



## Charcot-Marie-Tooth Association

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## Progress Report on the STAR Initiative

The CMTA held a meeting at the NIH Chemical Genomics Center in Rockville, Maryland, on November 20, 2008, to review progress and plans for the STAR initiative. The attendees included board members (Patrick Livney, Gary Gasper, Herbert Beron, Robert Kleinman, Phyllis Sanders, Dr. Michael Shy and Dr. Steven Scherer), a member of the STAR Scientific Advisory Board (Dr. Lawrence Wrabetz), the STAR scientists (Drs. Ueli Suter, Ned Mantei, Klaus Armin-Nave, and John Svaren), members of the Chemical Genomics Center (Drs. James Inglese and Christopher Austin) and the National Institutes of Health (Drs. John Porter and Amelie Gubitzi), and members of the CMTA staff (Pat Dreibelbis and Dana Schwertfeger).

CMTA Chairman Patrick Livney and Dr. Michael Shy (Wayne State University) reviewed the history of the STAR initiative. Key points included the recommendation, from the NIH Peripheral Neuropathy Conference in 2006 ([http://www.ninds.nih.gov/news\\_and\\_events](http://www.ninds.nih.gov/news_and_events)), to use high-throughput screening, and meetings between the CMTA board, members of the Myelin Repair Foundation, Dr. John Porter (Program Director at the National Institute for Neurological Disorders and Stroke; NINDS), and Dr. James Inglese (Deputy Director of the Chemical Genomics Center). Drs. Michael Shy, Steven Scherer, and Lawrence Wrabetz, in consultation with the investigators of the individual projects, then refined a plan that ultimately became the three current projects of the STAR initiative.

Drs. Ueli Suter and Ned Mantei (ETH-Hoenggerberg, Zurich, Switzerland) reviewed their group's progress in Project #1—to genetically engineer stable Schwann cell lines to express a form of the PMP22 gene that expresses a fluorescent "reporter" molecule. These cell lines will be used for high-throughput screening, which is an automated way of testing large numbers of compounds (even more than 1 million) for their effects on PMP22 expression. They have successfully made several cell lines that stably express their construct—a long (10,000 base-pairs) piece of the mouse PMP22 promoter, fused to the reporter ("green luciferase"). These cells could be screened now according to Dr. James Inglese, but Drs. Suter and Mantei are trying to make further refinements that will enable non-specific toxic effects of the compounds used in the high-throughput screen to be evaluated.

Dr. Klaus-Armin Nave (Max-Planck-Institute of Experimental Medicine, Goettingen, Germany) reviewed how he and his colleagues generated a rat model of CMT1A, and how progesterone antagonists were used to decrease PMP22 expression, thereby improving motor function and diminishing the severity of demyelination in these rats. In Project #2, his group will generate transgenic rats that express a very large (77,000 base-pairs) fragment that contains the entire human PMP22 gene. The human PMP22 gene will be modified to introduce a reporter ("green luciferase") in place of part of the PMP22 gene.

Dr. John Svaren (University of Wisconsin) reviewed the data that a combination of binding sites for two different transcription factors, Sox10 and EGR2, regulate the expression of



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several myelin-related genes. In Project #3, his group has found two such Sox10/EGR2 binding sites in the human PMP22 gene, and has evidence that at least one of these sites is active in regulating PMP22 expression. Continuing analysis of the human PMP22 gene is key for properly designing the next generation of PMP22 promoter/reporter constructs.

Dr. James Inglese (Deputy Director of the NIH Chemical Genomics Center) and Dr. Christopher Austin (Senior Advisor to the Director for Translational Research) outlined the pathway for developing new drugs. According to this outline, the STAR initiative has done the first step, identifying the target (PMP22 overexpression), and is currently engaging the next step—finding compounds that properly affect this target (diminish PMP22 expression). Typically, this is an iterative process that requires refining the “positive hits” found in a high-throughput screen to generate an active “lead compound” with the proper features to be used as a drug in humans. This refinement will likely benefit from the approach used at the Chemical Genomics Center—they use dose-response curves (they look at the effects of compounds over a range of concentrations), and use this data in compiling and analyzing “positive hits” of the high-throughput screen.

The next step is testing the lead compound(s) in appropriate biological models, like myelinating co-cultures and animal models with PMP22 overexpression; historically, ~90% of compounds have failed this step. These initial steps, however, are relatively cheap and fast compared to the subsequent clinical trials involving human subjects, which are expensive and have a high failure rate (~90%). Repurposing already approved drugs can potentially bypass much of the time and expense of clinical studies, as these drugs have already been shown to be safe in humans. The Chemical Genomics Center has been putting together a chemical library of drugs that have been approved in the US or abroad (Britain, Canada, Japan, and others) for just this reason.

Dr. John Porter (Program Director at the NINDS) emphasized that it is important to preselect criteria for preclinical trials (endpoints, randomization, properly powered studies), and to consider outsourcing preclinical studies to a professional preclinical trial organization. He will continue to advise the CMTA of granting opportunities as the research develops.

Dr. Michael Shy (Wayne State University) reviewed the history supporting the use of ascorbic acid to treat CMT1A. There are three ongoing clinical trials, one in North America (supported by the CMTA and the MDA) and two in Europe. All three trials are using the CMT Neuropathy Score as an endpoint; this should facilitate the comparison of the data from the trials. Dr. Shy also helped to establish six CMT Centers of Excellence (funded by the CMTA and the MDA) for the purpose of having CMT patients evaluated by peripheral neuropathy specialists and recording the resulting clinical data in the CMT database. This data will also be useful in generating a list of eligible participants for future clinical trials.