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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

Pyruvate dehydrogenase deficiency

Categories: rare genetic diseases, rare inborn errors of metabolism, rare neurological diseases

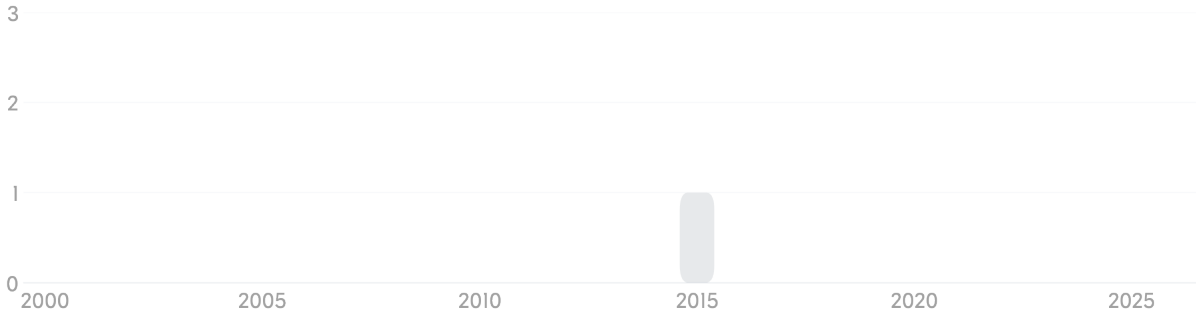
Gene therapies

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

Disease landscape:

Orphan designations: **1**

Approved drugs: **0**



De-risked by AI:

Top 1.9%
of research

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

Disease overview

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

Pyruvate dehydrogenase deficiency

Synonyms: PDH, PDHC, Pyruvate dehydrogenase complex deficiency.

Pyruvate dehydrogenase deficiency (PDHD) is a rare X-linked or autosomal recessive mitochondrial disorder caused by mutations in genes encoding components of the pyruvate dehydrogenase complex (PDC), most commonly PDHA1 (75-80% of cases) [1] [6] [15]. It disrupts carbohydrate metabolism, leading to lactic acidosis and progressive neurological impairments such as developmental delay, hypotonia, seizures, and structural brain anomalies (e.g., corpus callosum hypoplasia, Leigh syndrome) [1] [2] [6]. Onset ranges from severe neonatal forms with high mortality to later-onset cases with episodic symptoms. Diagnosis involves elevated blood/CSF lactate, genetic testing, and neuroimaging [6] [9] [15].

Population

- Estimated 1-9/100,000 births; 80-90% linked to PDHA1 (X-linked dominant), others (e.g., PDHB, DLAT) follow autosomal recessive inheritance [1] [6] [15].
- Males exhibit higher severity; ~40% mortality by age 4, with survivors often facing profound intellectual disability [4] [5] [15].

Current Therapeutic Strategies

- **Ketogenic diet**: First-line therapy to bypass impaired glycolysis, though limited impact on neurological damage [3] [6] [15].
- **Dichloroacetate**: Reduces lactic acidosis; phase 3 trials for FDA-approved formulation (SL1009) ongoing [3] [8] [15].
- **Adjunctive therapies**: Thiamine (responsive in specific mutations), phenylbutyrate (for select PDHA1 variants), and supportive care (seizure/acidosis management) [3] [6] [12] [16].

Burden of the Disease

- High mortality (43% die before age 3 months; 91% by age 4) [4] [5], with survivors requiring lifelong multidisciplinary care.
- Neurological morbidity (e.g., severe intellectual disability, cortical blindness) and recurrent hospitalizations contribute to significant financial/emotional strain [1] [15] [19].
- Structural brain anomalies (e.g., ventriculomegaly) in >85% of patients necessitate early neurodevelopmental interventions [2] [6] [15].

Literature overview

Most influential articles for LLM-classifier prediction.

