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)

Peroxisomal very long-chain fatty acid transport is targeted by herpesviruses and the antiviral host response

https://www.nature.com/articles/s42003-022-03867-y

This article highlights the connection between viruses and how they interact with human cells causing the appearance of adrenoleukodystrophy (ALD). The underlying cause of ALD is mutations in the ABCD1 gene responsible for producing a transfer protein that transports very long-chain fatty acids (VLCFA) to specific cell structures for their degradation. When mutations occur, the protein is impaired resulting in the accumulation of VLCFA inside the cells (mainly the ones of the nervous system) leading to the loss of their function and therefore loss of life. Studies have shown that some types of viruses are able to cause ALD and other conditions in normally healthy individuals. Viruses survive in the human body by entering cells and using their molecular machinery to replicate. In this case, some viruses interfere with the VLCFA degradation process as they prevent their transportation to organelles responsible for their metabolism and therefore alter homeostasis. Accumulation of VLCFA can alter the cell's rigidity and membrane structure allowing the virus to easily enter the cell and complete its life cycle. In all cases, viruses can trigger abnormal levels of VLCFA which may result in ALD and general neuroinflammation. More studies must be conducted to understand the mechanism underlying the viruses' ability to cause the accumulation of VLCFA, and how it affects the pathology of host cells.

Minoryx's Marketing Authorization Application for its lead candidate leriglitazone validated by EMA for orphan indication X-linked Adrenoleukodystrophy (X-ALD)

https://www.minoryx.com/media/minoryx%E2%80%98s-marketing-authorization-application-for-its-lead-candidate-leriglitazone-validated-by-ema-for-orphan-indication-x-linked-adrenoleukodystrophy-(x-ald)/

Minoryx Therapeutics is a biotech company that focuses on developing new therapies to treat disorders involving the central nervous system. The company has announced that they have applied for a Marketing Authorisation Application (MAA) with the European Medicines Agency (EMA). With an approved MAA, the company will be able to place Leriglitazone, their leading candidate for treating X-linked adrenoleukodystrophy (X-ALD) in adult males, onto the market. Leriglitazone is a new treatment developed by Minoryx. The MAA put forth by the company is based on the results of their ADVANCE study. The study was conducted in the U.S and Europe. The study's observations

demonstrated that Leriglitazone could decrease the progression of brain damage, the development of new cases of cerebral ALD (cALD), and the advancement of associated symptoms such as balance deterioration. Both paediatric and adult patients affected by X-ALD are at risk of developing cALD, leading to severe brain inflammation, permanent disability, and loss of life within 2-4 years. Minoryx is also in collaboration with another clinical trial, NEXUS. The NEXUS study will include paediatric patients with X-ALD. Minoryx is working cooperatively with the EMA to ensure their product, Leriglitazone will be available for commercialisation and readily accessible to patients affected by X-ALD. The company is also discussing with the Food and Drug Administration (FDA) to gain approval to distribute the medication in the U.S. Minoryx Therapeutics is determined to distribute life-changing medications to a more considerable proportion of those affected by X-ALD. If Leriglitazone is approved, it will be the market's first therapeutic option available for adult X-ALD patients.

High incidence of null variants identified from newborn screening of X-linked adrenoleukodystrophy in Taiwan

https://pubmed.ncbi.nlm.nih.gov/36046390/

A study was conducted in Taiwan to demonstrate the efficacy and necessity of newborn screening for early implementation of treatment for Adrenoleukodystrophy (ALD). Currently, the treatment for ALD is to undergo a bone marrow transplantation. The treatment is most effective when it is implemented as soon as abnormalities within the brain appear. The study was performed at three different tiers. The first tier screened 181,342 newborns within clinics and hospitals. Those who presented within a certain threshold of a specific biomarker were screened a second time. A biomarker is a substance that can indicate the presence of a disease. If the cohort part of the second screening presented with certain levels of the targeted biomarker, they were then sent for a third confirmatory screening where the mutation of the ABCD1 gene was categorised. Newborns part of this third cohort were categorised based on three criteria: 1) If the mutation of the ABCD1 gene was disease-causing, 2) If the mutation of the ABCD1 gene may likely cause disease or 3) If the significance of the mutation of the ABCD1 could not be determined. Implementation of newborn screening has demonstrated a high success rate in diagnosing ALD in infantile patients in Taiwan. The results from the study correlated with the statistics in other U.S studies as well. With newborn screening, treatment with a bone marrow transplant can be implemented early to provide patients with the best long-term outcome.

