Alex TLC Research Summary
SEPTEMBER 2022

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

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

Vigil Neuroscience Presents Preclinical Data on VGL101 for Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

https://investors.vigilneuro.com/news-releases/news-release-details/vigil-neuroscience-presents-preclinical-data-vgl101-adult-onset

This article reviews the potency of the VGL101 drug developed to treat Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP). The condition is a rare, life limiting, inherited neuronal disease characterized by the dysfunction of microglia. Microglia are human cells in the central nervous system, which include the brain and spine, responsible for the immune response. However, mutations in genes can result in abnormal microglia, interfering with their natural ability to protect the central nervous system and therefore leading to the appearance of ALSP.

As it is a late-onset disease with a mean age of onset being 43, misdiagnoses are often. Specifically, the disease can be easily misdiagnosed as early symptoms include cognitive impairment and neuronal dysfunction, which are present in various neurological conditions like Alzheimer's. Due to the fast progression of the disease and the low survival rate, early diagnosis before the onset of symptoms is crucial. To effectively diagnose the condition, genetic testing is necessary for all members of a family. Early diagnosis could allow treatment with a new drug known as VG101. This drug acts by supporting and maintaining the microglia function enhancing their activity. When the treatment is administered in the early stages of the disease the life limiting and destructive symptoms may be able to be suppressed.

Adrenomyeloneuropathy (AMN)

Viking Therapeutics Announces FDA Has Lifted Clinical Hold on Phase 1b Trial of VK0214 in Patients with X-ALD

http://ir.vikingtherapeutics.com/2022-07-19-Viking-Therapeutics-Announces-FDA-Has-Lifted-Clinical-Hold-on-Phase-1b-Trial-of-VK0214-in-Patients-with-X-ALD

Viking Therapeutics, Inc. is a company that focuses on developing new and innovative treatments for metabolic and endocrine diseases such as adrenomyeloneuropathy (AMN). AMN is a variation of X-linked adrenoleukodystrophy (X-ALD), for further information visit the Alex TLC AMN condition page.

Viking Therapeutics has announced that the clinical hold on their developing treatment for X-ALD has been lifted. A clinical hold is issued by the Food and Drug Administration (FDA) to pause the progression of clinical trials on developing treatments when a company is obtaining permission for human trials. The clinical hold was lifted after results were submitted to the FDA, showing that the

treatment, VK0214, does not cause any mutations. With the hold lifted, Viking Therapeutics will resume studies and begin clinical trials as soon as possible. The company aims to enrol adult male patients affected by AMN, the most common variation of X-ALD. The study's primary goal will be to examine the safety of VK0214 and how patients tolerate the treatment. The company believes that the temporary delay of the clinical hold will not impact the designated timeline for developing VK0214 long-term.

Alexander Disease

Symptomatic care of late-onset Alexander disease presenting with area postrema-like syndrome with prednisolone

https://pubmed.ncbi.nlm.nih.gov/35831840/

In this article the author reviews a symptomatic case of late-onset Alexander disease focusing on how the condition manifested, and what treatments were followed. Alexander disease (AxD) is a rare progressive neurological disorder caused by specific mutations in neuronal human cells. There are two types of AxD, the common one being the infantile AxD (type I), which is characterized by an early onset of symptoms followed by progressive neurologic impairment, and the juvenile/adult AxD (type II). In this case report, a type II AxD was diagnosed in a 9-year-old male patient. The patient seemed healthy at birth but at the age of 6 years a brain scan was made after multiple seizures, generalized nausea, and vomiting appeared, revealing brain abnormalities. Multiple tests were made showing that the thyroid gland and the liver were not affected. Specialists diagnosed AxD, confirmed by genetic tests, and oral treatment with a drug called prednisolone alongside with anti-seizure medication was prescribed. After some months a positive response to treatment was noticed allowing a limitation on prednisolone in fear of the drug's long-term consequences. However, this resulted in the revival of symptoms including nausea and vomiting. There are still a lot of questions on how the symptoms responded to prednisolone and how long the effect will last. Overall, in this case, the possibility of treating the symptoms of type II AxD with prednisolone was presented, allowing a better life quality for the patient.

