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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

CDKL5-deficiency disorder

Categories: rare genetic diseases, rare neurological diseases

Gene therapies

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

Disease landscape:

Orphan designations: **6**

Approved drugs: **2**

De-risked by AI:

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

Top 0.2%
of research

Disease overview

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

CDKL5-deficiency disorder

Synonyms: CDD.

CDKL5 deficiency disorder (CDD) is a rare X-linked neurodevelopmental condition caused by pathogenic variants in the CDKL5 gene, characterized by early-onset drug-resistant epilepsy (beginning within weeks of birth) and severe global developmental delays. Key features include hypotonia, cortical visual impairment, motor disabilities, and stereotypic hand movements. Over 90% of patients experience daily seizures refractory to multiple antiseizure medications, with comorbidities including gastrointestinal dysfunction, sleep disturbances, and respiratory issues [1] [2] [6] [7] [12].

Population

Prevalence ~1:40,000—60,000 live births, predominantly female (4:1 ratio). Males exhibit more severe phenotypes, often with early mortality [2] [7] [12]. Most cases result from de novo mutations [6] [12].

Current Therapeutic Strategies

First-line management combines antiseizure medications (e.g., ganaxolone, FDA-approved in 2022) with ketogenic diets and neuromodulation (vagus nerve stimulation). Multidisciplinary care addresses motor, gastrointestinal, and respiratory complications [8] [11] [15] [17].

Burden of the Disease

Median 5-30 seizures/week, requiring lifelong caregiver support. >75% require enteral feeding due to dysphagia, 40% have suboptimal growth. Hospitalization rates exceed general epilepsy populations, with 22-26% experiencing aspiration pneumonia [4] [5] [7] [9] [17]. Caregivers report significant impacts on mental health and employment [5] [7].

Literature overview

Most influential articles for LLM-classifier prediction.

13.0% influence 15 Sep 2022

Expression of a Secretable, Cell-Penetrating CDKL5 Protein Enhances the Efficacy of Gene Therapy for CDKL5 Deficiency Disorder

Although delivery of a wild-type copy of the mutated gene to cells represents the most effective approach for a monogenic disease, proof-of-concept studies highlight significant efficacy caveats for treatment of brain disorders. Herein, we develop a cross-correction-based strategy to enhance the efficiency of a gene therapy for CDKL5 deficiency disorder, a severe neurodevelopmental disorder caused by CDKL5 gene mutations. We created a gene therapy vector that produces an Igk-TATk-CDKL5 fusion protein that can be secreted via constitutive secretory pathways and, due to the cell-penetration property of the TATk peptide, internalized by cells. We found that, although AAVPHP.B_Igk-TATk-CDKL5 and AAVPHP.B_CDKL5 vectors had similar brain infection efficiency, the AAVPHP.B_Igk-TATk-CDKL5 vector led to higher CDKL5 protein replacement due to secretion and penetration of the TATk-CDKL5 protein into the neighboring cells. Importantly, Cdkl5 KO mice treated with the AAVPHP.B_Igk-TATk-CDKL5 vector showed a behavioral and neuroanatomical improvement in comparison with vehicle or AAVPHP.B_CDKL5 vector-treated Cdkl5 KO mice. In conclusion, we provide the first evidence that a gene therapy based on a cross-correction approach is more effective at compensating Cdkl5-null brain defects than gene therapy based on the expression of the native CDKL5, opening avenues for the development of this innovative approach for other monogenic diseases.

Open article

Giorgio Medici 41 · Marianna Tassinari 22 · Giuseppe Galvani 41 · Stefano Bastianini 96 · Laura Gennaccaro 29 · Manuela Loi 46 · Nicola Mottolese 29 · Sara Alvente 25 · Chiara Berteotti 110 · Giulia Sagona 32 · Leonardo Lupori 44 · Giulia Candini · Helen Rappe Baggett · +5 · Elisabetta Ciani 156

12.0% influence 19 Jul 2024

Preclinical studies of gene replacement therapy for CDKL5 deficiency disorder.