Adrenomyeloneuropathy (AMN)

Braintale showcases together with Minoryx data from its biomarker platform for disease and treatment monitoring of X-linked Adrenoleukodystrophy and strengthens collaboration

https://www.braintale.eu/american-academy-of-neurology-aan-2022-braintale-showcases-together-with-minoryx-data-from-its-biomarker-platform-for-disease-and-treatment-monitoring-of-x-linked-adrenoleukodystrophy-and/

Braintale has partnered with Minoryx, a biotechnology company developing a treatment for adult X-linked adrenoleukodystrophy (X-ALD) patients, to showcase the effectiveness of Minoryx's new treatment, Leriglitazone. X-ALD is a neurogenerative disease. The most common variation affecting adult male and female patients is adrenomyeloneuropathy (AMN). Braintale has a digital platform that tracks biological markers (biomarkers). Biomarkers are things within the body that can show the presence of a particular disease and indicate how far the disease has progressed. Braintale and

Minoryx demonstrated that MyelinDex, a biomarker used by Braintale, is an appropriate marker for monitoring disease progression and tracking therapeutic effectiveness. The platform has also demonstrated that Leriglitazone is an effective treatment for adult male patients affected by AMN and its potential to improve the damages sustained to the brain during the disease. The collaboration between the two companies has increased for MyelinDex to be used in future clinical trials. Using MyelinDex as a biomarker in more trials will broaden the understanding of X-ALD whilst characterising the benefits of Leriglitazone further. The collaboration will help put Leriglitazone on the market so it can become available to patients of AMN.

Alexander disease

Alexander disease GFAP R239C mutant shows increased susceptibility to lipoxidation and elicits mitochondrial dysfunction and oxidative stress

https://pubmed.ncbi.nlm.nih.gov/35933901/

This article suggests that the rare Alexander's disease (AxD) is caused by mutations that lead to lipoxidation, mitochondrial dysfunction, and oxidative stress resulting in the various symptoms of the condition. The underlying causes of AxD are mutations in genes producing a protein, known as Glial Fibrillary Acidic Protein (GFAP), abundant in the nervous system and responsible for maintaining the shape and function of neural cells. When the GFAP mutations are present, progressive destruction of the white matter and brain cells occurs, allowing the appearance of symptoms such as seizures and neuronal impairment which can lead to the loss of life of the patient. Even though the cause of the condition is well known, the pathology involved is not studied excessively due to its rarity. Recent studies showed that the mutant GFAP strand named GFAP R239C possesses specific characteristics that justify the appearance of certain symptoms. One example is the susceptibility of mutant cells to lipoxidation, which is the procedure where lipid by-products are joined with essential molecules such as proteins and genetic material. This produces toxic substances in the cell, damaging the genetic material and resulting in its loss of function. Another example is mitochondrial dysfunction which refers to the functional impairment of mitochondria, cell structures responsible for producing energy. It is shown that the production of GFAP R329C alters the physiological structure and therefore function of the mitochondria, due to chemical changes in the cell's environment. Finally, abnormal oxidative stress has been recorded on the mutant neural cells, which refers to the toxic by-products produced by the metabolism of cellular substances. Particularly due to the expression of GFAP R239C the cells indicated a higher amount of those toxic substances, leading to cell dysfunction. Overall, understanding the condition's pathology can result in the development of successful treatment options due to the scientist's ability to target the symptoms of the disease and easing the symptoms of the condition will allow for better life quality for the patients.

Identification of association fibers using ex vivo diffusion tractography in Alexander disease brains

https://pubmed.ncbi.nlm.nih.gov/35983725/

This article identifies the association fibers that influence Alexander's disease's progression and severity, using multiple brain tests including diffusion tractography. Alexander's disease is a rare, neurological disorder affecting brain cells known as astrocytes. It is caused by mutations in the gene responsible for the normal production of glial fibrillary acidic protein (GFAP), which code for intermediate filaments in astrocytes. The term intermediate filaments refer to the fibrous network

that supports the cell. In this condition, GFAP and other proteins accumulate inside the cells, causing astrocytes' destruction due to the formation of Rosenthal fibers (RFs). As a result, deterioration of cells in the brain allow the appearance of serious and often life limiting symptoms, such as developmental delays, progressive neurological dysfunction, epilepsy, and general ataxia. Due to the severity of the disease, a medical procedure called ex vivo diffusion tractography was completed to identify the mutated fibers of the brain and to illustrate how they influence both the severity and the progression of the condition. Specifically, tractography is an imaging technique used to examine the connectivity of the human brain as well as the different fibers involved, based on the properties of the white matter in the brain. The studies were made using specimens from patients of different ages and sex revealing differences in the quality and quantity of the fibers. Generally, long association fibers showed significant sparing, short association fibers were decreased while radially directional fibers were preserved. Via this test, the correlation between the symptoms of the disease and the underlying cause is achieved, allowing successful treatment and enhanced understanding of the condition's manifestation. However, further studies are required to identify the exact effects of the association fibers and how they cause disease thus allowing the understanding of various neurodegenerative diseases involved in astrocyte dysfunction.

