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.

Adrenoleukodystrophy (ALD)

Poxel Announces PXL770 Awarded FDA Fast Track Designation for X-linked Adrenoleukodystrophy
https://www.poxelpharma.com/en_us/news-media/press-releases/detail/209/poxel-announces-pxl770-awarded-fda-fast-track-designation

A qualitative study exploring family communication following a diagnosis of adrenoleukodystrophy in the UK
https://www.alextlc.org/wp-content/uploads/2022/05/ALD-Genetic-Counselling-Dissertation-Summary.pdf

Newborn Screening for X-Linked Adrenoleukodystrophy in Nebraska: Initial Experiences and Challenges
https://www.mdpi.com/2409-515X/8/2/29

This article reviews a condition called Adrenoleukodystrophy (ALD) and the importance of newborn screening in the early diagnosis of the disease. Adrenoleukodystrophy is an inherited neurodegenerative disease caused by the pathogenic variant of a gene known as ABCD1. The term, neurodegenerative disease refers to conditions where cells of the nervous system lose their ability to function. In this case, most male patients diagnosed with adrenoleukodystrophy develop either childhood cerebral X-ALD (X-ALD, ccALD) or adrenomyeloneuropathy (AMN). Childhood cerebral X-ALD is the most severe and life limiting of ALD with an early onset, affecting 35% of male patients. It is characterized by progressive functional loss of neurons located in the central nervous system. Treatment can be successful during the first stages of the disease using a method known as hematopoietic stem cell transplantation (HSCT), where bone marrow is transplanted from a healthy donor to a patient. On the other hand, AMN has a late-onset affecting the majority of ALD cases (60%) in males. Various body organs are impacted as well, such as adrenal dysfunction. Adrenal dysfunction can be treated with hormones when early diagnosed. As a result, early diagnosis allows for successful treatment of the disease, slowing down the progression of it and leading, therefore, to better life quality for the patients.

Therapeutic potential of deuterium-stabilized (R)-pioglitazone - PXL065 - for X-linked adrenoleukodystrophy
https://pubmed.ncbi.nlm.nih.gov/35510808/

This article reviews the efficacy of a new drug called PXL065 used to treat X-linked Adrenoleukodystrophy (ALD). This condition is a rare neurometabolic (affecting the metabolism in neurons) disorder caused by mutations in the ABCD1 gene which encodes for a transport protein. The protein is responsible for transporting very-long-chain fatty acids

(VLCFA) across the cell membrane to the peroxisomes (organelles of the cell used to metabolize substances). When the protein is impaired the VLCFA is not transported to the peroxisomes leading to their accumulation in tissues and plasma. This results in two subtypes of the condition, the Adrenomyeloneuropathy (AMN) and the cerebral- ALD (C-ALD). The first one is diagnosed during adulthood and is characterized by spinal cord and nerve degeneration (loss of neurons or their function). On the other hand, C-ALD is diagnosed during childhood with neurological impairments being the primary cause of loss of life due to the deterioration of white matter in the brain. There is an available treatment for the condition but there are associated side effects. For that reason, scientists repurposed a drug – originally used to treat diabetes- called PXL065 which can be used to treat both subtypes of the disease. Throughout research conducted to evaluate the efficacy of the drug, chronic administration revealed reductions of VLFCA in plasma and tissue of mice. Moreover, it is able to repress inflammatory responses which could lead to ALD. The drug is currently assessed for both its success and safety, enabling it a potential treatment for the condition with minimal side effects for the patients.

Glycoprotein nonmetastatic melanoma protein B (GNMPB) as a novel biomarker for cerebral adrenoleukodystrophy

