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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

Pelizaeus-Merzbacher disease

Categories: rare genetic diseases, rare neurological diseases, rare ophthalmic disorders

Gene therapies

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

Disease landscape:

Orphan designations: **2**

Approved drugs: **0**

De-risked by AI:

Top 1.6%
of research

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

Disease overview

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

Pelizaeus-Merzbacher disease

Synonyms: Diffuse familial brain sclerosis, PMD, Pelizaeus-Merzbacher brain sclerosis, Sudanophilic leukodystrophy, Paelizeus-Merzbacher type.

Pelizaeus-Merzbacher disease (PMD) is an X-linked leukodystrophy caused by PLP1 gene mutations, disrupting myelin formation in the central nervous system. It primarily affects males, presenting with nystagmus, hypotonia, ataxia, and progressive spasticity. PMD manifests as **classic** (developmental delay with partial myelination) or severe **connatal** forms (neonatal onset, minimal myelination). Hypomyelination leads to motor and cognitive impairment, with lifespan ranging from childhood to adulthood depending on severity [1] [4] [16].

Population

Affects ~1/200,000–500,000 males globally, with rare symptomatic female carriers [1] [10] [16]. Over 90% of cases involve PLP1 duplications or point mutations [1] [13].

Current Therapeutic Strategies

- **Supportive care:** Physical therapy, antispasticity agents (baclofen), gastrostomy for dysphagia, and seizure management [4] [7] [9].
- **Emerging therapies:** Antisense oligonucleotides to reduce toxic PLP1 protein [3] [11], ketogenic diets to support oligodendrocyte function [4], and neural stem cell transplantation trials [5] [19].

Burden of the Disease

Progressive neurological decline often results in death by adolescence in connatal forms, while classic PMD may allow survival into mid-adulthood with severe disability [2] [9] [10]. Caregiver burden is high due to mobility loss, communication deficits, and recurrent hospitalizations [7] [16].

Literature overview

Most influential articles for LLM-classifier prediction.

19.5% influence 15 May 2019

Gene suppressing therapy for Pelizaeus-Merzbacher disease using artificial microRNA

Open article

Heng Li 582 · Hironori Okada · Sadafumi Suzuki · Kazuhisa Sakai · Hitomi Izumi · Yukiko Matsushima · Noritaka Ichinohe 154 · Yu-ichi Goto 608 · Takashi Okada 364 · Ken Inoue 335

Copy number increase or decrease of certain dosage-sensitive genes may cause genetic diseases with distinct phenotypes, conceptually termed genomic disorders. The most common cause of Pelizaeus-Merzbacher disease (PMD), an X-linked hypomyelinating leukodystrophy, is genomic duplication encompassing the entire proteolipid protein 1 (PLP1) gene. Although the exact molecular and cellular mechanisms underlying PLP1 duplication, which causes severe hypomyelination in the central nervous system, remain largely elusive, PLP1 overexpression is likely the fundamental cause of this devastating disease. Here, we investigated if adeno-associated virus-mediated (AAV-mediated) gene-specific suppression may serve as a potential cure for PMD by correcting quantitative aberrations in gene products. We developed an oligodendrocyte-specific Plp1 gene suppression therapy using artificial microRNA under the control of human CNP promoter in a self-complementary AAV (scAAV) platform. A single direct brain injection achieved widespread oligodendrocyte-specific Plp1 suppression in the white matter of WT mice. AAV treatment in Plp1-transgenic mice, a PLP1 duplication model, ameliorated cytoplasmic accumulation of Plp1, preserved mature oligodendrocytes from degradation, restored myelin structure and gene expression, and improved survival and neurological phenotypes. Together, our results provide evidence that AAV-mediated gene suppression therapy can serve as a potential cure for PMD resulting from PLP1 duplication and possibly for other genomic disorders.

14.1% influence 9 May 1995

Open article

Dominant-negative action of the jimpy mutation in mice complemented with an autosomal transgene for myelin proteolipid protein.

Andrew M. Schneider 130 · Ian R. Griffiths 208 · Carol Readhead · Klaus-Armin Nave 538

Mutations in genes encoding membrane proteins have been associated with cell death of unknown cause from invertebrate development to human degenerative diseases. A point mutation in the gene for myelin proteolipid protein (PLP) underlies oligodendrocyte death and dysmyelination in jimpy mice, an accurate model for Pelizaeus-Merzbacher disease. To distinguish the loss of PLP function from other effects of the misfolded protein, we took advantage of the X chromosomal linkage of the gene and have complemented jimpy with a wild-type PLP transgene. In this artificial heterozygous situation, the jimpy mutation emerged as genetically dominant. At the cellular level oligodendrocytes showed little increase in survival although endogenous PLP gene and autosomal transgene were truly coexpressed. In surviving oligodendrocytes, wild-type PLP was functional and immunodetectable in myelin. Moreover, compacted myelin sheaths regained their normal periodicity. This strongly suggests that, despite the presence of functional wild-type PLP, misfolded jimpy PLP is by itself the primary cause of abnormal oligodendrocyte death.

12.8% influence · 1 Jan 2024

Open article

Inherited white matter disorders: Hypomyelination (myelin disorders).

