 2011, is using a high dose over a two-year period and is expected to be the definitive work on ascorbic acid and CMT.

Adding it up....

The CMTA awarded \$508, 333 to all research projects, including STAR, in 2008. We also awarded \$419,451 in the first half of 2009, and we have outstanding obligations to disburse an additional \$225,000 by year’s end.