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# Towards a cure for Charcot-Marie-Tooth: a critical overview on new therapeutic approaches with patients as partners

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## 1. Charcot-Marie-Tooth disease: clinical and biological framework

Charcot–Marie–Tooth disease (CMT) comprises a heterogeneous group of inherited peripheral neuropathies affecting approximately 1 in 2,500 individuals worldwide. Clinically, CMT is characterized by slowly progressive distal muscle weakness and atrophy, sensory loss, reduced reflexes, and characteristic foot deformities. Based on neurophysiological criteria, CMT is classified into demyelinating (CMT1/CMT4), axonal (CMT2), and intermediate forms (Skre, 1974; Pareyson et al., 2017).

At the cellular level, demyelinating forms primarily involve defects in Schwann cell myelin formation and maintenance, whereas axonal forms are characterized by primary axonal degeneration. Despite these differences, disease progression across CMT subtypes ultimately converges on axonal dysfunction and loss, which closely correlates with clinical disability (Sahenk et al., 2008).

Although more than 130 causative genes have been identified, current clinical management remains largely symptomatic. Nevertheless, advances in molecular genetics, disease modeling, and therapeutic delivery have enabled the development of targeted therapeutic strategies that are now entering translational and early clinical phases. A recent account has been given in Session 3 of the Conference on „Therapeutic approaches on CMT neuropathies" by Kleopas Kleopa, and promising examples of specific research projects in the field can be found in the Youtube-playlist of selected talks and presentations given at the Conference.

## 2. Therapeutic strategies under development

### 1.2.1 Gene-based approaches

Gene-based therapies aim to address the primary genetic cause of CMT by restoring gene function, modulating gene dosage, or selectively silencing pathogenic alleles using viral vectors, antisense oligonucleotides (ASOs), small interfering RNA (siRNA), or genome-editing approaches.

In demyelinating CMT, particularly CMT1A caused by PMP22 duplication, several strategies aim to reduce toxic PMP22 overexpression. These include AAV-mediated RNA interference (Gautier et al., 2015; Stavrou et al., 2022), systemically delivered ASOs (Zhao et al., 2018), chemically modified siRNA formulations (Boutary et al., 2020), and CRISPR/Cas9-based

transcriptional repression strategies (Lee et al., 2020). Loss-of-function demyelinating neuropathies such as CMT1X or CMT4C are being addressed by Schwann-cell–targeted AAV-mediated gene replacement, restoring myelination and nerve function in preclinical models (Kagiava et al., 2016; Kagiava et al., 2021; Georgiou et al., 2023).

In axonal CMT, gene-based approaches include intrathecal AAV-mediated gene replacement for giant axonal neuropathy (El Mallakh et al., 2017; Bharucha-Goebel et al., 2024), allele-specific RNA interference for GARS-related CMT2D (Morelli et al., 2019), and early gene replacement in FIG4-related CMT4J (Winborn et al., 2018). In addition, intramuscular AAV-mediated delivery of neurotrophin-3 (NT3) provides a broadly applicable strategy supporting Schwann cell–axon interactions across multiple CMT subtypes (Sahenk et al., 2014).

More information on the genetic CMT therapy development is presented at the webinar given by Kleopas Kleopa in a series set up jointly by EAN, the ERN EURO NMD and ECRA in January 2026: "Current Progress in Charcot-Marie-Tooth disease (CMT) Treatments".

### 2.2.2 Pharmacological approaches

Pharmacological strategies primarily target downstream pathogenic mechanisms shared across multiple CMT forms and may complement gene-based interventions or serve as earlier therapeutic options.

In demyelinating CMT, approaches focus on PMP22 modulation, restoration of proteostasis, Schwann cell differentiation, unfolded protein response (UPR) activation, and inflammation. The most advanced example is PXT3003, an oral combination therapy designed to downregulate PMP22 expression, which has shown modest but measurable functional benefit in Phase III trials (Attarian et al., 2014; Attarian et al., 2021). Additional strategies include UPR and proteostasis modulation using IFB-088/Sephin1 (D'Antonio et al., 2013; Das et al., 2015), and proteasome activation via cGMP signaling using sildenafil (VerPlank et al., 2022).

