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)

Beneficial effects of the direct AMP-Kinase activator PXL770 in in vitro and in vivo models of X-Linked Adrenoleukodystrophy

https://jpet.aspetjournals.org/content/jpet/early/2022/06/25/jpet.122.001208.full.pdf

X-linked adrenoleukodystrophy (ALD) is a severe chronic disease that is very rare. Due to its rarity, research and resources invested in creating treatments for the disease are limited. ALD arises due to the defect of the gene called ABCD1, which reduces the levels of a compound called Very Long Chain Fatty Acids (VLFCAs). Because of the defect, VLCFAs accumulate in the body, resulting in impaired bodily systems. The study discusses the effectiveness of treating ALD with PXL770 in laboratory contexts (in vitro) and mice (in vivo).

AMP-activated protein kinase (AMPK) are compounds that reduce the effects of the disease at a cellular level. PXL770 is the first AMPK that has demonstrated clinical effectiveness and is also tolerable when used to treat ALD. The study investigated the effect of administrating PXL770 in vitro using the cells of patients suffering from ALD and in vivo using mice.

Administration of PXL770 decreased VLCFA levels in in vivo and in vitro experiments. The study showed the effectiveness of the treatment in decreasing the signs of ALD at a cell level.

The study's results demonstrate the benefits of PXL770 and will help further the development of the treatment to treat patients affected by ALD. Currently, there are no approved therapies that exist to treat ALD directly, only those which can help with symptom management of the condition. The development of PXL770 would mean that an approved therapy that directly treats the disease would be available to patients.

Adrenomyeloneuropathy (AMN)

Poxel Announces the Publication of Two Preclinical Articles on X-Linked Adrenoleukodystrophy for PXL065 and PXL770

https://www.poxelpharma.com/en_us/news-media/press-releases/detail/218/poxel-announces-the-publication-of-two-preclinical-articles

Poxel SA is a biopharmaceutical company focusing on developing treatments for chronic diseases such as X-linked adrenoleukodystrophy (X-ALD). The company announced the release of the research articles regarding both treatments,

PXL065 available at: https://pubmed.ncbi.nlm.nih.gov/35510808/

and PXL770 available at: https://pubmed.ncbi.nlm.nih.gov/35510808/

The research articles discuss how each treatment works, since PXL065 and PXL770 differ in how they aim to treat chronic diseases. Both treatments are being prepared for the next stage of clinical trials to demonstrate their effectiveness in treating X-linked adrenoleukodystrophy (X-ALD) in adrenomyeloneuropathy (AMN) patients.

X-ALD is characterised by the increase in a compound called Very Long Chain Fatty Acids (VLCFA), which accumulates in the body of patients. X-ALD is the most common leukodystrophy, and AMN is one of the more common variations of the disease. The published research articles discuss the abilities of the two treatments to reduce the biological characteristics of the disease within mice, such as the reduction of VLCFA levels with continual treatment.

PXL065 and PXL770 decreased the disease's progression in mice and will move on to the next phase of clinical trials. The clinical trials will help determine the differences between the two treatments and further the research into PXL065 and PXL770.

Publication of the research articles discussing how PXL065 and PXL770 work to decrease disease progression gives the two treatments credibility. Increasing the credibility of the two treatments helps incentivise researchers and funders to invest in PXL065 and PXL770.

SwanBio Presents Design of Innovative Natural History Study Aimed to Evolve Understanding of Adrenomyeloneuropathy and Inform Future Treatments

https://swanbiotx.com/investors-and-media/swanbio-presents-design-of-innovative-natural-history-study-aimed-to-evolve-understanding-of-adrenomyeloneuropathy-and-inform-future-treatments/

SwanBio has announced the details of their new development that can help track the natural progression of the disease adrenomyeloneuropathy (AMN). CYGNET was developed to assess AMN progression in patients and have that information relayed to research teams.

The study SwanBio will conduct will occur over two years where the following variables will be noted and tracked:

- Body swaying; this is often an early predictor of disease progression and can show how likely a patient will suffer from falls
- Traditional motor abilities, novel activity and how patients sleep will be observed using wearable tracking technology.
- The study will also track the quality of life, how severe the disease is, and functional impairment.

In addition to performing the study, SwanBio is performing a clinical trial to determine the safety and efficacy of their gene-therapy SBT101 for patients suffering from AMN.

CYGNET is the first AMN clinical study that uses wearable technology to assist with tracking disease progression. The nature of the study means that CYGNET may better characterise the disease, allowing researchers to progress in developing treatments for AMN. In February 2022, the FDA granted fast track designation to SBT101, the First Investigational AAV-Based Gene Therapy for Patients with Adrenomyeloneuropathy (AMN). SBT101 progressing to the clinical trial stage indicates that it could be a viable treatment for AMN that can be used once proven safe.

