



DEMYELINATING CMT: TYPE 1, TYPE X AND TYPE 4 STAR RESEARCH DEVELOPMENTS

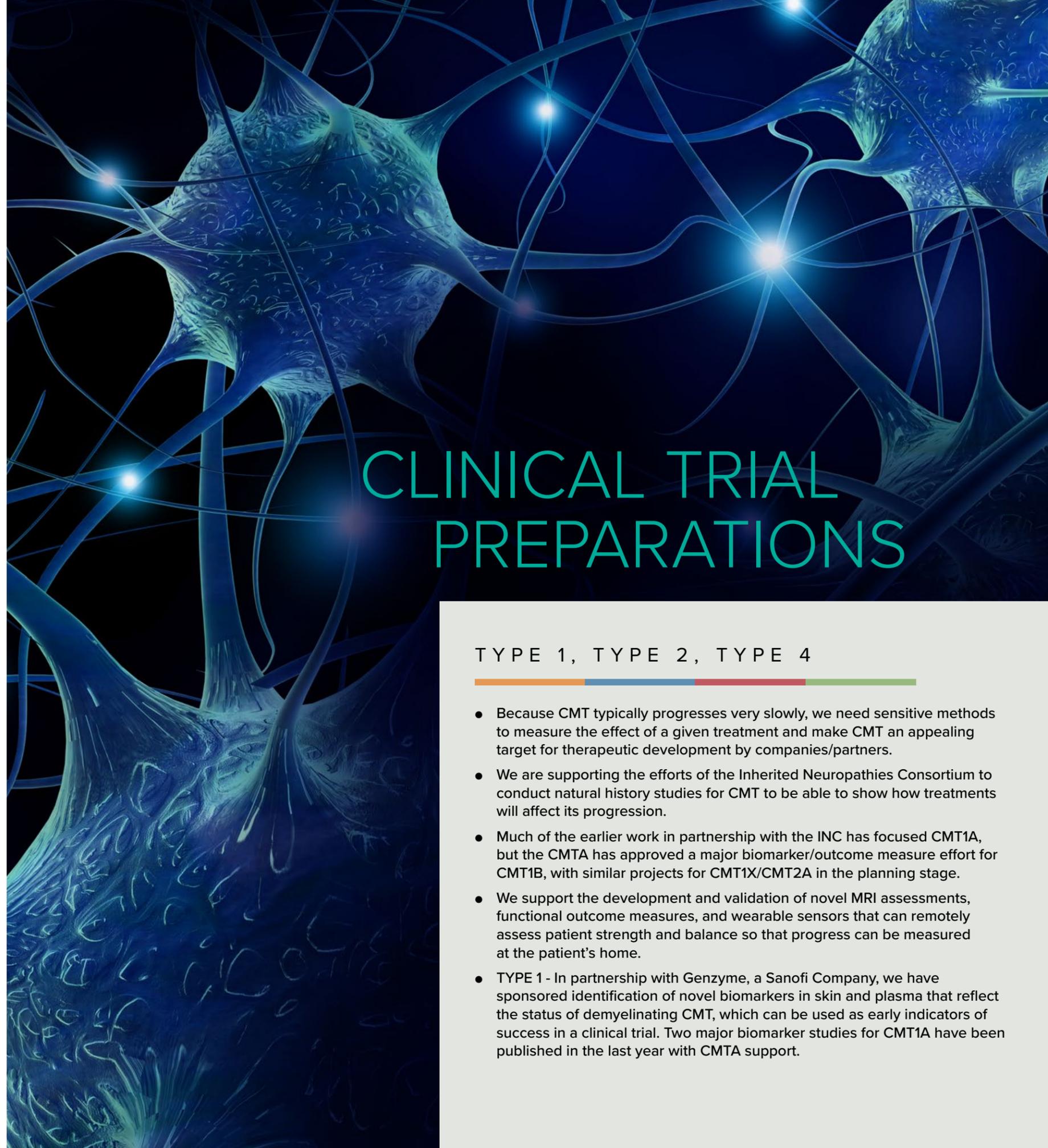
As part of this multi-pronged approach to identifying novel treatments for demyelinating CMT, the CMTA is supporting several promising therapeutic opportunities in collaboration with more than a dozen key partners:

GENETIC THERAPIES

- In collaboration with Ionis Pharmaceuticals, we are developing antisense oligonucleotides (ASOs), which have shown dramatic results in two rodent models of CMT1A.
- CMTA-funded studies by Dr. Kleopas Kleopa of the Cyprus Institute of Neurology and Genetics have shown that gene therapy is feasible in rodent models of CMT1X and CMT4C and there have been several interactions with gene therapy companies that are working with adeno-associated viruses (AAV), which can be engineered to deliver DNA to target cells. This approach is now being extended to use RNA interference to decrease the PMP22 levels found in CMT1A and to optimize delivery to the affected Schwann cells in demyelinating CMT.
- We are currently collaborating with one company to use CRISPR (genome editing) to treat demyelinating CMT, and additional collaborations with leading labs are underway.

DRUG DEVELOPMENT

- In partnership with InFlectis BioScience, we are developing agents to restore myelin protein balance for CMT1A and CMT1B. Phase 1 clinical trials have concluded and InFlectis is gearing up for Phase 2 trials.
- The progression of all types of CMT occurs as the longest axons are compromised in a process called axon degeneration. We are working with partners to develop chemical inhibitors of the triggers of axon degeneration. We are currently testing the applicability of this approach to multiple models of CMT, collaborating with several companies, including Regency Pharmaceuticals, on candidate drugs to promote axon survival and preserve nerve function.
- We are supporting work done by Dr. Maurizio D'Antonio of the San Raffaele Scientific Institute to test new drug classes for CMT1B, which are being developed for stress-related disorders such as stroke, Alzheimer's and retinal degeneration.
- We are supporting work at the University of Wisconsin and Memorial Sloan Kettering to identify new targets for drug development in CMT1A.
- We supported Acceleron Pharmaceuticals' efforts (since ended) to strengthen affected muscles in individuals with demyelinating CMT.



CLINICAL TRIAL PREPARATIONS

TYPE 1, TYPE 2, TYPE 4

- Because CMT typically progresses very slowly, we need sensitive methods to measure the effect of a given treatment and make CMT an appealing target for therapeutic development by companies/partners.
- We are supporting the efforts of the Inherited Neuropathies Consortium to conduct natural history studies for CMT to be able to show how treatments will affect its progression.
- Much of the earlier work in partnership with the INC has focused CMT1A, but the CMTA has approved a major biomarker/outcome measure effort for CMT1B, with similar projects for CMT1X/CMT2A in the planning stage.
- We support the development and validation of novel MRI assessments, functional outcome measures, and wearable sensors that can remotely assess patient strength and balance so that progress can be measured at the patient's home.
- TYPE 1 - In partnership with Genzyme, a Sanofi Company, we have sponsored identification of novel biomarkers in skin and plasma that reflect the status of demyelinating CMT, which can be used as early indicators of success in a clinical trial. Two major biomarker studies for CMT1A have been published in the last year with CMTA support.