In axonal CMT, therapeutic strategies aim to prevent axonal degeneration and restore axonal transport and mitochondrial dynamics. Inhibition of SARM1, a central executor of axon degeneration, is strongly protective in CMT2A models (Osterloh et al., 2012; Gerdts et al., 2015; Sato-Yamada et al., 2022). HDAC6 inhibition restores microtubule acetylation and axonal transport in several axonal CMT models (d'Ydewalle et al., 2011). Metabolic correction in SORD-related neuropathies using aldose reductase inhibitors represents a further targeted approach (Cortese et al., 2020).

## 3. Biomarkers and outcome measures

The slow clinical progression of CMT presents a major challenge for clinical trials and underscores the need for sensitive and treatment-responsive biomarkers. Established clinical scales such as the CMT Neuropathy Score (CMTNS) and CMT Examination Score (CMTES) remain fundamental for assessing disability but often lack sensitivity over short observation periods (see also D.5.1. and D.5.2.).

Blood-based biomarkers such as neurofilament light chain reflect axonal injury and are elevated in CMT, although correlations with disease progression in humans remain limited. Schwann cell–derived proteins, including periaxin, have emerged as promising biomarkers of disease severity in demyelinating CMT. In parallel, quantitative muscle MRI has proven to be a highly sensitive tool for detecting disease progression over 12-month intervals.

## 4. Translational challenges and patient partnership

Despite substantial therapeutic progress, translation of CMT therapies remains limited by incomplete genetic diagnosis in a subset of patients, the need for early intervention prior to

irreversible axonal loss, challenges in outcome measurement, and difficulties in delivering advanced therapies to peripheral nerves. These barriers are amplified by the rarity and heterogeneity of the disease.

In this context, the active involvement of patients as partners is particularly important (see D.6.2.). Patients contribute unique insights into disease burden, symptom variability, and outcomes that are meaningful in daily life, informing trial design and endpoint selection. Their engagement facilitates recruitment, long-term follow-up, and natural history studies, which are essential for biomarker validation and therapeutic assessment. Embedding patient partnership across the research continuum ultimately strengthens the translational relevance and societal impact of CMT research.

## 5. Overview: planned and ongoing clinical trials

EU4Health Program
Milestone no. 13: List of running and planned clinical trials

**Literature**

Overview preclinical research and ongoing clinical trials
https://cmtrf.org/research/cmt-research-pipeline/

Review: Charcot-Marie-Tooth disease: a review of clinical developments and its management - What's new in 2025?
https://www.tandfonline.com/doi/epdf/10.1080/14737175.2025.2470980?needAccess=true

**List of ongoing clinical trials and literature references**

1. **Applied Therapeutics**

a. **INSPIRE Trial, NCT05397665**
Govorestat
Aldose reductase inhibitor
People with SORD deficiency (CMT-SORD)
Phase II/III
https://www.appliedtherapeutics.com/pipeline/govorestat/
Cortese et al. Genotype and phenotype spectrum of Charcot-Marie-Tooth disease due to mutations in SORD. 2025. BRAIN https://academic.oup.com/brain/advance-article/doi/10.1093/brain/awaf021/8010720

2. **UCL Queen Square centre for neuromuscular disorders**
**SENSE trial, NCT06113055**
HSN1 (Hereditary Sensory Neuropathy)
SPTLC1 or SPTLC2 mutations
L-Serine (amino acid therapy)
Phase II
https://cmtausa.org/research-projects/hereditary-sensory-neuropathy-serine-trial-sense-trial/
Garofalo et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. 2011. Journal of Clinical Investigation https://pubmed.ncbi.nlm.nih.gov/22045570/

3. **NMD Pharma®**
**SYNAPSE-CMT, NCT06482437**

NMD670
ClC-1 – chloride channel modulator
CMT1 and CMT2 patients
Phase IIa
https://www.nmdpharma.com/news/nmd-pharma-initiates-phase-2-study-of-nmd670-in-patients-with-cmt-type-1-and-2
Skjærlund Grønnebæk et al. Neuromuscular transmission deficits in patients with CMT and ClC-1 inhibition in CMT animal models. 2024. Ann Clin Transl Neurol. https://onlinelibrary.wiley.com/doi/epdf/10.1002/acn3.52252

