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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

X-linked Charcot-Marie-Tooth disease type 1

Categories: rare developmental anomalies during embryogenesis, rare genetic diseases, rare neurological diseases +1

Gene therapies

Forecast for the first gene therapies based drug for the disease.

Disease landscape:

Orphan designations: **0**

Approved drugs: **0**

De-risked by AI:

Top 0.2%
of research

Highest probability of becoming an approved therapy from the research stage.

Disease overview

AI-generated summary. Verify critical details against original sources.

X-linked Charcot-Marie-Tooth disease type 1

Synonyms: CMT1X, CMTX1.

X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is the second most common hereditary neuropathy, caused by GJB1 gene mutations impairing connexin 32 gap junction function [1] [5] [13]. It manifests as progressive distal muscle weakness/atrophy, sensory loss, and areflexia, with males showing earlier/severe symptoms due to X-linked dominant inheritance [5] [13] [17]. Nerve conduction studies reveal intermediate slowing (25-45 m/s) with axonal degeneration [1] [9]. Central nervous system involvement (transient white matter lesions, dysarthria) occurs rarely [9] [13].

Population

- Accounts for 10-16% of CMT cases and 5.1-13.8% of genetically confirmed CMT [2] [5] [9]
- Affects 1.9-3.6 per 100,000, with complete penetrance in males and variable expressivity in female carriers [5] [13]

Current Therapeutic Strategies

- Supportive care: Orthotics, physical therapy, and neuropathic pain management (gabapentin/pregabalin) [7] [16]
- Emerging therapies: Gene replacement (AAV-mediated GJB1 delivery) and neurotrophin-3 (AAV1.tMCK.NT3) in clinical trials [14] [15]
- Experimental targets: CSF-1 receptor inhibitors and connexin 32 chaperones in preclinical studies [1] [3]

Burden of the Disease

- Progressive ambulatory decline: 34% of males require assistive devices by adulthood [13] [18]
- Chronic pain (68% patients) and fatigue directly correlate with disability severity [4] [16]
- Family planning challenges: 100% transmission risk from affected males to daughters [2] [17]
  Neurophysiological hallmark: Non-uniform conduction slowing (30-40 m/s in males) with temporal dispersion [5] [13]

Literature overview

Most influential articles for LLM-classifier prediction.

22.5% influence 6 Aug 2019

Gene replacement therapy after neuropathy onset provides therapeutic benefit in a model of CMT1X

Open article

Alexia Kagiava 50 Jan Richter 77 Christina Tryfonos Christos Karaiskos Amanda Heslegrave 290 Irene Sargiannidou 64 Alexander M. Rossor 194 Henrik Zetterberg 3775 Mary M. Reilly 814 Christina Christodoulou 131 Kleopas A. Kleopa 178

Abstract X-linked Charcot-Marie-Tooth disease (CMT1X), one of the commonest forms of inherited demyelinating neuropathy, results from GJB1 gene mutations causing loss of function of the gap junction protein connexin32 (Cx32). The aim of this study was to examine whether delayed gene replacement therapy after the onset of peripheral neuropathy can provide a therapeutic benefit in the Gjb1-null/Cx32 knockout model of CMT1X. After delivery of the LV-Mpz.GJB1 lentiviral vector by a single lumbar intrathecal injection into 6-month-old Gjb1-null mice, we confirmed expression of Cx32 in lumbar roots and sciatic nerves correctly localized at the paranodal myelin areas. Gjb1-null mice treated with LV-Mpz.GJB1 compared with LV-Mpz.Egfp (mock) vector at the age of 6 months showed improved motor performance at 8 and 10 months. Furthermore, treated mice showed increased sciatic nerve conduction velocities, improvement of myelination and reduced inflammation in lumbar roots and peripheral nerves at 10 months of age, along with enhanced quadriceps muscle innervation. Plasma neurofilament light (NEFL) levels, a clinically relevant biomarker, were also ameliorated in fully treated mice. Intrathecal gene delivery after the onset of peripheral neuropathy offers a significant therapeutic benefit in this disease model, providing a proof of principle for treating patients with CMT1X at different ages.

12.1% influence 4 Feb 2021

AAV1.NT-3 gene therapy for X-linked Charcot–Marie–Tooth neuropathy type 1

Open article

Abstract X-linked Charcot-Marie-Tooth neuropathy (CMTX) is caused by mutations in the gene encoding Gap Junction Protein Beta-1 (GJB1)/Connexin32 (Cx32) in Schwann cells. Neurotrophin-3 (NT-3) is an

important autocrine factor supporting Schwann cell survival and differentiation and stimulating axon regeneration and myelination. Improvements in these parameters have been shown previously in a CMT1 model, Trembler J mouse, with NT-3 gene transfer therapy. For this study, scAAV1.tMCK.NT-3 was delivered to the gastrocnemius muscle of 3-month-old Cx32 knockout (KO) mice. Measurable levels of NT-3 were found in the serum at 6-month post gene delivery. The outcome measures included functional, electrophysiological and histological assessments. At 9-months of age, NT-3 treated mice showed no functional decline with normalized compound muscle action potential amplitudes. Myelin thickness and nerve conduction velocity significantly improved compared with untreated cohort. A normalization toward age-matched wildtype histopathological parameters included increased number of Schmidt-Lanterman incisures, and muscle fiber diameter. Collectively, these findings suggest a translational application to CMTX1.