Alpha Mannosidosis

SPARKLE registry, Europe's first registry dedicated to collecting real-world evidence in patients with Alpha Mannosidosis, has enrolled more than 50 patients across Europe

https://www.prnewswire.com/news-releases/chiesi-global-rare-diseases-announces-presentations-on-lysosomal-storage-diseases-at-the-society-for-the-study-of-inborn-errors-of-metabolism-annual-symposium-301616952.html

Chiesi Global Rare Diseases is a company focusing on rare and ultra-rare diseases. Chiesi Global Rare Diseases was established to bring innovative treatments for patients affected by rare and ultra-rare diseases to improve their well-being and care for patients and caregivers. The company has detailed the importance of continuous communication between doctors and patients. The dialogue is crucial in personalising the treatment plans for those affected by lysosomal-storage diseases such as Alpha Mannosidosis. Alpha Mannosidosis is an ultra-rare heredity disease due to a mutation of the MAN2B1 gene. The mutation causes an enzyme, alpha-mannosidase, not to break down complex sugars within the cell. As a result, there is a harmful build-up of these sugars within cells throughout the body. There is limited knowledge about the disease, so the company is working with the scientific community to increase awareness and information about Alpha Mannosidosis. Velmanase Alfa is the first drug therapy for treating Alpha Mannosidosis. The drug has been authorised by the European Medicines Agency (EMA). Velmanase Alfa is an enzyme-replacement therapy (ERT) performed by supplementing normal alpha-mannosidase in the body. This way, the cells in the body can successfully break down complex sugars. The company presented data on the long-term efficacy of Velmanase Alfa. In addition, they have also presented the SPARKLE registry, the first European registry dedicated to collecting information from patients with Alpha Mannosidosis regardless of their treatment plans. The registry aims to collect information regarding the progression of the disease and the long-term effectiveness of Velmanase Alfa. Chiesi Global Rare Diseases is working to increase knowledge of lysosomal-storage diseases such as Alpha Mannosidosis. With increased information, more therapies can be developed that can be used for tailored treatment plans to suit different patients.

Canavan Disease

Myrtelle's rAAV-Olig001-ASPA Gene Therapy Candidate for Canavan Disease Receives Advanced Therapy Medicinal Product Classification from the European Medicines Agency

https://myrtellegtx.com/myrtelles-raav-olig001-aspa-gene-therapy-candidate-for-canavan-disease-receives-advanced-therapy-medicinal-product-classification-from-the-european-medicines-agency/

Myrtelle is a gene therapy company that focuses on developing innovative treatments for neurodegenerative diseases. The company has announced that the European Medicines Agency (EMA) has categorised its leading gene therapy candidate for Canavan disease, rAAV-Olig001-ASPA, an Advanced Therapy Medicinal Product (ATMP). ATMP classifications were established for regulating cell and gene therapies and supporting the development of such products. Canavan disease (CD) is a life limiting childhood genetic disease that impacts the brain. CD results from a mutation that decreases the production of myelin, the insulating material around neurons, ultimately causing a deterioration in brain health. The disease leads to a degeneration of white matter as it progresses. As CD advances, children develop severe symptoms that can lead to loss of life within ten years. rAAV-Olig001 was developed to target the myelin cells in the brain selectively. Myelin allows for the proper functioning of neurons and makes up the white matter within the brain. The company has a program in the first phase of clinical trials to observe disease progression and the efficacy of implementing rAAV-Olig001 as a treatment plan. The therapy intends to improve myelin production, thus augmenting brain health in paediatric patients. The company has entered an agreement with Pfizer for worldwide licensing to develop and commercialise the new therapy for CD. Currently, there is no treatment for the disease, only palliative care. rAAV-Olig001 shows potential as a therapy that can decrease the disease's progression and improve the well-being of patients. The ATMP classification will assist the company in authorising the new therapy for broader accessibility to patients affected by CD.

Giant Axonal Neuropathy (GAN)

TSHA-120 treated patients in GAN demonstrated durable improvement and recoverability of sensory nerve amplitude potential (SNAP), a definitive clinical endpoint, compared to natural history

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

This article reviews the progress of Taysha gene therapies in developing successful drugs for giant axonal neuropathy (GAN) alongside with their potential effects. Giant axonal neuropathy is a rare inherited disease affecting both central and peripheral nervous systems, with symptoms appearing before age five. The first signs of the condition include muscle weakness, seizures, and lack of feeling in the limbs, characterized by progressive cognitive loss. Due to the severity of the disease Taysha gene therapies developed a drug known as TSHA-120 to stop the progression of the condition. Specifically, patients enhanced sensory and neurological function while tests confirmed the regeneration of nerve fibers, stabilizing and improving clinical symptoms. The treatment was tested in multiple cases and positive outcomes allowed the medical approval of the drug. Overall, TSHA-20 can be used as a treatment for GAN as medical results showed a decline in symptoms and general recuperation of the patient's condition.

Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)

H-ABC tubulinopathy revealed by label-free second harmonic generation microscopy

https://www.nature.com/articles/s41598-022-18370-x

This article discusses the potential use of second harmonic generation microscopy (SHG) in diagnosing H-ABC tubulinopathy by detecting changes in the tubulin network within nerve cells. The condition H-ABC is a genetic disease caused by mutations in the TUBB4A genes responsible for producing tubulins, structures that support and maintain the shape of cells. Those types of mutations mainly occur in the human nervous system, affecting the morphology of various nerve cells, and therefore altering their function causing hypomyelination and myelin degeneration. As myelin is a substance responsible for nurturing, protecting, and ensuring the correct function of nerve cells, hypomyelination and myelin degeneration can lead to atrophy in the brain and the cerebellum. To diagnose the H-ABC and other neurodegenerative diseases caused by myelin abnormalities, SHG is used as it enables the detection of changes in the intracellular tubule network. Specifically, SHG is an imaging technique that can be used as a diagnostic tool allowing the illustration of complex cell structures. Studies allowed the visualization of both healthy and mutated nerve tissues in mice, confirming the underlying cause of the disease and how it affects the myelin concentration surrounding the cells of the nervous system. Overall, advanced diagnostic tools such as SHG are required to efficiently identify the disease due to the severity of the condition, allowing for advanced treatment options.

Krabbe Disease

Forge Reports Positive Clinical Data on Brain Development and Motor Function from the RESKUE Novel Phase 1/2 Gene Therapy Trial in Patients with Krabbe Disease at the SSIEM Annual Symposium

https://www.forgebiologics.com/2022/08/30/forge-reports-positive-clinical-data-on-brain-development-and-motor-function-from-the-reskue-novel-phase-1-2-gene-therapy-trial-in-patients-with-krabbe-disease-at-the-ssiem-annual-symposium/#

Forge Biologics has developed FBX-101 to treat infantile Krabbe Disease. Krabbe disease results from the mutation of the galactocerebrosidase (GALC) gene. The disease causes progressive neurodegeneration that is often life limiting. The GALC gene is responsible for the breakdown of fats within the cell. Without a functional GALC gene, the fat, psychosine, accumulates to toxic levels within the cell, especially those in the myelin, the insulating material surrounding the nerves in the brain. The accumulation of this fat can cause severe damage to the nerves, ultimately resulting in the loss of motor functions. The current standard for treating infantile Krabbe Disease is to undergo a bone marrow transplant, and the current model has associated immune challenges. Early implementation of a transplant can help patients initially; however, they will frequently develop motor issues later on. FBX-101 is a gene-therapy replacement treatment administered after bone marrow transplants that delivers a functional copy of the GALC gene to the nervous system. The company's phase 1 clinical trial, RESKUE, has shown that the first patient tolerated FBX-101. This method of administrating FBX-101 after bone marrow transplants reduces the immune challenges associated with transplants. Additionally, the GALC gene's activity increased, and the patient demonstrated improved motor abilities and normal brain development compared to patients who only received the transplant treatment. Even though FBX-101 is still in its phase 1 clinical trials, the data presented thus far shows the potential benefits of the treatment in prolonging the life expectancy of patients with Krabbe

Disease. The administration of FBX-101 will also reduce the adverse immune side effects associated with bone marrow transplants, making for easier recoveries after the treatment.

Mucolipidosis type IV

TPC2 rescues lysosomal storage in mucolipidosis type IV, Niemann–Pick type C1, and Batten disease

https://www.embopress.org/doi/full/10.15252/emmm.202115377?cookieSet=1

This article highlights the role of TPC2 molecules in preventing lysosomal destruction and therefore preventing lysosomal storage diseases (LSDs), such as mucolipidosis type IV. Lysosomes are structures within cells responsible for the metabolism and the degradation of molecules. When the normal lysosomal function is impaired, LSDs can give rise to various serious neurological conditions usually having early-onset symptoms alongside with serious health complications for the patients. Due to the severity of the LSDs, multiple experiments had been made to find successful treatment with minor side effects. Studies showed that the underlying cause of LSDs is mutations in genes that produce proteins located in the lysosome's membrane. Possible treatments involve a small molecule known as TPC2, that activates mechanisms resulting in the amelioration of symptoms. In particular, a characteristic of LSDs is the accumulation of substances that lead to cell dysfunction. However, TPC2 is able to promote the cellular excretion of the substances accumulated inside nerve cells, permitting their normal function. More experiments must be made to properly understand the underlying cause of LSDs and how different treatments restore the physiological function of the nerve cells in patients.

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