Background picture

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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

Alexander disease

Categories: rare genetic diseases, rare neurological diseases

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 2.2%
of research

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

Disease overview

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

Alexander disease

Synonyms: AxD.

Alexander disease is a rare, progressive leukodystrophy caused by dominant GFAP gene mutations, leading to astrocytic Rosenthal fibers and white matter degeneration. It manifests as infantile (most common), juvenile, or adult-onset forms, with symptoms including seizures, developmental regression, megalencephaly, swallowing difficulties, and spasticity. Diagnosis relies on MRI findings and genetic testing [1] [5] [6].

Population

- Affects ~1/2.7 million in Japan; ~500 cases reported globally [1] [6] [18]
- 80% present before age 2 (infantile), 14% juvenile (4-15 years), and 6% adult-onset [5] [13] [17]
- 95% cases arise from de novo GFAP mutations; rare familial autosomal dominant inheritance [5] [19]

Current Therapeutic Strategies

- **Symptomatic management:** Antiseizure drugs (e.g., valproic acid, 95% effective for vomiting [3]), reflux medications, nutritional support [5] [7] [9]
- **Emerging therapies:** Antisense oligonucleotides (ION373) reduce GFAP expression in trials, showing symptom reversal in preclinical models [11] [14] [19]
- **Supportive care:** Multidisciplinary PT/OT/speech therapy, feeding tubes, and scoliosis/respiratory interventions [5] [7] [9]

Burden of the Disease

- Infantile form: Median survival 14 years; adult-onset often progresses >25 years [7] [9]
- High care needs: 63% require feeding tubes; 47% develop scoliosis; 34% need respiratory support [7] [9] [13]
- Economic impact: Chronic hospitalization, specialized equipment, and lost caregiver productivity [5] [7] [13]

Literature overview

Most influential articles for LLM-classifier prediction.

56.6% 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 ...

23.4% influence 1 May 1999

Formation of GFAP Cytoplasmic Inclusions in Astrocytes and Their Disaggregation by αB-Crystallin

Open article

Yutaka Kōyama 176 James E. Goldman 352

In several neuropathological conditions, alphaB-crystallin and glial fibrillary acidic protein (GFAP) accumulate and form cytoplasmic inclusions in astrocytes. To explore the pathogenesis of the inclusions and the possible functions of the accumulated alphaB-crystallin, GFAP and alphaB-crystallin were overexpressed in cultured astrocytes by transient transfection. Human GFAP formed filamentous, cytoplasmic inclusions in mouse astrocytes, NIH3T3 cells, rat C6 glioma cells, and human U251 glioma cells. These human GFAP inclusions did not contain the endogenous vimentin or beta-tubulin, and the intermediate filament and microtubular networks of the transfected cells appeared normal. alphaB-crystallin and hsp25 were associated with the GFAP inclusions. Increasing intracellular alphaB-crystallin levels using recombinant adenoviruses, either before or after GFAP inclusions were formed, decreased the number of inclusion-bearing astrocytes and converted the human GFAP from an inclusion to a spread, filamentous form. These results suggest that alphaB-crystallin reorganizes abnormal intermediate filament aggregates into the normal filamentous network.

20.0% influence 1 Mar 2006

Plectin regulates the organization of glial fibrillary acidic protein in Alexander disease.

Open article

Rujin Tian 12 Martin Gregor 65 Gerhard Wiche 250 James E. Goldman 352

Alexander disease (AxD) is a rare but fatal neurological disorder caused by mutations in the astrocyte-specific intermediate filament protein glial fibrillary acidic protein (GFAP). Histologically, AxD is characterized by cytoplasmic inclusion bodies called Rosenthal fibers (RFs), which contain GFAP, small heat shock proteins, and other undefined components. Here, we describe the expression of the cytoskeletal linker protein plectin in the AxD brain. RFs displayed positive immunostaining for plectin and GFAP, both of which were increased in the AxD brain. Co-localization, co-immunoprecipitation, and in vitro overlay analyses demonstrated direct interaction of plectin and GFAP. GFAP with the most common AxD mutation, R239C (RC GFAP), mainly formed abnormal aggregates in human primary astrocytes and murine plectin-deficient fibroblasts. Transient transfection of full-length plectin cDNA converted these aggregates to thin filaments, which exhibited diffuse cytoplasmic distribution. Compared to wild-type

GFAP expression, RC GFAP expression lowered plectin levels in astrocytoma-derived stable transfectants and plectin-positive fibroblasts. A much higher proportion of total GFAP was found in the Triton X-insoluble fraction of plectin-deficient fibroblasts than in wild-type fibroblasts. Taken together, our results suggest that insufficient amounts of plectin, due to RC GFAP expression, promote GFAP aggregation and RF formation in AxD.

Related companies

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

Company	Lead candidate	Stage
Astellas Pharma US (Northbrook, IL, USA)	UMass/Astellas AAV vector expressing an artificial microRNA (no public candidate name) Sponsored-research program with UMass Chan to develop an AAV (AAV9 described in preclinical abstracts) vector encoding an artificial miRNA to silence mutant GFAP and reduce GFAP pathology; UMass (Gao/Xie lab) leads preclinical work while Astellas provides drug-discovery support under a sponsored research agreement.	Preclinical / sponsored research (research agreement announced June 20, 2024) [1] [2] [3] [4] [5]

Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
zilganersen	oligonucleotides	FDA	2020-09-18	nan	Ionis Pharmaceuticals
2'-O-(2-methoxyethyl)-D-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid	oligonucleotides	EMA	2019-10-17	nan	Ionis Development (Ireland) Limited