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare neurodevelopmental disorder

Open article

caused by a mutation in the X-linked CDKL5 gene. CDKL5 is a serine/threonine kinase that is critical for axon outgrowth and dendritic morphogenesis as well as synapse formation, maturation, and maintenance. This disorder is characterized by early-onset epilepsy, hypotonia, and failure to reach cognitive and motor developmental milestones. Because the disease is monogenic, delivery of the CDKL5 gene to the brain of patients should provide clinical benefit. To this end, we designed a gene therapy vector, adeno-associated virus (AAV)9.Syn.hCDKL5, in which human CDKL5 gene expression is driven by the synapsin promoter. In biodistribution studies conducted in mice, intracerebroventricular (i.c.v.) injection resulted in broader, more optimal biodistribution than did intra-cisterna magna (i.c.m.) delivery. AAV9.Syn.hCDKL5 treatment increased phosphorylation of EB2, a bona fide CDKL5 substrate, demonstrating biological activity in vivo. Our data provide proof of concept that i.c.v. delivery of AAV9.Syn.hCDKL5 to neonatal male Cdkl5 knockout mice reduces pathology and reduces aberrant behavior. Functional improvements were seen at doses of 3e11 to 5e11 vector genomes/g brain, which resulted in transfection of ≥50% of the neurons. Functional improvements were not seen at lower doses, suggesting a requirement for broad distribution for efficacy.

Gregory Voronin · Jana Narasimhan 51 · Jamila Gittens · Josephine Sheedy 54 · Philip Lipari · Melinda Peters · Steven J. DeMarco 26 · Liangxian Cao 59 · Yakov Varganov · Min Jung Kim 203 · Lisset Pear · Eman Fotouh · Supriya Sinha 3 · +10 · Marla Weetall 210

11.6% influence 2 Sep 2025

Safety and efficacy of Igk-TATk-CDKL5 gene therapy in mosaic CDKL5 deficiency.

Open article

Giorgio Medici 41 · Marianna Tassinari 22 · Manuela Loi 46 · Angelica Marina Bove · Beatrice Casadei Garofani · Greta Volpedo 61 · Nicola Mottolese 29 · Gabriele Matteoli 15 · Viviana Lo Martire 69 · Chiara Berteotti 110 · Giulia Candini · Federica Trebbi · Antonella Riva 124 · +3 · Elisabetta Ciani 156

CDKL5 Deficiency Disorder (CDD) is a severe neurodevelopmental disorder caused by mutations in the X-linked CDKL5 gene, resulting in early-onset seizures, developmental delays, and cognitive and sensorimotor impairments. While emerging therapies show promise, substantial challenges remain in developing a cure for CDD. In our prior work, we developed an innovative gene therapy strategy based on an Igk-TATk-CDKL5 fusion protein, which enhances brain distribution of the therapeutic protein, significantly improving treatment efficacy in a Cdkl5 knockout male mouse model. However, CDKL5 dosage sensitivity may pose challenges in patients with mosaic loss of CDKL5 function, potentially limiting the treatment's effectiveness or even exacerbating clinical symptoms. In this study, we aimed to address this gap by evaluating the safety and efficacy of Igk-TATk-CDKL5 therapy in a heterozygous female mouse model (Cdkl5 +/-), which better represents the majority of human CDD patients. We found that introducing Igk-TATk-CDKL5 significantly improved behavioral phenotypes and corrected brain structural defects, such as dendritic morphology and connectivity. Importantly, no adverse effects were observed in the brain or peripheral organs (e.g., the heart), indicating that CDKL5 overexpression in the heterozygous condition was well tolerated. These findings support the therapeutic potential of Igk-TATk-CDKL5 and suggest that a possible cross-correction mechanism may contribute to its efficacy, even in the

context of mosaic CDKL5 deficiency. This approach may therefore offer promising therapeutic outcomes for patients with CDD.

9.9% influence 9 Feb 2023

Epilepsy-Related CDKL5 Deficiency Slows Synaptic Vesicle Endocytosis in Central Nerve Terminals

Open article

Christiana Kontaxi 11 · Daniela Ivanova 21 · Elizabeth C. Davenport 23 · Peter C. Kind 238 · Michael A. Cousin 204

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a severe early-onset epileptic encephalopathy resulting mainly from de novo mutations in the X-linked CDKL5 gene. To determine whether loss of presynaptic CDKL5 function contributes to CDD, we examined synaptic vesicle (SV) recycling in primary hippocampal neurons generated from Cdkl5 knockout rat males. Using a genetically encoded reporter, we revealed that CDKL5 is selectively required for efficient SV endocytosis. We showed that CDKL5 kinase activity is both necessary and sufficient for optimal SV endocytosis, since kinase-inactive mutations failed to correct endocytosis in Cdkl5 knockout neurons, whereas the isolated CDKL5 kinase domain fully restored SV endocytosis kinetics. Finally, we demonstrated that CDKL5-mediated phosphorylation of amphiphysin 1, a putative presynaptic target, is not required for CDKL5-dependent control of SV endocytosis. Overall, our findings reveal a key presynaptic role for CDKL5 kinase activity and enhance our insight into how its dysfunction may culminate in CDD. SIGNIFICANCE STATEMENT Loss of cyclin-dependent kinase like 5 (CDKL5) function is a leading cause of monogenic childhood epileptic encephalopathy. However, information regarding its biological role is scarce. In this study, we reveal a selective presynaptic role for CDKL5 in synaptic vesicle endocytosis and that its protein kinase activity is both necessary and sufficient for this role. The isolated protein kinase domain is sufficient to correct this loss of function, which may facilitate future gene therapy strategies if presynaptic dysfunction is proven to be central to the disorder. It also reveals that a CDKL5-specific substrate is located at the presynapse, the phosphorylation of which is required for optimal SV endocytosis.

