Alex TLC Research Summary
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Research summary of recent leukodystrophy research and clinical trials, includes article summaries and direct links to websites and articles.

Adrenomyeloneuropathy (AMN)

SwanBio Therapeutics Initiates First-in-Human Study of AAV Gene Therapy for Adrenomyeloneuropathy
https://swanbiotx.com/investors-and-media/swanbio-therapeutics-initiates-first-in-human-study-of-aav-gene-therapy-for-adrenomyeloneuropathy/

The Lancet Neurology publishes results from Minoryx Therapeutics Phase 2/3 ADVANCE clinical trial of leriglitazone in X-linked Adrenoleukodystrophy
https://www.minoryx.com/media/the-lancet-neurology-publishes-results-from-minoryx-therapeutics-phase2-3-advance-clinical-trial-of-leriglitazone-in-x-linked-adrenoleukodystrophy/

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)

Vigil Neuroscience Announces First Patient Dosed in the IGNITE Phase 2 Clinical Trial to Evaluate VGL101 in Patients with ALSP
https://investors.vigilneuro.com/news-releases/news-release-details/vigil-neuroscience-announces-first-patient-dosed-ignite-phase-2

Study of VGL101 in Patients with ALSP Clinical Trial Pages

Vigil Neuroscience clinical trial website is now live: https://alspstudy.com/

The clinical trial posting on clinicaltrials.gov is live:
https://clinicaltrials.gov/ct2/show/NCT05677659?cond=alsp&draw=2&rank=1

Canavan Disease

Myrtelle's rAAV-Olig001-ASPA Gene Therapy Candidate for Canavan Disease Receives Orphan Drug Designation from the European Medicines Agency
https://myrtellegtx.com/myrtelles-raav-olig001-aspa-gene-therapy-candidate-for-canavan-disease-receives-orphan-drug-designation-from-the-european-medicines-agency/

Myrtelle Announces Positive Interim Data in Phase 1/2 Clinical Trial of Its Proprietary Investigational Gene Therapy rAAV-Olig001-ASPA in Canavan Disease
https://myrtellegtx.com/myrtelle-announces-positive-interim-data-in-phase-1-2-clinical-trial-of-its-proprietary-investigational-gene-therapy-raav-olig001-aspa-in-canavan-disease/

Myrtelle and rAAVen Therapeutics to Develop Novel Gene Therapy Vectors
https://myrtellegtx.com/myrtelle-and-raaven-therapeutics-to-develop-novel-gene-therapy-vectors/

Metachromatic leukodystrophy (MLD), Adrenoleukodystrophy (ALD), and Krabbe disease

Experiences of patients and their family members with metachromatic leukodystrophy, adrenoleukodystrophy, and Krabbe disease: a qualitative systematic review protocol
https://pubmed.ncbi.nlm.nih.gov/36458855/

In this review, the experiences of patients and their families with neurodegenerative diseases such as Metachromatic leukodystrophy (MLD), Adrenoleukodystrophy (ALD), and Krabbe disease were collected to illustrate their day-to-day impact. Neurodegenerative conditions cause both cognitive and neurological impairments affecting everyday activities posing great challenges for both patients and their families. In this research, a collection of those challenges accompanied by dissatisfaction with the possible treatments and the caregiver burden is presented. Nonetheless, the aim of the research is to highlight the impact of those conditions both in the community and at home.

Glutaric aciduria type I (GA-I)

Treatment of glutaric aciduria type I (GA-I) via intracerebroventricular delivery of GCDH
https://www.sciencedirect.com/science/article/pii/S2667325822003545?via%3Dihub

This article explains the underlying mechanism of glutaric aciduria type I (GA-I), and how delivery of GCDH can be a candidate treatment for the condition. GA-I is an inherited, metabolic, neurodegenerative disorder affecting the central nervous system, specifically the brain. The condition is caused due to deficiency of the glutaryl-CoA dehydrogenase (GCDH) responsible for the metabolism of molecules known as amino acids. In GA-I patients, the enzyme is not produced enough leading to an incomplete or impaired metabolic pathway which allows the accumulation of a by-product known as glutaric acid (GA). An abnormal amount of GA in the brain can cause toxicity and neurodegeneration, resulting in GA-I symptoms including hypotonia, macrocephaly, and encephalopathic crisis. Without a treatment plan, the life expectancy of patients suffering from GA-I is only 2 or 3 years. Nonetheless, there is an available treatment either by substance supplementation or dietary control, where a reduction in the GA levels is observed. As those treatments are limited scientists are currently developing a gene replacement strategy to treat the condition. Gene replacement therapy allows the successful delivery of the functional gene copy enabling the production of the GCDH in the correct amounts. Studies in mice indicated positive results and a higher survival rate once the treatment was delivered. Specifically, once the gene is administered, the GCDH expression in the central nervous system is restored to normal resulting in the amelioration of GA-I symptoms. Studies also revealed a higher success rate and elimination of symptoms when the treatment is administered in an early stage. Overall, due to the severity of the

condition, a treatment plan is an urgent need with gene therapy being so far the best possible option for GA-I treatment.

