Alex TLC Research Summary
July 2026

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

Clinical trial updates

Alexander disease (AxD)

Ionis announces license agreement with Recordati for zilganersen in Alexander disease (AxD) in all countries outside the U.S.

https://ir.ionis.com/news-releases/news-release-details/ionis-announces-license-agreement-recordati-zilganersen

Ionis have entered into a license agreement with Recordati to commercialise zilganersen for Alexander disease for all countries outside of the United States. This is a significant step towards providing access to a disease modifying treatment for Alexander disease patients.

Vanishing White Matter Disease (VWMD)

Calico Life Sciences Announces Fosigotifator Granted Breakthrough Therapy Designation by the U.S. FDA for the Treatment of Vanishing White Matter Disease

https://www.calicolabs.com/press/calico-life-sciences-announces-fosigotifator-granted-breakthrough-therapy-designation-by-the-u-s-fda-for-the-treatment-of-vanishing-white-matter-disease/

Calico have been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for Fosigotifator, a potential treatment for Vanishing White Matter (VWM) disease. Breakthrough Therapy designation is intended to speed up the review of medicines that treat a serious or life-threatening condition and have shown preliminary clinical evidence indicating the potential for substantial improvement over available therapies.

Research summaries

Adrenoleukodystrophy (ALD)

Clinically Relevant Outcome Measures in Women with Adrenoleukodystrophy

https://pmc.ncbi.nlm.nih.gov/articles/PMC13071096/

Adrenoleukodystrophy (ALD) is a rare inherited condition caused by changes in the *ABCD1* gene on the X chromosome. Although ALD is often associated with severe brain disease and adrenal problems

in men, many women develop symptoms later in life. These symptoms usually affect the spinal cord and nerves (myeloneuropathy), leading to stiffness, balance problems, bladder symptoms, pain, or difficulty walking. Researchers have used several clinical rating scales to measure symptoms in women with ALD, but these tools vary widely and are not always sensitive enough to detect early changes or track progression over time. This review looked at all the clinical assessment scales that have been used in studies of women with ALD. Researchers compared scales that assess disability, walking and mobility, neurological function, quality of life, pain, fatigue, sleep, restless legs syndrome, depression, and sexual health to identify which are most useful for monitoring disease progression and evaluating future treatments. No single assessment captured all aspects of the disease. The Expanded Disability Status Scale (EDSS) which assesses disease severity appeared to be the most useful for tracking long-term progression of mobility and spinal cord symptoms but has limitations due the slow progression of the disease. The International Restless Legs Syndrome Rating Scale (IRLS) may also be valuable for women with restless legs symptoms to assess the presence and severity of symptoms. The EDSS and IRLS were found to have potential for differentiating symptomatic and asymptomatic women. The Japanese Orthopedic Association (JOA) scores and Severity Score System for Progressive Myelopathy (SSPROM) assess myelopathy and differentiated symptomatic and asymptomatic women with slowly progressing neurological symptoms. General quality-of-life measures from self-report questionaries, such as the SF-36 (measures health status and quality of life), reflected the overall impact of ALD and may detect differences in physical and mental health. The authors also outline key priorities for future research, including developing more accurate ways to monitor disease progression and evaluate treatment responses specifically in women.

GM2 gangliosidosis

The RAINBOW study: A phase 2 trial evaluating the 3-month pharmacokinetic and pharmacodynamic data and 18-month clinical and safety outcomes of nizubaglustat in GM2 gangliosidosis or Niemann-pick type C disease

https://www.sciencedirect.com/science/article/pii/S1096719226004476

GM2 gangliosidoses and Niemann–Pick type C (NPC) disease are rare inherited conditions that damage the brain and nervous system over time. People living with these disorders can experience difficulties with movement, balance, speech, swallowing, learning, and seizures. While treatments are available to help slow NPC disease, there are currently no disease-modifying therapies approved for GM2 gangliosidoses, highlighting the need for new treatment options. The RAINBOW study investigated the safety and potential benefits of a new oral medicine called nizubaglustat. Thirteen participants aged 12 years and older with either GM2 gangliosidoses or NPC disease took part in the phase 2 clinical trial. Participants initially received either nizubaglustat or a placebo for 12 weeks, before most continued treatment with nizubaglustat for up to 18 months. Researchers found that nizubaglustat was generally well tolerated, with most side effects being mild or moderate. The medicine also reduced levels of glucosylceramides, fatty substances that build up in these diseases, suggesting it was successfully targeting the underlying disease process. Over the 18-month treatment period, many participants showed improvements or remained stable in measures of balance, movement, and neurological function. Importantly, seizure frequency also decreased in those receiving treatment. Although this was a small study involving only 13 participants, the results are encouraging. Nizubaglustat appeared to have a favourable safety profile while showing signs that it may slow disease progression and improve symptoms in both GM2 gangliosidoses and NPC disease. These

findings support further investigation in larger phase 3 clinical trials to confirm whether nizubaglustat can become an effective treatment for people living with these rare neurological disorders.