With the assistance of CYGNET, researchers can better understand how AMN works and progresses through the body and develop gene-therapy treatments accordingly. SBT101 could become an approved therapy for AMN that treats the disease instead of just the symptoms of the condition.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

A New NOTCH3 Gene Mutation Associated With a CADASIL Diagnosis

https://www.cureus.com/articles/103191-a-new-notch3-gene-mutation-associated-with-a-cadasil-cerebral-autosomal-dominant-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy-diagnosis

This article refers to the identification of a new gene mutation underlying the condition Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). CADASIL is an adult-onset rare inherited disease and cause of stroke due to impairments in blood vessels. Specifically, mutations in the healthy gene (NOTCH3 is the name of the specific mutation) can lead to an increased thickness and fibrousness of arteries affecting normal blood flow and possibly resulting in loss of life. Therefore, the obstruction of blood flow can lead not only to stroke but to behavioural issues such as mood swings and migraines. Due to the condition's rarity and the broad range of symptoms, diagnosis is not always easy, resulting in numerous undiagnosed medical cases. Typical diagnosis suggests brain scans where haemorrhages and white matter abnormalities can be detected, indicating the presence of CADASIL. However, more genetic tests regarding the NOTCH3 mutation should be made to effectively detect the disease. As there is no curative treatment, early diagnosis of the condition can allow for effective management of symptoms.

Canavan Disease

BridgeBio Pharma Announces Early Positive Data for BBP-812, its Investigational AAV9 Gene Therapy for Canavan Disease

https://bridgebio.com/news/bridgebio-pharma-announces-early-positive-data-for-bbp-812-its-investigational-aav9-gene-therapy-for-canavan-disease/

This article reviews the progress of innovative gene therapy, for Canavan disease. Canavan disease is a rare neurodegenerative disease characterized by the destruction of myelin, a protective layer that insulates and protects neurons (cells of the nervous system). The primary cause of the condition is the accumulation of a toxic substance called N-acetylaspartate (NAA) which leads to myelin loss. In healthy individuals, NAA is metabolized by the enzyme aspartoacylase, whilst in patients diagnosed with Canavan disease, the enzyme is produced in lower amounts due to gene mutations, resulting in NAA accumulation. Impairments in the myelin can lead to the inability of the neuron to send or receive signals interfering with normal development. As a result, the disease has a high fatality rate, and no definitive treatment exists. However, a company named BridgeBio Pharma is focusing on developing a new treatment using gene therapy to treat Canavan. Through gene therapy, healthy copies of the mutated gene are inserted into the patient resulting in expression of the enzyme in the correct amount. In that way, the organism is able to metabolize NAA and diminish at the same time the devastating symptoms of the disease. Reducing the symptoms could lead to a higher survival rate, allowing normal development during childhood and ensuring a better life quality for the patients and their families.

Myrtelle Announces Positive Data for Its investigational Proprietary rAAV-Olig001-ASPA Gene Therapy in Canavan Disease at the National Tay Sachs & Allied Diseases Association Conference

https://myrtellegtx.com/myrtelle-announces-positive-data-for-its-investigational-proprietary-raav-olig001-aspa-gene-therapy-in-canavan-disease-at-the-national-tay-sachs-allied-diseases-association-conference/

This article highlights the possible usage of rAAV-Olig001-ASPA Gene Therapy created by Myrtelle for treating Canavan Disease (CD). Specifically, CD is an inherited condition caused by mutations in the Aspartoacylase gene (ASPA) which is responsible for producing the enzyme Aspartoacylase (ASPA) leading to abnormally low quantities of the enzyme in neural cells. That results in the accumulation of ASPA in neural cells and the effects can be devasting as the protective sheath covering neurons (known as myelin) is destroyed. This affects the ability of the neurons to communicate and transfer the information from the brain to organs and cells. As a result, CD can cause irreversible damage, and as there is no available treatment it can be life limiting. However, Myrtelle was able to develop a gene therapy that could treat CD. By the term gene therapy, scientists refer to the insertion of functional genes to restore their normal function. Patients that were administered the innovative treatment showed positive data indicating that it could restore the function of ASPA. Specifically, gene therapy for CD targets directly the neural cells allowing normal production of ASPA. Overall, a re-evaluation of the new gene therapy should be made to ensure the safety and efficacy of the drug before used to treat CD.

Leigh syndrome

Cyclerion Therapeutics Announces CY6463 Data Demonstrating Improved Cellular Energetics in Preclinical Models of Mitochondrial Disease

https://ir.cyclerion.com/news-releases/news-release-details/cyclerion-therapeutics-announces-cy6463-data-demonstrating

This article overviews the possible treatment of mitochondrial (organelles responsible for producing energy used by cells) and central nervous system diseases using a biological stimulator known as CY6463. Cyclerion Therapeutics is a biopharmaceutical company focusing on the development of treatment to re-establish cognitive function in patients suffering from serious central nervous system (CNS) diseases. Cognitive function refers to multiple mental abilities necessary for normal mental and physical development. The company developed the stimulator CY6463 which enhances the pathway responsible for regulating critical neuronal function. In many disorders impairments in that pathway may result in the appearance of various serious neurological conditions. Data obtained from experiments revealed the stimulator's ability to both promote mitochondrial function and reduce inflammation in cells. As a result, the stimulator could act as a treatment for serious CNS (such as Alzheimer's) and mitochondrial conditions (such as Leigh syndrome), reducing the appearance of symptoms and rendering life easier for patients.