Burçak Özeş 21 · Morgan Myers · Kyle Moss · Jennifer L. McKinney 27 · Alicia Ridgley · Lei Chen 96 · Shasha Bai 174 · Charles K. Abrams 63 · Mona M. Freidin 34 · Jerry R. Mendell 290 · Zarife Sahenk 214

11.8% influence 13 Feb 2018

Intrathecal gene therapy in mouse models expressing CMT1X mutations

Open article

Alexia Kagiava 50 · Christos Karaiskos · Jan Richter 77 · Christina Tryfonos · George Lapathitis · Irene Sargiannidou 64 · Christina Christodoulou 131 · Kleopas A. Kleopa 178

Gap junction beta-1 (GJB1) gene mutations affecting the gap junction protein connexin32 (Cx32) cause the X-linked Charcot-Marie-Tooth disease (CMT1X), a common inherited neuropathy. Targeted expression of virally delivered Cx32 in Schwann cells following intrathecal injection of lentiviral vectors in the Cx32 knockout (KO) mouse model of the disease has led to morphological and functional improvement. To examine whether this approach could be effective in CMT1X patients expressing different Cx32 mutants, we treated transgenic Cx32 KO mice expressing the T55I, R75W or N175D CMT1X mutations. All three mutants were localized in the perinuclear compartment of myelinating Schwann cells consistent with retention in the ER (T55I) or Golgi (R75W, N175D) and loss of physiological expression in the non-compact myelin. Following intrathecal delivery of the GJB1 gene we detected the virally delivered wild-type (WT) Cx32 in non-compact myelin of T55I KO mice, but only rarely in N175D KO or R75W KO mice, suggesting dominant-negative effects of the R75W and N175D mutants but not of the T55I mutant on co-expressed WT Cx32. GJB1 treated T55I KO mice showed improved motor performance, lower ratios of abnormally myelinated fibers and reduction of inflammatory cells in spinal roots and peripheral nerves compared with mock-treated littermates. Either partial (N175D KO) or no (R75W KO) improvement was observed in the other two mutant lines. Thus, certain CMT1X mutants may interfere with gene addition therapy for CMT1X. Whereas gene addition can be used for non-interfering CMT1X mutations, further studies will be needed to develop treatments for patients harboring interfering mutations.

8.6% influence 6 Mar 2025

A dose escalation and safety study of AAVrh10-mediated Schwann cell-targeted gene therapy for CMT1X.

Open article

Melina Christou · Irene Sargiannidou 64 · Revekka Papacharalambous · Jan Richter 77 · Christina Tryfonos · Christina Christodoulou 131 · Alexia Kagiava 50 · Kleopas A. Kleopa 178

X-linked Charcot-Marie-Tooth disease (CMT1X) is an inherited demyelinating neuropathy caused by loss-of-function mutations in the GJB1 gene, encoding the gap junction protein connexin32 (Cx32). Cx32 plays a critical role in Schwann cell function and myelin formation in the peripheral nervous system. We have developed a gene replacement therapeutic approach using a humanized AAVrh10 vector construct expressing GJB1 under the control of the Schwann cell-specific human myelin protein zero (MPZ) promoter. Lumbar intrathecal injection of increasing AAVrh10-hMPZ.GJB1 doses (low: 1 × 1011 vg, standard: 2 × 1011 vg and high: 1 × 1012 vg) into Gjb1-null mice resulted in adequate, dose-dependent biodistribution of the vector in anterior lumbar roots and peripheral nerves, as well as high rates of Schwann cell-specific Cx32 expression in the standard- and high-dose groups. Both standard and high vector doses provided significant therapeutic benefit evaluated by behavioural, electrophysiological and morphological outcomes. Intrathecal delivery of AAVrh10-hMPZ.GJB1 induced the production of anti-AAVrh10 antibodies at 6 weeks post-injection. However, no histopathological or inflammatory changes were observed in neural or peripheral tissues, besides a mild increase in inflammatory cell numbers in sciatic nerves of mice treated with the high dose only. This study provides proof of concept for a clinically translatable AAVrh10-mediated gene therapy approach for CMT1X.

8.5% influence 10 Mar 2021

AAV9-mediated Schwann cell-targeted gene therapy rescues a model of demyelinating neuropathy

Open article

Mutations in the GJB1 gene, encoding the gap junction (GJ) protein connexin32 (Cx32), cause X-linked Charcot-Marie-Tooth disease (CMT1X), an inherited demyelinating neuropathy. We developed a gene therapy approach for CMT1X using an AAV9 vector to deliver the GJB1/Cx32 gene under the myelin protein zero (Mpz) promoter for targeted expression in Schwann cells. Lumbar intrathecal injection of the AAV9-Mpz.GJB1 resulted in widespread biodistribution in the peripheral nervous system including lumbar roots, sciatic and femoral nerves, as well as in Cx32 expression in the paranodal non-compact myelin areas of myelinated fibers. A pre-, as well as post-onset treatment trial in Gjb1-null mice, demonstrated

improved motor performance and sciatic nerve conduction velocities along with improved myelination and reduced inflammation in peripheral nerve tissues. Blood biomarker levels were also significantly ameliorated in treated mice. This study provides evidence that a clinically translatable AAV9-mediated gene therapy approach targeting Schwann cells could potentially treat CMT1X.

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Related companies

AI-generated summary of companies related to the forecast. Verify critical details against original sources.

Company	Lead candidate	Stage
Kylix Bio (location not publicly listed)	AAV-mediated GJB1 (Connexin-32) gene replacement for CMT1X Intrathecally delivered AAV gene-replacement program designed to restore functional GJB1 (Cx32) expression in Schwann cells to treat X-linked CMT (CMT1X). Kylix states it is advancing an AAV-mediated GJB1 program and is performing IND-enabling studies; the company works closely with the Charcot-Marie-Tooth Association to translate these programs toward the clinic.	IND-enabling / preclinical (translating into clinical-stage development per CMTA profile) 1 2 3 4

Drug discovery timeline

Orphan designations and approvals related to the disease.