Alex TLC Research Summary
MAY 2022

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

Adrenoleukodystrophy (ALD)

Restless Legs Syndrome in X-linked Adrenoleukodystrophy
https://reader.elsevier.com/reader/sd/pii/S138994572200051X?token=A147979A9E7F6D40DCC4D97A66302B80B76F9101A60294E9B4348B3768B9412FBE16D52159927FE4C6795DD0971771AF&originRegion=eu-west-1&originCreation=20220411092053

This article examines the association between Restless Legs Syndrome (RLS) and X-linked (specific way of inheriting genes) Adrenoleukodystrophy. This condition, also known as ALD, refers to a neurodegenerative (loss of neurons or their function) disease caused by the production of an impaired protein, affecting the metabolism of very long acid chains. From research conducted with 32 participants, ALD turned out to be linked to RLS. All participants were over 18 years old with the median age being 34. From the 32 participants, 21 were female and 11 were male. The RL syndrome suggests intense urge to move the lower limbs, interfering with sleep and impairing the quality of life. The research showed possible interrelation between RLS and gender, as females were the participants affected the most. Furthermore, neuronal loss caused by ALD, can lead to RLS. Acknowledgement of the RLS's prevalence in patients with ALD is a useful way to propose treatments about the syndrome enabling a better life quality for the patients.

Newborn Screen for X-Linked Adrenoleukodystrophy Using Flow Injection Tandem Mass Spectrometry in Negative Ion Mode
https://www.mdpi.com/2409-515X/8/2/27/htm

This article reviews the usage of a technique called Flow Injection Tandem Mass Spectrometry in Negative Ion Mode (FIA) to detect and diagnose Adrenoleukodystrophy. This genetic condition refers to the accumulation of toxic substances in the cells, due to the production of an impaired protein, resulting in death of neuronic cells. For diagnosing the disease, a specific biomarker is used in newborn screening. Patients with Adrenoleukodystrophy are characterised by an accumulation of that specific biomarker which enables diagnosis feasible. During newborn screening, blood from newborns is taken and examined. Typical newborn screening was found to identify newborns having a risk of developing Adrenoleukodystrophy. However, through a method known as FIA, both the validity and speed of diagnosis are improved, leading to quicker diagnosis. This new approach can also identify the false positive samples, which are samples wrongly characterised as positive. Overall, this new technique can be used to correctly diagnose Adrenoleukodystrophy leading to early and effective treatment which can improve the patient's life.

Alexander Disease

Anastasis drives senescence and non-cell autonomous neurodegeneration in the astrogliopathy Alexander disease

https://pubmed.ncbi.nlm.nih.gov/35105675/

This article reviews the process of anastasis and how it affects a condition known as Alexander syndrome. Anastasis is described as the ability of the cell to avoid cell death. Several studies have been conducted using animal and human cells to understand the complex mechanism of anastasis, as the process is linked to the appearance of specific medical conditions. For example, Alexander disease is a condition where anastasis of cells known as astrocytic glia occur, leading to the production of toxic substances. In particular, astrocytic glia are neurons located in the central nervous system and the brain, playing a major role in transferring electrical messages between the cells. When the astrocytic glia goes through anastasis, production and accumulation of toxic substances result to the destruction of neurons (or their loss of function) which may give rise to the Alexander syndrome. Overall, acknowledgment of the mechanisms involved in anastasis could lead to better understanding of Alexander disease. Therefore, development of a successful treatment is feasible, resulting to better quality life for the patients.

Adrenomyeloneuropathy (AMN)

Updated Preclinical Data Support Potential of First AAV-Based Gene Therapy as a Treatment for Adrenomyeloneuropathy

https://swanbiotx.com/investors-and-media/updated-preclinical-data-support-potential-of-first-aav-based-gene-therapy-as-a-treatment-for-adrenomyeloneuropathy/

This article reviews preclinical data supporting the efficacy of SBT101 gene therapy as a treatment for Adrenomyeloneuropathy (AMN). This neurological condition refers to the loss of neurons -or their function- of the central nervous system affecting, especially the spinal cord and other organs such as the adrenal glands. This occurs due to the expression of an impaired gene called ABCD1 which leads to the production of mutant proteins. There are no yet confirmed cures for this condition but SBT101 could act as a potential gene therapy. Gene therapy includes targeted changes in the genes (structures carrying the genetic information of an organism) to treat, delay or stop a disease. Specifically, SBT101 gene therapy acts by increasing the healthy ABCD1 gene expression, showing a dose-dependent improvement of the condition. Preclinical data also revealed the absence of adverse effects without affecting the rest of the organism's tissues. As a result, SBT101 gene therapy could be an effective and safe treatment used for patients suffering from AMN without the risk of adverse effects. The severity of the disease's symptoms can be therefore delayed, allowing a better life quality for the patients diagnosed with AMN.