GM1 Gangliosidosis

Passage Bio announces interim clinical data from first six patients with GM1 Gangliosidosis in Imagine-1 Study

https://www.passagebio.com/investors-and-news/press-releases-and-statements/news-details/2022/Passage-Bio-Announces-Positive-Interim-Clinical-Data-from-First-Six-Patients-with-GM1-Gangliosidosis-in-Imagine-1-Study/default.aspx

GM2 Gangliosidosis

Azafaros Receives FDA Fast Track Designation and IND Clearance to Initiate a Phase 2 Trial for lead asset AZ-3102 in GM2 Gangliosidosis
https://www.azafaros.com/breaking-news-azafaros-receives-fdas-ind-clearance-and-fast-track-designation/

Krabbe Disease

Forge Biologics Receives Priority Medicines (PRIME) Designation from the European Medicines Agency (EMA) for Novel Gene Therapy FBX-101 for the Treatment of Patients with Krabbe Disease

https://www.forgebiologics.com/2023/01/17/forge-biologics-receives-priority-medicines-prime-designation-from-the-european-medicines-agency-ema-for-novel-gene-therapy-fbx-101-for-the-treatment-of-patients-with-krabbe-disease/

European Medicines Agency (EMA) has granted priority medicines (PRIME) designation to FBX-101, Forge's lead candidate and novel gene therapy for treating patients with Infantile Krabbe disease. The designation follows positive safety and efficacy data from the ongoing Phase 1/2 RESKUE trial presented by Maria Escolar, MD, MS, Forge's Chief Medical Officer, in late 2022. The results demonstrated that the treatment is safe, well-tolerated, and increased GALC enzyme activity in plasma and CSF in patients treated with FBX-101 after receiving an unrelated umbilical cord transplant. Patients in the lowest dose cohort showed encouraging signs of normal white matter integrity and improved motor development as compared to Krabbe patients who were untreated or treated asymptomatically with transplant.

What is the EMA?

Similar to the role of the FDA in the US, the European Medicines Agency (EMA) is an agency of the European Union (EU) responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU. EMA is a networking organization whose activities involve thousands of experts from across Europe. These experts carry out the work of EMA's scientific committees. The mission of the European Medicines Agency (EMA) is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union (EU).

For more information on the EMA, visit their site here

What is PRIME?

PRIME is a regulatory designation given by the EMA that provides early and proactive support to developers of promising medicines, to advance and speed up their development and usher them to reach patients faster. The goal is to help patients benefit as early as possible from innovative new therapies that have demonstrated the potential to address an unmet medical need and offer new therapies sooner to patients with unmet medical needs. To be accepted for PRIME, a medicine must show its potential to benefit patients with unmet medical needs based on early clinical data. For more information on PRIME, visit the EMA site here

What does this mean for patients in Europe?

Forge Biologics is looking to open additional clinical trial sites in Europe in 2023.

POLR3-related leukodystrophy

Riluzole partially restores RNA polymerase III complex assembly in cells expressing the leukodystrophy-causative variant POLR3B R103H
https://molecularbrain.biomedcentral.com/articles/10.1186/s13041-022-00974-z

This article reviews Riluzole as a possible candidate for the treatment of neurodegenerative diseases such as POLR3-related leukodystrophy. Specifically, this type of leukodystrophy is caused by mutations in genes encoding subunits of Polymerase III (Pol III). Pol III is part of the cell's replicative machinery responsible for synthesizing genetic molecules involved in multiple pathways allowing the survival and replication of the cell. However, Pol III is composed of different subunits and the efficiency of its action depends on how tightly regulated those parts' function is. In this case, POLR3-related leukodystrophy is caused due to mutations in the gene producing the POLR3 subunit, resulting in the improper assembly of Pol III and its accumulation in the cell. The condition is rare with neurodegenerative effects in the central nervous system leading to progressive neurological symptoms such as motor and cognitive impairments. There is currently no treatment available. Scientists studied the effects of the mutant POLR3 subcomplex on the cell and how it is affected by a molecule known as Riluzole. Originally, the drug was used to treat various neurological diseases as well as cancer due to its effect on molecule assembly. It was found, through studies on yeast molecules, that Riluzole had a positive impact on Pol III assembly. In conclusion, the mechanism of the drug's action is still unknown with ongoing research indicating Riluzole as a possible candidate for the treatment of POLR3-related leukodystrophy.

TUBB4A-associated leukodystrophy

TUBB4A-associated leukodystrophy: the disease and search for an effective treatment
https://www.openaccessgovernment.org/leukodystrophy/124977/

This article reviews the underlying mechanism of TUBB4A leukodystrophy and the ongoing research to find a treatment. TUBB4A is a rare, life-limiting neurodegenerative disorder caused by mutations in the TUBB4A gene. The mutations result in the production of a mutated protein responsible for disrupting the myelin sheath surrounding the nerve cells. The sheath ensures the correct transfer of the nerval signal between neurons allowing sufficient and fast delivery. In patients, the mutations cause hypomyelination of neurons leading to white matter degeneration and therefore the appearance of neural impairments such as paralysis, motor problems, and trouble with feeding. As

mentioned above TUB44A is a rare condition; according to Dr Josh Bonkowsky at the University of Utah leukodystrophies affect 1 in 7,000 births globally with only 9% of these cases being TUBB4A. It is very common for the condition to be misdiagnosed due to its rarity and variation of its symptoms. In order to correctly diagnose the disease, advanced biological methods including analysis of the genetic material must be made. However, treatment is still under development. Specifically, the treatment will focus on targeting the mutated gene and neutralizing the mutated proteins. In conclusion, TUBB4A is a life limiting, neurodegenerative disorder affecting the nervous system with ongoing research for a possible treatment.