26.2% influence 15 Mar 2008

A combined therapeutic approach for pyruvate dehydrogenase deficiency using self-complementary adeno-associated virus serotype-specific vectors and dichloroacetate

Open article

Zongchao Han 75 · Kristen M. Berendzen 21 · Zhong Li 192 · Ira Surolia · Nitin Chouthai 34 · Weihong Zhao 101 · Njeri Maina · Arun Srivastava 312 · Peter W. Stacpoole 309

We determined the ability of self-complementary adeno-associated virus (scAAV) vectors to deliver and express the pyruvate dehydrogenase E1α subunit gene (PDHA1) in primary cultures of skin fibroblasts from 3 patients with defined mutations in PHDA1 and 3 healthy subjects. Cells were transduced with scAAV vectors containing the cytomegalovirus promoter-driven enhanced green fluorescent protein (EGFP) reporter gene at a vector:cell ratio of 200. Transgene expression was measured 72 h later. The transduction efficiency of scAAV2 and scAAV6 vectors was 3- to 5-fold higher than that of the other serotypes, which were subsequently used to transduce fibroblasts with wild-type PDHA1 cDNA under the control of the chicken beta-action (CBA) promoter at a vector:cell ratio of 1000. Total PDH-specific activity and E1α protein expression were determined 10 days post-transduction. Both vectors increased E1α expression 40—60% in both control and patient cells, and increased PDH activity in two patient cell lines. We also used dichloroacetate (DCA) to maximally activate PDH through dephosphorylation of E1α. Exposure for 24 h to 5 mM DCA increased PDH activity in non-transduced control (mean 37% increase) and PDH deficient (mean 44% increase) cells. Exposure of transduced patient fibroblasts to DCA increased PDH activity up to 90% of the activity measured in untreated control cells. DCA also increased expression of E1α protein and, to variable extents, that of other components of the PDH complex in both non-transduced and transduced cells. These data suggest that a combined gene delivery and pharmacological approach may hold promise for the treatment of PDH deficiency.

12.2% influence 1 Oct 2000

Recombinant adeno-associated virus vector-based gene transfer for defects in oxidative metabolism.

Defects in oxidative metabolism may be caused by mutations either in nuclear genes or in mitochondrial DNA (mtDNA). We tested the hypothesis that recombinant adeno-associated virus (rAAV) could be used to complement mtDNA mutations. AAV vector constructs were designed to express the reporter gene encoding green fluorescent protein (GFP), fused to a targeting presequence that directed GFP to be translocated into mitochondria. These vectors mediated expression of mitochondrial-localized GFP, as indicated by fluorescence microscopy and electron microscopy, in respiring human embryonic kidney 293 cells and nonrespiring mtDNA-deficient (rho 0) cells. However, when sequences encoding hydrophobic segments of proteins normally encoded by mtDNA were inserted between the presequence and GFP, mitochondrial import failed to occur. In similar experiments, a fusion was created between pyruvate dehydrogenase (PDH) E1 alpha subunit, a nuclear-encoded mitochondrial gene with its own targeting presequence, and GFP. With this construct, expression of GFP was observed in mitochondria in vitro and in vivo. We conclude that the hydrophobicity of mtDNA-encoded proteins limits their ability to be transported from the cytoplasm. However, rAAV-based gene therapy may hold promise for gene therapy of PDH deficiency, the most common biochemically proven cause of congenital lactic acidosis.

Open article

Renius Owen 50 · Alfred P. Lewin · Alyson Peel · Jianming Wang 544 · John Guy · William W. Hauswirth 664 · Peter W. Stacpoole 309 · Terence R. Flotte 420

8.4% influence

21 Feb 2007

Open article

Down-regulation of expression of rat pyruvate dehydrogenase E1alpha gene by self-complementary adeno-associated virus-mediated small interfering RNA delivery.

Zongchao Han 75 · Marina S. Gorbatyuk 116 · James W. Thomas 513 · Alfred S. Lewin 371 · Arun Srivastava 312 · Peter W. Stacpoole 309