Stefanie Perrier 21 · Laurence Gauquelin 22 · Geneviève Bernard 262

Hypomyelinating leukodystrophies are a subset of genetic white matter diseases characterized by insufficient myelin deposition during development. MRI patterns are used to identify hypomyelinating disorders, and genetic testing is used to determine the causal genes implicated in individual disease forms. Clinical course can range from severe, with patients manifesting neurologic symptoms in infancy or early childhood, to mild, with onset in adolescence or adulthood. This chapter discusses the most common hypomyelinating leukodystrophies, including X-linked Pelizaeus-Merzbacher disease and other PLP1-related disorders, autosomal recessive Pelizaeus-Merzbacher-like disease, and POLR3-related leukodystrophy. PLP1-related disorders are caused by hemizygous pathogenic variants in the proteolipid protein 1 (PLP1) gene, and encompass classic Pelizaeus-Merzbacher disease, the severe connatal form, PLP1-null syndrome, spastic paraplegia type 2, and hypomyelination of early myelinating structures. Pelizaeus-Merzbacher-like disease presents a similar clinical picture to Pelizaeus-Merzbacher disease, however, it is caused by biallelic pathogenic variants in the GJC2 gene, which encodes for the gap junction protein Connexin-47. POLR3-related leukodystrophy, or 4H leukodystrophy (hypomyelination, hypodontia, and hypogonadotropic hypogonadism), is caused by biallelic pathogenic variants in genes

encoding specific subunits of the transcription enzyme RNA polymerase III. In this chapter, the clinical features, disease pathophysiology and genetics, imaging patterns, as well as supportive and future therapies are discussed for each disorder.

11.6% influence 1 Jul 2024

Gene therapy for the leukodystrophies: From preclinical animal studies to clinical trials.

Open article

Jasna Metović 72 Yedda Li 21 Yi Gong 76
Florian Eichler 259

Leukodystrophies are progressive single gene disorders affecting the white matter of the brain. Several gene therapy trials are in progress to address the urgent unmet need for this patient population. We performed a comprehensive literature review of all gene therapy clinical trials listed in www.clinicaltrials.gov through August 2024, and the relevant preclinical studies that enabled clinical translation. Of the approximately 50 leukodystrophies described to date, only eight have existing gene therapy clinical trials: metachromatic leukodystrophy, X-linked adrenoleukodystrophy, globoid cell leukodystrophy, Canavan disease, giant axonal neuropathy, GM2 gangliosidoses, Alexander disease and Pelizaeus-Merzbacher disease. What led to the emergence of gene therapy trials for these specific disorders? What preclinical data or disease context was enabling? For each of these eight disorders, we first describe its pathophysiology and clinical presentation. We discuss the impact of gene therapy delivery route, targeted cell type, delivery modality, dosage, and timing on therapeutic efficacy. We note that use of allogeneic hematopoietic stem cell transplantation in some leukodystrophies allowed for an accelerated path to clinic even in the absence of available animal models. In other leukodystrophies, small and large animal model studies enabled clinical translation of experimental gene therapies. Human clinical trials for the leukodystrophies include ex vivo lentiviral gene delivery, in vivo AAV-mediated gene delivery, and intrathecal antisense oligonucleotide approaches. We outline adverse events associated with each modality focusing specifically on genotoxicity and immunotoxicity. We review monitoring and management of events related to insertional mutagenesis and immune responses. The data presented in this review show that gene therapy, while promising, requires systematic monitoring to account for the precarious diseas ...

10.7% influence 18 Dec 2014

Transgenic replacement of Cx32 in gap junction-deficient oligodendrocytes rescues the phenotype of a hypomyelinating leukodystrophy model.

Oligodendrocytes are coupled by gap junctions (GJs) formed mainly by connexin47 (Cx47) and Cx32. Recessive GJC2/Cx47 mutations cause Pelizaeus-Merzbacher-like disease, a hypomyelinating leukodystrophy, while GJB1/Cx32 mutations cause neuropathy and chronic or acute-transient encephalopathy syndromes. Cx32/Cx47 double knockout (Cx32/Cx47dKO) mice develop severe CNS demyelination beginning at 1 month of age leading to death within weeks, offering a relevant model to study disease mechanisms. In order to clarify whether the loss of oligodendrocyte connexins has cell autonomous effects, we generated transgenic mice expressing the wild-type human Cx32 under the control of the mouse proteolipid protein promoter, obtaining exogenous hCx32 expression in oligodendrocytes. By crossing these mice with Cx32KO mice, we obtained expression of hCx32 on Cx32KO background. Immunohistochemical and immunoblot analysis confirmed strong CNS expression of hCx32 specifically in oligodendrocytes and correct localization forming GJs at cell bodies and along the myelin sheath. TG(+)Cx32/Cx47dKO mice generated by further crossing with Cx47KO mice showed that transgenic expression of hCx32 rescued the severe early phenotype of CNS demyelination in Cx32/Cx47dKO mice, resulting in marked improvement of behavioral abnormalities at 1 month of age, and preventing the early mortality. Furthermore, TG(+)Cx32/Cx47dKO mice showed significant improvement of myelination compared with Cx32/Cx47dKO CNS at 1 month of age, while the inflammatory and astrogliotic changes were fully reversed. Our study confirms that loss of oligodendrocyte GJs has cell autonomous effects and that re-establishment of GJ connectivity by replacement of least one GJ protein provides correction of the leukodystrophy phenotype.

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Christos Karaiskos
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Kleopas A. Kleopa 178

Related companies

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

Company	Lead candidate	Stage
Myrtelle, Inc. (New York, NY, USA)	rAAV-mediated microRNA (unnamed research candidate) Recombinant AAV vector engineered to deliver a gene-silencing microRNA to oligodendrocytes to reduce toxic PLP1/Plp1 overexpression (strategy intended to treat PMD caused by PLP1 duplication).	Research / preclinical (company describes the program as an investigational/research program; no public clinical trial identified). [1] [2] [3] [4]

Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting PLP1 pre-mRNA	oligonucleotides	FDA	2023-09-15	nan	Ionis Pharmaceuticals, Inc.
2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting PLP1 pre-mRNA	oligonucleotides	EMA	2023-08-16	nan	Ionis Development (Ireland) Limited