Poxel Announces PXL770 Awarded FDA Fast Track Designation for X-linked Adrenoleukodystrophy

https://www.newcontact.eu/secure/media/com_newcap/files/files/PXL770%20FTD_ENG_2022%2004%2011%20vFinal.pdf

This article refers to the Fast Track Designation (FTD) award to Poxel for the design of the PXL770 drug, used to treat Adrenoleukodystrophy (ALD). Adrenoleukodystrophy is an inherited neurodegenerative (loss of neurons or their function) disease caused by the mutant variant of the ABCD1 gene which produces an impaired protein responsible for metabolising very long chain fatty acids. There are two forms of the condition, one is the cerebral ALD where neurons in the central nervous system and brain are destroyed whereas adrenomyeloneuropathy (AMN) affects the peripheral nerves of the spinal cord. There is not a definite cure about the condition, rendering the creation of a treatment an urgent need. Poxel, a biopharmaceutical company devoted on developing drugs for rare and chronic

disease, was awarded with FTD, which allows the development of drugs to resolve unmet urgent medical needs. Specifically, the Food and Drug Administration (FDA) granted FTD for the development of PXL770 drug which is used for treating ALD. This will help scientists evolve and produce an effective drug that would delay and probably treat ALD, rendering life easier for the patients suffering from this condition.

Cerebrotendinous Xanthomatosis (CTX)

Voice of the Patient report from the Patient-Focused Drug Development Meeting on Cerebrotendinous Xanthomatosis (CTX)
https://ctxalliance.org/wp-content/uploads/2022/04/Unlock-CTX-meeting-report-FINAL-digital-file.pdf
Cerebrotendinous xanthomatosis (CTX) is a very rare genetic disease caused by a mutation of the gene CYP27A1. The CTX global community members came together to discuss their experiences regarding diagnosis, treatment, and how the disease has impacted their lives. The burdens members of the community have faced frequently include lengthy diagnosis periods, the symptoms affecting the patients and the impacts these symptoms have had on patients and their families.
The members who spoke at the meeting all had unique experiences with diagnoses. The age of diagnosis ranged from a few days old up to adulthood. Similarly, with the symptoms experienced. CTX patients present with a wide variety of symptoms, but a few are common; cataracts, chronic diarrhoea, developmental delays and issues with the quality of life. Many patients diagnosed in adulthood recalled childhood issues with cataracts and diarrhoea. Many members detailed the strain on family dynamics and emotional and mental well-being that having or caring for someone with CTX has had on them.
There is currently one treatment used to treat CTX directly, an off-label replacement therapy, chenodeoxycholic acid (CDCA). Treatment with CDCA has proven to improve some of the symptoms of CTX but not all. Because CDCA is an off-label treatment, there have been many times when access to the medication was hindered, resulting in the regression of a patient's symptoms. Individuals who have used CDCA over a prolonged time have noted its reduced efficiency.
Implementing CDCA early on is essential. Additional support such as occupational and physical therapy would also benefit patients long-term. Meetings like this also allow community members to come together to support each other and learn from others on how to help loved ones suffering from CTX adequately.

Krabbe disease

PassageBio announces publication of preclinical data that supports ongoing clinical study of PBKR03 in Krabbe Disease
Press Release: **https://www.passagebio.com/investors-and-news/press-releases-and-statements/news-details/2022/Passage-Bio-Announces-Publication-of-Preclinical-Data-that-Support-Ongoing-Clinical-Study-of-PBKR03-in-Krabbe-Disease/default.aspx**
Clinical Trial Information: **https://www.alextlc.org/passage-bio-press-release-krabbe-disease/**
Note: clinical site open in the Netherlands and site soon to open in Manchester
PassageBio. Inc is a medical company that creates gene therapy medication in clinical settings. The company focuses on creating therapies that will target central nervous system (CNS) disorders. Disorders of the CNS often result in degeneration of cognitive and movement abilities. Researchers recently published a paper detailing the studies using PBKR03, a gene replacement therapy to treat infantile Krabbe Disease.