Leigh Syndrome

Mitochondrial dysfunction triggers a maladaptive peroxisomal response, driving lipid accumulation

https://www.sciencedirect.com/science/article/pii/S2213231726001643

This study explores how problems in mitochondria—the cell's main energy producers—affect another organelle called the peroxisome, which also helps break down fats. The researchers used cells lacking NDUFS4, a key part of mitochondrial complex I. Without this protein, mitochondria cannot properly burn fatty acids, causing the cells to accumulate excess fat. Normally, peroxisomes help process very-long-chain fatty acids, especially when mitochondria are stressed. In these NDUFS4-deficient cells, peroxisomes increased in number, suggesting the cell was trying to compensate. However, the new peroxisomes were not fully functional. Key enzymes needed for fat breakdown were reduced, meaning the peroxisomes could not effectively handle the overload. As a result, fats build up inside the cell, lipid droplets enlarge, and both organelles become stressed. The study proposes that healthy communication between mitochondria, peroxisomes, and lipid droplets is essential for managing metabolic stress. When this coordination breaks down, cells become vulnerable to lipid imbalance, which may contribute to diseases like Leigh syndrome. This is an important finding and provides a therapeutic target for future research to potentially reduce lipid stress in mitochondrial disorders.

Peroxisome Biogenesis Disorder (PBD)

In vivo base editing rescues liver pathophysiology and peroxisome dysfunction in a mouse model of Zellweger spectrum disorder

https://www.nature.com/articles/s41551-026-01651-5

Zellweger spectrum disorder (ZSD) is a rare inherited condition caused by changes in genes that help cells build peroxisomes. Peroxisomes play an essential role in breaking down certain fats and removing harmful substances from the body. When they do not work properly, toxic substances build up, causing damage to multiple organs, particularly the liver and brain. Current treatments mainly focus on managing symptoms and cannot correct the underlying genetic cause. In this study, researchers investigated whether a gene-editing technique called base editing could repair one of the most common disease-causing changes in the PEX1 gene, which affects around 30% of people with ZSD. Using a mouse model of the disease, they delivered the editing tool directly to the liver, where it corrected up to 60% of the faulty genes. The treatment restored peroxisome function, reduced the build-up of harmful fats and toxic bile acid compounds, improved liver health, and helped the mice gain weight. Similar benefits were seen when the editing tool was delivered using either a viral vector or a non-viral lipid nanoparticle system, although the latter produced lower levels of gene correction. The researchers also tested the approach in cells donated by people with ZSD, where more than 80% of the faulty PEX1 genes were successfully corrected, restoring normal peroxisome activity. Importantly, the treatment caused very few unintended genetic changes. Although these findings are still at the preclinical stage, they provide encouraging evidence that base editing could one day become a treatment that targets the root cause of ZSD, offering hope for people and families affected by this devastating condition.

Vanishing White Matter Disease (VWMD)

Pediatric pharmacokinetics and pharmacodynamics of guanabenz for the treatment of vanishing white matter

https://www.nature.com/articles/s41598-026-47959-9

Vanishing white matter (VWM) is a rare inherited neurological disease that mainly affects children. It damages the brain's white matter, leading to progressive problems with movement, coordination, speech, and thinking. Even minor illnesses, fever, or head injuries can trigger sudden and irreversible worsening of symptoms. Studies in mice suggested that guanabenz, a medicine originally developed to treat high blood pressure, could protect brain cells affected by VWM. Before testing whether the drug is effective in children, researchers first needed to understand how it is processed by the body (pharmacokinetics) and how it affects the body (pharmacodynamics), helping to identify doses that are both safe and potentially beneficial. In this phase 1/2 clinical trial, 32 children with genetically confirmed VWM received guanabenz. The researchers measured drug levels in the blood, monitored blood pressure, heart rate and body temperature, and recorded any side effects. They also compared the results with computer models based on previous animal and adult studies to assess how accurately these models predicted drug exposure in children. The study found that the modelling approach predicted guanabenz concentrations reasonably well and that the doses used achieved blood levels thought to be potentially therapeutic. However, hallucinations emerged as an unexpected dose-limiting side effect, and larger reductions in blood pressure appeared to increase this risk. These findings suggest that blood pressure could help monitor treatment safety and that future studies may need to use lower or more carefully adjusted doses. Overall, this research provides valuable guidance for designing future clinical trials of guanabenz in children with VWM.

Concise Articles

Canavan Disease (CD)

Proven Durability: Groundbreaking Gene Therapy Persistence Data

https://myrtellegtx.com/proven-durability-groundbreaking-gene-therapy-persistence-data/

Please be aware these summaries are produced voluntarily by Biomedical Science students and are their interpretations of the information and findings. This information is reviewed by our Research Analyst Kristina Backlund MMSc. The National Lottery Community Fund and Ionis Pharmaceuticals, Inc have contributed to the funding of the Research Analyst role.

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