https://www.nature.com/articles/s41598-022-11552-7.pdf

This article reviews the possible function of the glycoprotein nonmetastatic melanoma protein B (GNMPB) as a biomarker for a condition known as cerebral adrenoleukodystrophy (cALD). Specifically, cALD is a subtype of Adrenoleukodystrophy (ALD) which is an inherited, neurodegenerative condition (progressive loss of neurons or their function) caused by the pathogenic variant of the ABCD1 gene. The normal gene codes for a protein responsible for transporting very long acid chains (VLFCA) to structures called peroxisomes inside the cell. Peroxisomes are responsible for the metabolism of the cell's toxic wastes. When the gene is mutated, the protein is not able to transfer the VLFCA, resulting in their accumulation in tissues such as the adrenal cortex, testis, and nervous system. There are treatments for cALD but early diagnosis is necessary to secure their success. For that reason, biomarkers for the disease are necessary as scientists can diagnose and track its progression. In particular, biomarkers are molecules used to determine a condition based on their quantity as abnormal numbers are an indication of disease. It is crucial to mention that GNMPB is normally expressed by various cells including neuron cells. During research conducted using body fluids of young male patients, GNMPB was found to be a suitable biomarker to diagnose cALD as elevated numbers were associated with the condition. Early diagnosis using biomarkers could lead to successful treatment, easing the symptoms of the disease and allowing for better life quality.

Adrenomyeloneuropathy (AMN)

Additional Preclinical Data Supports Clinical Advancement of First AAV-Based Gene Therapy for Adrenomyeloneuropathy

https://swanbiotx.com/investors-and-media/additional-preclinical-data-supports-clinical-advancement-of-first-aav-based-gene-therapy-for-adrenomyeloneuropathy/

SwanBio Therapeutics is a gene therapy company that specialises in the advancement of treatments for inherited neurological conditions. The company has provided additional data about the gene therapy SBT101 to support the utilisation of the therapy to treat adrenomyeloneuropathy (AMN). This data comes after extensive studies using non-human primates and rodent models. AMN is a progressive neurodegenerative disease that arises due to the lack of the gene called ABCD1 gene. A deficiency in this gene leads to an accumulation of a compound called Very-long chain fatty acids (VLCFA) within the spinal cord and other organs. This leads to the loss of mobility, severe pain and other symptoms that decrease the quality of life of an individual. The aim of administrating SBT101 is to increase the presence of the gene. By doing this, the root cause of the disease is addressed and treated. The preclinical data using animal models demonstrated that SBT101 was well tolerated by the animal models and notable improvements in functionality were observed. The data from the preclinical studies means that SwanBio will now begin clinical trials where they will administer SBT101 to patients in the second half of 2022. Currently the U.S. Food and Drug Administration (FDA) has no approved therapy treatments for treating AMN. With the positive results of the preclinical data and the initiation of the clinical studies, SBT101 could become the first FDA approved therapy for treating AMN

Poxel Announces PXL065 and PXL770 Granted Orphan Drug Designation from the U.S. FDA for X-Linked Adrenoleukodystrophy
https://www.poxelpharma.com/en_us/news-media/press-releases/detail/213/poxel-announces-pxl065-and-pxl770-granted-orphan-drug
Poxel SA is a biopharmaceutical company with a focus on developing innovative treatments for severe chronic diseases such as x-linked adrenoleukodystrophy (ALD). The company has announced that the U.S. Food and Drug Administration (FDA) has given them the Orphan Drug Designation (ODD) to the treatments PXL065 and PXL770. Both these treatment with be used to treat patients with adrenomyeloneuropathy (AMN). ALD is a rare neurodegenerative disease resulting from mutations in a gene called the ABCD1 gene. Adrenomyeloneuropathy (AMN), is the most common variant of ALD. ODD is awarded to new therapies that treat diseases impacting fewer than 200 000 people in the U.S. ODD grants a company exclusive marketing rights over the treatment as well as FDA approval. This provides the company with a financial pathway to fund clinical trials. With the FDA granting the Orphan Drug Designation for PXL065 and PXL770, Poxel SA has an additional source of finances to support the further studying of the treatments. The company can continue onward to phase two of the clinical trials of PXL065 and PXL770. Many steps are involved in the proceedings of putting new drugs and therapies onto the market. With the FDA granting ODD to Poxel, their studies around the treatments for AMN can continue unimpeded by financial constraints. PXL065 and PXL770 can compensate for the unmet needs regarding the lack of therapies for AMN.

Adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia (ALSP)

Natural History Study in Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)
https://clinicaltrials.gov/ct2/show/NCT05020743

Alexander Disease

Effects of Alexander disease-associated mutations on the assembly and organization of GFAP intermediate filaments
https://pubmed.ncbi.nlm.nih.gov/35511821/
This article reviews the mutations on the gene encoding GFAP protein which underlie the appearance of Alexander disease. Alexander disease is a genetic disorder affecting the central nervous system resulting in brain degeneration. It is caused by mutations in the gene producing the GFAP protein produced mainly in cells called astrocytes. Astrocytes are responsible for the normal conduction of nerve signals. In total 14 mutations have been identified resulting in abnormal characteristics of the cytoskeleton's filament. The cytoskeleton is responsible for maintaining the normal structure and shape of cells via the presence of filaments (bundles of parallel fibres). When mutations occur, the filaments appear shorten with irregular width and a rough appearance. Due to those changes, the GFAP proteins accumulate in brain tissues as the protein is insoluble, developing Alexander's disease. It is found that 95% of patients diagnosed with the condition are affected by these mutations resulting in developmental delays. The mechanism leading to elevated GFAP in patients affected by Alexander disease is still unknown, but an early diagnosis can lead to effective treatment and therefore delay the symptoms of the condition.

Giant Axonal Neuropathy (GAN)

Taysha Gene Therapies receives orphan drug designation from the European Commission for TSHA-120 for the treatment of Giant Axonal Neuropathy (GAN)
https://ir.tayshagtx.com/news-releases/news-release-details/taysha-gene-therapies-receives-orphan-drug-designation-0

Metachromatic Leukodystrophy (MLD)

Orchard Therapeutics Announces Agreement Enabling Access and Reimbursement for Libmeldy for All Eligible MLD Patients in Germany

https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-agreement-enabling-access-and

This article reviews the agreement made by Orchard Therapeutics, allowing the usage of the drug Libmeldy for treating Metachromatic Leukodystrophy (MLD) in Germany. Orchard Therapeutics is a global industry responsible for generating gene therapies for rare diseases such as MLD. Specifically, MLD is a genetically inherited disease affecting tissues and organs such as the brain, liver, gallbladder, kidneys, and spleen. The underlying cause of the condition is the accumulation of sulfatides due to mutations in the arylsulfatase-A (ARSA) gene. Sulfatides are a subtype of lipids responsible for the correct function of the nervous system. Therefore, their accumulation interferes with the normal role of the neurons leading to neurological problems such as the inability to walk, see, eat, and swallow. By the age of five, the mortality rate is over 50% enabling the search for a treatment an urgent need. Agreement between companies allowed the free screening of new-borns in Germany and other European countries allowing early diagnosis and possible treatment with the newly approved drug, Libmeldy. This drug acts by reducing the effects of the impaired ARSA protein in patients with early onset symptoms. As a result, Libmeldy is approved in various countries including Germany, allowing the successful treatment of patients, giving them the chance of having a better life quality.

Pelizaeus-Merzbacher Disease (PMD)

Myrtelle Inc. Announces Expansion of Its Pipeline with a Novel Gene Therapy Program for Pelizaeus-Merzbacher Disease (PMD)

https://myrtellegtx.com/myrtelle-inc-announces-expansion-of-its-pipeline-with-a-novel-gene-therapy-program-for-pelizaeus-merzbacher-disease-pmd/

Rare Disease

Clinical diagnosis of metabolic disorders using untargeted metabolomic profiling and disease-specific networks learned from profiling data

https://www.nature.com/articles/s41598-022-10415-5#citeas

This article reviews a range of techniques known as untargeted metabolomics to successfully diagnose metabolic disorders. Metabolic disorders arise when a certain aspect of the metabolism of substances is compromised. However, it is challenging to properly diagnose those disorders as the symptoms are non-specific or not well understood. Consequently, a method called CTD (Connect The Dots) is able to measure 16 different inborn errors in metabolism (IEMs) which cause the manifestation of various syndromes. Specifically, inborn errors refer to impairments in the metabolism which are inherited from the parents to the child. Using the CTD technique supplement information can be collected, analyzed, and interpreted allowing the scientists to compare the unknown sample with a broad range of other biochemical pathways (chemical reactions during the metabolism of a substance). This is possible as IEMs cause abnormal accumulation or depletion of chemicals which can be detected using untargeted metabolomics. When typical methods of diagnosis fail to provide an accurate diagnosis, CTD can be used to both diagnose and examine the etiology of the condition. Accuracy of CTD can therefore improve a patient's life, as the correct treatment can be administered before the appearance of symptoms.