Giant Axonal Neuropathy (GAN)

TSHA-120 treated patients in GAN demonstrated durable improvement and recoverability of sensory nerve amplitude potential (SNAP)

https://ir.tayshagtx.com/news-releases/news-release-details/taysha-gene-therapies-reports-second-quarter-2022-financial

Taysha Gene Therapies, Inc. is a gene therapy company focused on developing and commercialising Adeno-associated virus (AAV) based therapies to treat disorders impacting the central nervous system. AAV-based medicines make use of viruses that have been designed to transport treatment directly to the affected target area. The company has announced their results of treating patients with Giant Axonal Neuropathy (GAN) during clinical trials with their AAV-based gene therapy, TSHA-120. Early on in life, patients with GAN demonstrate a decline in the function of their sensory nerves. Sensory nerves are responsible for the senses of touch, scent, taste, and sight. The senses are measured using sensory nerve action potential (SNAP). Once SNAP reaches zero, recovery of the sensory nerve function in untreated patients is impossible.

Patients in the study were nine years or older, and all demonstrated a SNAP score of zero before treatment with TSHA-120. The study's results demonstrated that with the treatment of TSHA-120, sensory nerve function improved and stabilised. With the positive results of the study, the Medicine and Healthcare products Regulatory Agency (MHRA) has agreed to the commercial manufacturing of

TSHA-120. The agency has recommended that the company release commercially graded dosages to a few patients, which will become available in September 2022. Taysha Gene Therapies hopes to acquire further regulatory updates by the end of 2022, allowing more significant demographic access to the medication.

GM1 Gangliosidosis

Advanced Imagine-1 clinical trial for GM1 gangliosidosis to recruitment of final cohort, Cohort 4, in dose-ascending phase of study following recommendation by Independent Data Monitoring Committee

https://www.passagebio.com/investors-and-news/press-releases-and-statements/news-details/2022/Passage-Bio-Reports-Second-Quarter-2022-Financial-Results-and-Provides-Recent-Business-Highlights/default.aspx

Passage Bio, Inc. is a genetic medicines company that aims to develop treatments for patients affected by diseases of the Central Nervous System (CNS) where there are currently limited or no available treatment options. GM1 gangliosidosis is an inherited disorder that progressively destroys the brain and spinal cord nerve cells. The company announced the results they have obtained so far from their program, the Image-1 program. The data from the Image-1 program demonstrates the possibility of the company's treatment being the first disease-modifying treatment for GM1 gangliosidosis. The clinical trial is structured in an ascending dosage format. The dosages given to patients increase with each cohort once safety, efficacy and tolerability have been examined.

Passage Bio showed new data demonstrating that their treatment has continual and significant improvements in treating the disease. Data from 2 patients in cohort 1 showed that the administration of PBGM01 was tolerated well and safely. The data emerging from the results of cohort 3, which consisted of early infantile patients given the medication at low dosages, has given the company the confidence to proceed with recruiting the final cohort of patients for the clinical trials. The final group, cohort 4, will also consist of early infantile patients; however, they will be administered with high medication dosages instead. Passage Bio, Inc. is continually working to develop a treatment for GM1 gangliosidosis with promising results. Assuming the final cohort of patients during the clinical trials demonstrates positive data in treating the disease, the company may be able to move to the next stage in developing a disease-modifying treatment.

Metachromatic Leukodystrophy (MLD)

Homology Medicines Announces Optimized, In Vivo Gene Therapy Candidate for the Treatment of Metachromatic Leukodystrophy

https://www.homologymedicines.com/news-story/homology-medicines-announces-optimized-in-vivo-gene-therapy-candidate-for-the-treatment-of-metachromatic-leukodystrophy

This article refers to the potency of an innovative in vivo gene therapy, created by Homology medicines, to treat Metachromatic Leukodystrophy (MLD). Homology Medicines is a company dedicated to producing genetic treatments for rare inherited diseases, such as MLD, using in vivo gene therapy. In that way, functional genes are inserted intravenously into the patients allowing their normal function. Specifically, regarding MLD, Homology Medicines was able to develop a drug by targeting the underlying cause of the condition.

The condition is caused by mutations in the ARSA gene responsible for producing a protein necessary for the breakdown of toxic substances, known as sulfatides, in cells. Sulfatides have deteriorating effects on the nervous system cells, resulting in serious, progressive, and life limiting

neurological impairments. For that reason, the drug proposed by Homology Medicines acts by inserting functional ARSA genes in a single intravenous administration, allowing normal protein production. Studies revealed the success of the drug showing elevated protein production not just in the nervous system but also in peripheral organs. Therefore, the optimization of the drug could act as a single-dose treatment for patients affected by MLD, increasing their survival rate.