4. **Inflectis BioScience**
   **IFB-088 (Sephin1)**
   Proteastasis modulator (inhibition dephosphorylation of eIF2α
   CMT1A, 1B, 1E
   Phase I
   https://inflectisbioscience.com/our-pipeline/
   Bai et al. Treatment with IFB-088 Improves Neuropathy in CMT1A and CMT1B Mice. 2020. Mol Neurobiol. https://link.springer.com/article/10.1007/s12035-022-02838-y

5. **Augustine Therapeutics**
   **AGT-100216**

   HDAC 6 inhibitor, peripherally selective

   CMT1 and CMT2 (broad potential)

   Phase I (healthy adults, CMT patients next)

   https://www.augustinetx.com/pipeline

   https://www.augustinetx.com/media/augustine-therapeutics-announces-first-patient-dosed-in-phase-i-clinical-trial-evaluating-lead-candidate-agt-100216-for-the-treatment-of-charcot-marie-tooth-disease

   Rossaert and Van Den Bosch, HDAC6 inhibitors: Translating genetic and molecular insights into a therapy for axonal CMT. 2020. Brain Research.

   https://www.sciencedirect.com/science/article/pii/S0006899320300482?via%3Dihub

   Benoy et al. Development of Improved HDAC6 Inhibitors as Pharmacological Therapy for Axonal Charcot–Marie–Tooth Disease. 2017. Neurotherapeutics.

   https://www.neurotherapeuticsjournal.org/article/S1878-7479(23)01476-9/fulltext

   d'Ydewalle et al. 2011 HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. 2011. Nature medicine. https://www.nature.com/articles/nm.2396

6. **CKD Pharmaceuticals (Novartis)**
   **CKD-510**
   HDAC6 inhibitor
   CMT1 and CMT2
   Phase I

7. **Actio Biosciences**
   **ABS-0871**
   TRPV4 ion channel inhibitor
   CMT2C (TRPV4 mutation)
   Phase I
   https://actiobiosciences.com/actio-biosciences-announces-first-participant-dosed-in-phase-1-clinical-trial-of-abs-0871-a-novel-trpv4-inhibitor-for-the-treatment-of-charcot-marie-tooth-disease-2c/

8. **VANDA Pharmaceuticals inc.**
   **VCA-894A**
   Antisense oligonucleotide
   CMT2S (IGHMBP2 mutation) – custom for one patient
   Phase I (first dose administered June 2025)

9. **ENCell**
   **EN001**
   allogeneic Wharton's jelly mesenchymal stem cell therapy (IV infusion)
   CMT1A
   Phase I → Ib
   https://www.encellinc.com/en/sub/rnd/pipeline.asp
   Report on its use in Duchenne Muscular Dystrophy (phase I trial): https://thejcn.com/DOIx.php?id=10.3988/jcn.2024.0299

10. **Orthogonal Neuroscience**
    ORT247
    mAb inhibitor of EphA4 receptors
    CMT1 and CMT2

11. **Helixmith**
    **Engensis (VM202), NCT05361031**
    Phase I/IIa
    CMT1A
    Plasmid DNA expressing two isoforms of hepatocyte growth factor
    https://www.helixmith.com/eng/s2/s2_1_1_5.php
    https://www.clinicaltrials.gov/study/NCT05361031?term=AREA%5BBasicSearch%5D(vm202)&rank=6

12. **Alcyone Therapeutics**
    ACTX technology
    Gene replacement - AAV9 vector carrying the IGHMBP2 gene
    Phase I/IIa
    CMT2S
    https://www.clinicaltrials.gov/study/NCT05152823

13. **Pharnext S.C.A.**
    **PREMIER - NCT04762758**
    PXT3003 - baclofen, naltrexone hydrochloride [HCl], and D-sorbitol
    CMT1A
    Phase III, trial ended
    https://clinicaltrials.gov/study/NCT04762758
    Chumakov et al. Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. 2014. Orphanet J Rare Dis. https://pmc.ncbi.nlm.nih.gov/articles/PMC4279797/

14. **Novartis (DTx Pharma)**
    **DTx-1252**
    Preclinical phase → IND planned
    siRNA targeting PMP22
    https://www.novartis.com/news/media-releases/novartis-builds-neuroscience-pipeline-and-xrna-platform-capabilities-acquisition-dtx-pharma

## Key References


Skre H. Genetic and clinical aspects of Charcot–Marie–Tooth disease. Clinical Genetics. 1974.

