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 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 is a clinical stage biopharmaceutical company with the focus of 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 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.

Alexander Disease

Adult-Onset Alexander Disease: New Causal Sequence Variant in the GFAP Gene
https://ng.neurology.org/content/nng/8/3/e681.full.pdf

This article reviews the discovery of a mutation in the GFAP gene responsible for the appearance of adult-onset Alexander Disease (AOAD). Alexander disease is a serious neurological condition characterized by central nervous system disorders such as brain tissue degeneration, autonomic dysfunction, clumsiness, and general progressive muscle weakness. The condition can be diagnosed via brain scans whilst mutation in the glial fibrillary acid protein gene (GFAP) is found to underlie the disease. The protein coded by the GFAP is used to maintain and shape specific neural cells, known as astrocytes (cells in the central nervous

system). When the gene is mutated, the protein accumulates in the astrocytes due to shape impairments, causing AOAD symptoms. The identification of the mutant gene was possible through a medical case of a 57-year-old male experiencing AOAD. Accordingly, to the patient, symptoms appeared one year after a mild brain injury. However, brain scans showed typical signs of the condition, while genome studies revealed a mutant variant of the GFAP gene. Further studies on the GFAP identified the gene as a pathogen and responsible for causing AOAD. Overall, even if brain scans are the primary successful method used to identify the condition, upcoming research needs to address if the condition can be manifested after a brain injury or if the accumulation of GFAP mutated proteins is the only reason for AOAD appearance.

Adrenomyeloneuropathy (AMN)

Minoryx raises €51 million to support Marketing Authorization Application and launch preparations for X-linked Adrenoleukodystrophy (X-ALD) therapy
https://www.minoryx.com/media/minoryx-raises-e51-million-to-support-marketing-authorization-application-and-launch-preparations-for-x-linked-adrenoleukodystrophy-(x-ald)-therapy/

Minoryx is a Phase III biotech company that has managed to raise 51 million euros to support their research into treating disorders of the central nervous system (CNS). The company, which is based in Spain, will use the funding to further develop and prepare the drug Leriglitazone for males affected by adrenomyeloneuropathy (AMN) within the EU. AMN is one of the more common forms of the CNS disorder X-linked adrenoleukodystrophy (X-ALD). It is an inherited neurodegenerative disease characterised by progressive spastic inability to move to your legs, sensory dysfunction and incontinence. Studies show that 60% of adult patients that develop AMN will also develop the other common variation of X-ALD, Cerebral adrenoleukodystrophy (cALD). The results of this are often permanent disability and loss of life within 2-4 years of developing cALD. Clinical trials of Leriglitazone have demonstrated that the drug can reduce the damages caused within the brain due to the disease. With the funding received, Minoryx is working towards making the drug Leriglitazone available within the United States of America. They are collaborating with the U.S. Food and Drug Administration (FDA) to ensure the drug's approval. The company will also use the funding to expand the availability of the drug to female and paediatric patients suffering from AMN as well. Currently, there is no approved drug treatment available for patients affected by AMN. With the funding that Minoryx has received, they will be able to rapidly develop and distribute Leriglitazone to a broader demographic of patients beside male patients residing in the EU.

Lysosomal Storage Disorders

Label-free multiplex electrochemical immunosensor for early diagnosis of lysosomal storage disorders
https://www.researchgate.net/publication/361086405_Label-free_multiplex_electrochemical_immunosensor_for_early_diagnosis_of_lysosomal_storage_disorders

This article refers to the creation of a specific immunosensor able to detect lysosomal storage disorders (LSD) in the primary stage, allowing early diagnosis and therefore early treatment. Lysosomal storage disorders are inherited and characterized by an accumulation of lipids in cells. This can result in neurological impairments affecting parts of the brain and multiple organs. The patients seem normal at birth with the first symptoms appearing during childhood. When the condition is diagnosed on-set, treatment is available. LSDs are usually detected with the help of biological methods that can be time-consuming, expensive, or even hard to achieve due to the large sample size needed. For that reason, the production of an immunosensor, a sensor able to detect abnormal quantities of a substance, offers an almost

immediate diagnosis allowing for early treatment. Using that specific immunosensor, LSDs such as Krabbe disease can be identified. The sensor is used to identify the Krabbe condition where there is a deficiency of an enzyme known to degrade toxic waste in the white matter of the brain. All the LSDs have a devastating effect if they remain untreated or if they are treated late. Hence, the creation of the specific immunosensor is able to detect LSDs early enough to prevent the symptoms, allowing for a better life quality for patients and their families.