Mutations in the E1alpha subunit gene (PDHA1) of the pyruvate dehydrogenase complex (PDC) are common causes of congenital lactic acidosis. An animal model of E1alpha deficiency could provide insight into the pathological consequences of mutations and serve to test potential therapies. Small interfering RNAs (siRNAs) were designed to cleave the messenger RNA (mRNA) of the E1alpha subunit and were tested in vitro to assess the feasibility of producing a gene knockdown in rats. HEK 293 cells were co-transfected with a rat PDHA1 expression vector and eight naked siRNAs that specifically targeted rat E1alpha mRNA. Quantitative PCR (qPCR) analyses showed that four siRNAs reduced rat PDHA1 RNA levels up to 85% by 24h and up to 65% by 56h, compared to negative and positive controls. Since oligonucleotide-mediated siRNA delivery provided only transient suppression, we next selected two siRNA candidates and generated self-complementary, double-stranded adeno-associated virus (scAAV) vectors (serotypes 2 and 5) expressing a rat short hairpin siRNA expression cassette (scAAVsi-PDHA1). Rat lung fibroblast (RLF) cultures were infected with scAAVsi-PDHA1 vectors. The RLF PDHA1 mRNA level was reduced 53-80% 72h after infection and 54-70% 10 days after infection in RLF cultures. The expression of E1alpha and the specific activity of pyruvate dehydrogenase were also decreased at 10 days after infection in RLF cultures. Thus, scAAV siRNA-mediated knockdown of PDHA1 gene expression provides a strategy that may be applied to create a useful animal model of PDC deficiency.

8.1% influence · 1 Aug 2025

Open article

Next Generation AAV-F Capsid gene therapy rescues disease pathology in a model of Pyruvate Dehydrogenase Complex Deficiency

Anna Keegan 11 · Özge Çetin 7 · Ellie Chilcott 12 · Juan Antinao Díaz 22 · Simon Eaton 623 · Simon N. Waddington 394 · John R. Counsell 61 · Shamima Rahman 348 · Rajvinder Karda 57

Abstract Pyruvate dehydrogenase complex deficiency (PDHD) is a severe mitochondrial disorder most frequently caused by pathogenic variants in PDHA1, leading to neurodevelopmental delay and early mortality, necessitating brain-targeted interventions. Using a brain-specific Pdha1 knockout mouse model, we compared intracerebroventricular delivery of AAV9 capsid and a recently described synthetic neurotropic AAV-F capsid, both expressing human PDHA1 coding sequence driven by a constitutive CAG promoter. Newborn mice received, titre matched AAV9 or AAV-F or AAV9 at ten-fold higher dose. Low-dose AAV-F and high-dose AAV9 significantly improved survival, and restored PDH enzyme activity,

metabolite profiles, and brain histopathology to near wild-type levels. However, treated mice showed reduced locomotion by P100 and impaired motor function. Importantly, AAV-F achieved broad CNS transduction with minimal liver expression, outperforming AAV9 at lower dose. There results support the therapeutic potential of AAV-based gene therapy for PDHD and highlighting AAV-F as a promising capsid for efficient, CNS specific delivery.

7.8% influence 1 Sep 2002

Gene therapy for pyruvate dehydrogenase E1alpha deficiency using recombinant adeno-associated virus 2 (rAAV2) vectors.

Open article

Renius Owen 50 Ronald J. Mandel 111 Chandramohan V. Ammini Thomas J. Conlon 127 Douglas S. Kerr 129 Peter W. Stacpoole 309 Terence R. Flotte 420

To determine the feasibility of gene transfer to correct defects in the E1alpha subunit of the pyruvate dehydrogenase (PDH) complex (PDC), we constructed rAAV vectors that expressed PDH E1alpha, either alone or with a green fluorescent protein tag, from a hybrid cytomegalovirus (CMV) enhancer/chicken beta-actin (CB) promoter. These vectors were functional in vitro, as judged by increased expression of mRNA in vector-transduced deficient cell lines and correction of the biochemical defect in PDH activity in these cells. Approximately 30% of wild-type levels of PDH activity were restored under conditions with which only about 15% of cells were transduced. These same vectors were then used in vivo to transduce neurons within the rat striatum. Gene transfer, expression, and translocation into mitochondria were observed, without any obvious untoward effects. In vivo vector-mediated PDH expression persisted for at least 1 year after injection, indicating the stability of gene transfer. These studies provide the basis for future efforts to develop a recombinant AAV (rAAV)-based gene therapy approach for the correction of PDC deficiency.

Related companies

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

Company	Lead candidate	Stage
—	—	—

Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
Sodium phenylbutyrate	small molecules	EMA	2015-11-11	nan	Fondazione Telethon Ets