Pareyson D., Saveri P., Pisciotta C. New developments in Charcot–Marie–Tooth neuropathy and related diseases. Nature Reviews Neurology. 2017.

Sahenk Z., Chen L., Mendell J.R. Effects of neurotrophin-3 on nerve regeneration in inherited peripheral neuropathies. Annals of Neurology. 2008.

Gautier B., Hajjar H., Soares S., et al. AAV-mediated RNA interference targeting PMP22 reverses demyelinating neuropathy in CMT1A. Nature Medicine. 2015.

Stavrou M, Kagiava A, Choudury SG, Jennings MJ, Wallace LM, Fowler AM, et al. A translatable RNAi-driven gene therapy silences PMP22/Pmp22 genes and improves neuropathy in CMT1A mice. J Clin Invest. 2022;132(13)

Zhao H.T., Damle S., Ikeda-Lee K., et al. PMP22 antisense oligonucleotides reverse CMT1A features in rodent models. Journal of Clinical Investigation. 2018.

Boutary S., Caillaud M., El Madani M., et al. Squalenoyl siRNA PMP22 nanoparticles reverse demyelination in CMT1A models. Nature Communications. 2020.

Kagiava A., Karaiskos C., Richter J., et al. AAV-mediated Schwann cell–targeted gene therapy rescues demyelination in CMT1X. Brain. 2016.

Kagiava A, Karaiskos C, Richter J, Tryfonos C, Jennings MJ, Heslegrave AJ, et al. AAV9-mediated Schwann cell-targeted gene therapy rescues a model of demyelinating neuropathy. Gene Ther. 2021;28(10-11):659-75.

Georgiou E, Kagiava A, Sargiannidou I, Schiza N, Stavrou M, Richter J, et al. AAV9-mediated SH3TC2 gene replacement therapy targeted to Schwann cells for the treatment of CMT4C. Mol Ther. 2023;31(11):3290-307

El Mallakh R.S., Tenenbaum L., Lehtonen E., et al. AAV-mediated gene therapy for giant axonal neuropathy. Molecular Therapy. 2017.

Bharucha-Goebel DX, Todd JJ, Saade D, Norato G, Jain M, Lehky T, et al. Intrathecal Gene Therapy for Giant Axonal Neuropathy. N Engl J Med. 2024;390(12):1092-104

Winborn C.S., Travis S.M., Tóth Z., et al. FIG4 gene therapy rescues neuronal and peripheral nerve pathology in CMT4J. Journal of Clinical Investigation. 2018.

Attarian S., Vallat J.M., Magy L., et al. An exploratory randomized phase 2 study of PXT3003 in CMT1A. Lancet Neurology. 2014.

Attarian S., Young P., Meyer zu Hörste G., et al. PXT3003 efficacy and safety in CMT1A: phase III results. Orphanet Journal of Rare Diseases. 2021.

D'Antonio M., Musner N., Scapin C., et al. Resetting translational homeostasis restores myelination in CMT1B mice. Journal of Neuroscience. 2013.

Das I., Krzyzosiak A., Schneider K., et al. Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. Nature Medicine. 2015.

VerPlank J.J.S., Tyrkalska S.D., Fleming A., et al. Proteasome activation by cGMP signaling restores proteostasis in demyelinating neuropathy. Journal of Clinical Investigation. 2022.

Osterloh J.M., Yang J., Rooney T.M., et al. dSarm/SARM1 is required for activation of an injury-induced axon death pathway. Science. 2012.

Gerdts J., Summers D.W., Milbrandt J., DiAntonio A. Axon self-destruction: links among SARM1 and NAD metabolism. Science. 2015.

Sato-Yamada A., Monnier P.P., Vivien D., et al. SARM1 deletion rescues axonal degeneration in a rat model of CMT2A. Brain. 2022.

d'Ydewalle C., Krishnan J., Chiheb D.M., et al. HDAC6 inhibitors reverse axonal loss in CMT models. Nature Medicine. 2011.

Cortese A., Zhu Y., Rebelo A.P., et al. Biallelic mutations in sord are a common cause of potentially treatable genetic neuropathy Journal of Neurology, Neurosurgery and Psychiatry 93, Ausg. 6, 2022: A14-A14. DOI:10.1136/jnnp-2022-ABN.41