Second European CMT Specialists Conference

EUROPEAN CMT RESEARCH ASSOCIATION | University of Antwerp | EUROPEAN CMT FEDERATION

PUBLICATIONS/READINGS:

Recent Therapeutical Advances for CMT (Gorka Fernandez) M7 / WP 2

Readings for preparing

Plenary Session 1: Basic Sciences and the many faces of CMT

Plenary Session 3: Therapeutic approaches on CMT neuropathies

There is a range of pharmacological, gene-based, and molecular interventions, many of which are in preclinical or clinical development:

• PXT3003: This is the most advanced pharmacological candidate for CMT1A, consisting of a fixed-dose combination of baclofen, naltrexone, and sorbitol. It targets PMP22 over-expression and is in phase III clinical trials, having shown efficacy in improving clinical and electrophysiological outcomes in earlier studies.[1-4]

• Gene silencing therapies: Antisense oligonucleotides (ASOs), siRNA, shRNA, and CRISPR-Cas9 approaches are being developed to suppress PMP22 expression in CMT1A and to target other gain-of-function mutations. Notably, customized ASO therapy

has shown efficacy in CMT2E (NEFL mutations) by reducing axonal degeneration biomarkers in patient-derived models.[1][5-7]

• Gene replacement therapies: Viral vector-mediated gene replacement is under investigation for loss-of-function forms such as CMT1X (GJB1 mutations), CMT4C (SH3TC2), and CMT2A (MFN2). These approaches are progressing from rodent to larger animal models, with some nearing clinical translation.[1][6-7]

• HDAC6 inhibitors: These agents improve axonal transport and have shown benefit in preclinical models of both demyelinating and axonal CMT subtypes.[1-2][4][8]

• SARM1 inhibitors: Targeting axonal degeneration, SARM1 inhibition is a promising strategy for CMT2A and other axonal forms, currently in preclinical development.[8]

• Metabolic modulators: For SORD-related CMT, govorestat (an aldose reductase inhibitor) is in clinical trials and may become the first approved drug for this subtype.[2][9]

• Other molecular targets: These include modulation of the neuregulin pathway (myelin thickness), unfolded protein response (for misfolded myelin proteins such as MPZ in CMT1B), targeting macrophage activation, lipid metabolism, Nav1.8 sodium channels, and the P2X7 receptor in Schwann cells.[1][4][9-10]

• Peptide therapies: For CMT2A, peptides that enhance mitochondrial fusion are in preclinical testing.[8]

1. Gene Therapy and Other Novel Treatment Approaches for Charcot-Marie-Tooth Disease. Pisciotta C, Pareyson D. Neuromuscular Disorders : NMD. 2023;33(8):627-635. doi:10.1016/j.nmd.2023.07.001.
2. Charcot-Marie-Tooth Disease: A Review of Clinical Developments and Its Management - What's New in 2025?. De Grado A, Serio M, Saveri P, Pisciotta C, Pareyson D. Expert Review of Neurotherapeutics. 2025;25(4):427-442. doi:10.1080/14737175.2025.2470980.
3. The Current State of Charcot-Marie-Tooth Disease Treatment. Okamoto Y, Takashima H. Genes. 2023;14(7):1391. doi:10.3390/genes14071391.
4. Recent Advances in the Treatment of Charcot-Marie-Tooth Neuropathies. Bolino A, D'Antonio M. Journal of the Peripheral Nervous System: JPNS. 2023;28(2):134-149. doi:10.1111/jns.12539.
5. Customized Antisense Oligonucleotide-Based Therapy for Neurofilament-Associated Charcot-Marie-Tooth Disease. Medina J, Rebelo A, Danzi MC, et al. Brain : A Journal of Neurology. 2024;147(12):4227-4239. doi:10.1093/brain/awae225.
6. Gene Therapies for CMT Neuropathies: From the Bench to the Clinic. Stavrou M, Kleopa KA. Current Opinion in Neurology. 2024;37(5):445-454. doi:10.1097/WCO.0000000000001289.
7. Charcot-Marie-Tooth Neuropathies: Current Gene Therapy Advances and the Route Toward Translation. Stavrou M, Kagiava A, Sargiannidou I, Georgiou E,

Kleopa KA. Journal of the Peripheral Nervous System: JPNS. 2023;28(2):150-168. doi:10.1111/jns.12543.

8. Charcot-Marie-Tooth Disease Type 2A: An Update on Pathogenesis and Therapeutic Perspectives. Alberti C, Rizzo F, Anastasia A, et al. Neurobiology of Disease. 2024;193:106467. doi:10.1016/j.nbd.2024.106467.
9. Updated Review of Therapeutic Strategies for Charcot-Marie-Tooth Disease and Related Neuropathies. Pisciotta C, Saveri P, Pareyson D. Expert Review of Neurotherapeutics. 2021;21(6):701-713. doi:10.1080/14737175.2021.1935242.
10. Mechanisms and Treatments in Demyelinating CMT. Fridman V, Saporta MA. Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics. 2021;18(4):2236-2268. doi:10.1007/s13311-021-01145-z.
11. Current Treatment Methods for Charcot-Marie-Tooth Diseases. Dong H, Qin B, Zhang H, Lei L, Wu S. Biomolecules. 2024;14(9):1138. doi:10.3390/biom14091138.

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