Metachromatic Leukodystrophy (MLD)

Passage Bio receives FDA clearance of IND application for PBML04 for treatment of Metachromatic Leukodystrophy
https://www.passagebio.com/investors-and-news/press-releases-and-statements/news-details/2022/Passage-Bio-Receives-FDA-Clearance-of-IND-Application-for-PBML04-for-Treatment-of-Metachromatic-Leukodystrophy/default.aspx

This article reviews the success of Passage Bio to proceed with the investigation of a new drug (IND) known as PBML04 used to treat metachromatic leukodystrophy (MLD). The company is mostly focused on developing drugs for central nervous system disorders, such as MLD using gene therapies (replacing the impaired genes with healthy ones). In this case, MLD is a fatal inherited lysosomal disease, causing deficiency of the arylsulfatase-A (ARSA) enzyme resulting in the accumulation of toxic sulfatides in both central and peripheral nervous systems. Lysosomal diseases affect lysosomes, organelles in the cell which contain enzymes responsible for the metabolism of toxic substances, causing their abnormal concentration in cells. As a result, MLD is characterized by progressive muscle loss, weakness, and developmental delays having a high loss of life within the first five years of age. Treatment with PBML04 targets early-onset MLD via the functional copies of the ARSA gene. The success of the new drug could allow the establishment of a new, innovative treatment for the early stage MLD, delaying or even preventing the symptoms of the condition.

Rare Diseases

Mental health care for rare disease in the UK – recommendations from a quantitative survey and multi-stakeholder workshop
https://www.researchgate.net/publication/360606301_Mental_health_care_for_rare_disease_in_the_UK_-_recommendations_from_a_quantitative_survey_and_multi-stakeholder_workshop

In the UK alone, an estimated 3.5 million individuals are impacted by rare conditions. A study was performed to determine how the psychological consequences of living with a rare condition has affected both carers and patients. This study aimed to demonstrate the effects through a systemic analysis. The findings of the study would be used in developing recommendations and that could become policies to improve the experience of these individuals. Initially, researchers reviewed previous studies around the subject to create a foundation for the basis of the study. 8 carers and 8 patients were interviewed about the mental health implications that rare conditions have had in their lives and a large-scale survey was conducted. The survey relied on the respondents' self-assessment of their experiences since the diagnosis of a rare condition. The assessments revolved around the themes of; the emotional impact of the rare disease, events that promoted further stress, the quality of care received, availability of professional psychological support and other sources of support. The study found that there were many factors that exacerbated the negative impacts on the mental wellbeing of both patients and carers. Many experienced an increased strain on their daily experiences due to a lack of awareness from the public as well as healthcare professionals. Individuals reported difficulty accessing both financial and mental support throughout their experience. Recommendations were proposed to improve the care of the mental wellbeing of patients and carers. This included healthcare professionals to increase their knowledge around rare diseases so they can approach the

topic with the necessary sensitivity and guide carers and patients to the appropriate support structures, for healthcare professionals to routinely check on the mental wellbeing of those impacted by rare diseases, and that co-ordinated care should also include handling the mental health of carers and patients.

Valuing the "Burden" and Impact of Rare Diseases: A Scoping Review
https://doi.org/10.3389/fphar.2022.914338

Within Europe alone, approximately 30 million people are affected by a rare disease. The wide range of symptoms impact the lives of people in numerous manners. The burden of disease that determines the impact includes the clinical, economic and/or political implications associated with the disease. This burden is expressed as the cost of disease and/or disability exerted on the individual, society, or healthcare system. Various experts in rare diseases were interviewed in this review to find the appropriate tools for measuring the burden. The most prevalent method of examining the burden of rare diseases was to use the Cost-Of-Illness (COI) approach. This method included the costs associated with direct medical care (e.g., physician visits) and indirect care (e.g., education-related costs). Studies from European countries and non-European countries were used to compile the data for this review. Surveys and questionnaires from patients and carers were utilised to provide a more personal perspective. Although this review made use of both experts and a wide range of available data, disparities between what was included as a COI complicated the review. Several studies used to compile the data for this review did not include other factors such as the cost of mental health support facilities. Furthermore, many rare diseases do not have clinical treatments and thus were not included in multiple studies regarding the COI. The data available in the literature examined focused on one or few diseases. In the U.S. there have been efforts to conduct a wide range survey of the COI on multiple diseases. Comprehensive data on the COI around rare diseases is important. The allocation of funds towards special care facilities makes use of the COI. It provides the necessary stakeholders with solid information to justify further investments in researching and developing treatments for rare diseases.