Krabbe Disease is a rare disorder characterised by the loss of developmental milestones previously achieved, apnoea, peripheral neuropathy, severe weakness, a lack of response to stimuli, seizures, blindness, and deafness. The study initially used mice where they replicated the disease and its behaviour as it would be seen in a human infant. They then treated the mice with PBKR03. Improvements in the signs of the disease were observed. PassageBio. Inc. then moved onward using a canine model using the same gene therapy. They observed improvements in mobility without any assistive devices, functioning of the nerves and survival. These results were also achieved without bone-marrow transplants or immune suppressant medications.

The gene replacement therapy demonstrated its ability to decrease the progression of the disease and damage caused by Krabbe Disease. As a result of the studies done on both small and large animals, the company has decided to use PBKR03 to treat infantile Krabbe Disease. Since publishing the paper, they have administered the gene therapy to their first candidate, a child with infantile Krabbe Disease.

With this method of treating Krabbe disease, treatment can be less physically and mentally strenuous than other methods such as a bone marrow transplant and immune suppression. The quality of life and life expectancy for patients suffering from this can increase substantially. With PKBR03 being approved for clinical trials, due to the robust preclinical data which underpinned the companies decision to move forward with PBKR03 for infantile Krabbe disease.

Metachromatic Leukodystrophy (MLD)

Orchard Therapeutics Announces Reimbursement Agreement Making Libmeldy Available for All Eligible MLD Patients in Italy

https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-reimbursement-agreement-making

Orchard Therapeutics is a leading company in gene therapies. They recently announced a reimbursement agreement with the Italian Medicines Company, Agenzia Italiana del Farmaco (AIFA), to allow all children suffering from Metachromatic Leukodystrophy (MLD) in Europe to have access to Libmeldy. This is the second reimbursement Orchard Therapeutics has achieved covering all MLD patients within the European market.

MLD is a rare inherited disease that can be life-threatening. It results in the progressive degeneration of the nervous system, impacting an individual's motor, behavioural and cognitive abilities. Libmeldy is used for treating patients who present with early-onset MLD. The qualifications to be approved for using Libmeldy include:

i) The early infantile or late juvenile variations with no visible clinical manifestations.
ii) In the early juvenile form, clinical manifestations have appeared, but mobility has not been hindered severely, and cognitive abilities have not declined.

Libmeldy is the first approved therapy for qualifying patients with early-onset MLD. Although Libmeldy has been approved for use on children suffering from MLD, it is not without side effects. It has the associated risks that come with gene therapy. Other medical interventions such as bone marrow transplants are employed first before Libmeldy, and these have their own associated risks. However, when Libmeldy is administered, information is made available on how to handle any adverse reactions that may be observed in patients.

Patients and carers of patients suffering from early-onset MLD located within the European market for Libmeldy will now have greater access to the therapy. Although the

therapy has undergone safety evaluations and is used clinically, it is also important to consider the risks associated with Libmeldy as gene therapy. Gene Therapy using Libmeldy has been approved for use within the NHS for those patients with MLD who meet the criteria.

Rare Disease

Improving Transition from Paediatric to Adult Care for Young People Living with a Rare Disease

https://www.costellomedical.com/wp-content/uploads/2022/03/Rare-Diseases-Paediatric-to-Adult-Care-Transition_Roundtable-Report.pdf

The improvements in treating rare and complex diseases have improved the quality of life and life expectancy for patients. More children who were diagnosed with these diseases are now reaching adulthood. As a result, pressure has been placed on healthcare facilities to implement age-appropriate services that can help the continuity of quality care. Costello Medicine and Cambridge Rare Disease Network have hosted a roundtable discussion to see where improvements can be made to ease patients' experience with rare and complex diseases. Karen Harrison, from Alex TLC, was part of the team and shared both her own personal experiences, and also those of the families supported within the charity, which helped to guide the report.

Communication was an issue as there was insufficient liaising between patients and specialists. The timing of the transition also proved to be dissatisfactory. Communications of role changes and expectations of patients, their guardians and specialists were not done early enough for the parties to feel sufficiently prepared. The stark difference between paediatric care and adult care proved stressful for many and induced a sense of fear and reluctance within patients to proceed. Various solutions were brainstormed to target the main issues brought forward. Multidisciplinary team meetings were proposed. Patients and their guardians would meet with both the adult and paediatric teams early on to discuss and plan accordingly for the future. This would help improve communication, co-ordination and timing surrounding the transition period before patients are moved to adult services.

Discussions around age-appropriate services included altering the interior of established wards to suit the tastes of adolescents and young adults or creating new wards. Text and email were also proposed as communication methods rather than face-to-face communication. When patients and carers are allowed space to talk and share experiences, solutions can be proposed and implemented for the future. Roundtable discussions like these help the community to identify and target problems and ensure that accountability for patient care is taken.