8.0% influence 13 Aug 2025

Epigenetic Reactivation of CDKL5 Rescues CDKL5 Deficiency Disorder

Open article

CDKL5 deficiency disorder (CDD) is a severe X-linked neurodevelopmental condition characterized by

early-onset epilepsy, intellectual disability, and motor dysfunction. Here, we present a dual-effector CRISPR-based epigenome editing platform that enables targeted reactivation of the silenced CDKL5 allele. Using a split dCas9 system compatible with AAV9 delivery, we achieved simultaneous transcriptional activation and DNA demethylation of the CDKL5 promoter in both murine and human models of disease. In heterozygous Cdkl5 E6del mice, intracerebroventricular delivery of the editor restored Cdkl5 protein expression, re-engaged downstream signaling, and rescued motor and cognitive deficits. In patient-derived neural stem cells and cortical organoids, CDKL5 reactivation normalized gene expression and restored neuronal network activity. These findings establish a scalable, mutation-independent strategy for treating CDD and highlight the therapeutic potential of epigenetic reprogramming for X-linked disorders.

Kyle D. Fink 72 · Julian Halmai 28 · David Cameron · Casiana E Gonzalez · Mandeep S. Singh 160 · A A Ansari · Viktoria Haghani 19 · Emma Monsen · Alyssa Paynton-Cheney · Jennifer J Waldo 8 · Tim R. Fenton 149 · Roy Ben-Shalom 42 · Jill L. Silverman 138

Related companies

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

Company	Lead candidate	Stage
Ultragenyx Pharmaceutical Inc. (Novato, CA, USA)	UX055 (AAV9/hCDKL5) AAV9-based gene-replacement therapy designed to deliver a functional human CDKL5 gene to neurons (neuron-specific promoter), administered into the CSF. Early preclinical studies reported motor and cognitive improvements in CDKL5 knockout mice and correction of neuronal hyperexcitability in human brain organoid models.	Pre-clinical [1] [2]
Elaaj Bio (wholly owned subsidiary of the Loulou Foundation; UK)	ELJ-101 ELJ-101 is an AAV-based CDKL5 gene therapy (hu68 capsid) administered directly to the CNS (intra-cisterna magna) to restore CDKL5 expression in the brain. Developed from the James M. Wilson lab; Elaaj reports completing nonclinical work and is advancing IND-enabling activities with a planned first-in-human trial projected for early 2027.	Pre-clinical / IND-enabling (first-in-human expected early 2027 per sponsor) [1] [2] [3]
Amicus Therapeutics (Cranbury, NJ, USA)	AAV-based CDKL5 gene therapy (preclinical program developed in collaboration with the University of Pennsylvania) Amicus has collaborated with the University of Pennsylvania (Wilson Lab) on AAV gene therapy research for CDKL5 (and has also explored CDKL5 protein-replacement approaches). The program has been described in company press releases and investor filings as a preclinical research program.	Pre-clinical (research/collaboration) [1] [2]

GEMMABio (Greater Philadelphia region, USA)	No separate public clinical candidate for CDKL5; collaborating to support ELJ-101 (Elaaj Bio) GEMMABio is a genetic medicines company (founded by James M. Wilson) that has entered a collaboration with Elaaj Bio to provide advice, datasets, and support for IND submission and clinical protocol/operations to advance ELJ-101 toward the clinic.	Collaborator / advisory to ELJ-101 (supporting IND-enabling and clinical planning) [1] [2]

Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
allopurinol	small molecules	FDA	2024-11-12	nan	Jainu Jogani
Fenfluramine hydrochloride	small molecules	EMA	2023-03-20	nan	UCB Pharma
fenfluramine hydrochloride	small molecules	FDA	2022-06-07	nan	UCB, Inc.
Ganaxolone [ZTALMY]	small molecules	EMA	2019-11-13	2023-07-28	Immedica Pharma AB
Balipodect	small molecules	FDA	2019-06-19	nan	Takeda Development Center Americas, Inc.
ganaxolone [Ztalmy]	small molecules	FDA	2017-06-28	2022-06-01	Marinus Pharmaceuticals