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)

Sex-specific newborn screening for X-Linked adrenoleukodystrophy
https://onlinelibrary.wiley.com/doi/10.1002/jimd.12571

Role of MRI in X-linked adrenoleukodystrophy—A case report
https://www.sciencedirect.com/science/article/pii/S1930043322007130

Spectrum of Clinical and Imaging Characteristics of 48 X-Linked Adrenoleukodystrophy Patients: Our Experience from a University Hospital
https://pubmed.ncbi.nlm.nih.gov/36076658/

Bluebird Bio ALD Gene Therapy - Resource for patients and families residing outside of the US
https://www.alextlc.org/bluebird-bios-gene-therapies/?fbclid=IwAR1E7p2oc5Mp74TeBYZ979ktols_8IPsc3EkGUegxFAiEybmT5217Pe4cfw

X-linked adrenoleukodystrophy patient fibroblast-iPSC-derived astrocytes reveal phenotype-specific metabolic, inflammatory, and microRNA alterations
https://www.biorxiv.org/content/10.1101/2022.09.09.507263v2.full.pdf
This article refers to the metabolic differences between the various subtypes of X-linked Adrenoleukodystrophy (ALD) as shown by novel studies using astrocytes. It is known that neural cells known as astrocytes play a major role in ALD pathogenesis. This study highlights the mechanisms underlying the symptoms of ALD and the differences observed between cALD, AMN, and healthy cells (CTL). Furthermore, patient-induced pluripotent stem cells (iPSCs) are used, as these are cells able to differentiate into any cell type including astrocytes. Results showed ABCD1 gene loss and elevated VLCFA levels in both AMN and cALD in comparison with CTL. Moreover, cALD demonstrated a higher energy demand than AMN astrocytes, which allows the appearance of inflammation. A decrease in the mitochondrial genetic material is present in both AMN and cALD, with cALD having the highest decrease. It is shown that dysfunctional mitochondria can result in the generation of reactive oxygen species, which are toxic molecules altering the normal metabolism of various substances. Nonetheless, the presence of specific immune molecules in AMN showed a better protective effect, unlike cALD astrocytes, by enhancing the recruitment of neural cells to the point of inflammation. The study allowed the comparison of chemical substances in the cells and resulted in a better understanding of the effects and causes generated by the different types of ALD. Overall, a better acknowledgment of the mechanism underlying the pathogenicity of ALD can allow the development of successful treatments for the subtypes of the disease.

Targeted Brain Delivery of Dendrimer-4-Phenylbutyrate Ameliorates Neurological Deficits in a Long Term ABCD1-Deficient Mouse Model of X-Linked Adrenoleukodystrophy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9542479/
This article refers to the development of an innovative treatment that directly targets the brain to ameliorate the symptoms of X-Linked Adrenoleukodystrophy (ALD). Adrenoleukodystrophy is a genetic condition that results from mutations in the ABCD1 gene coding for a protein able to transfer very long chain fatty acids (VLCFA). In healthy individuals, the protein transports VLCFA to the organelle responsible for its destruction. However, in patients diagnosed with ALD, non-transportation of the VLCFA leads to their accumulation in cells and specifically in cells of the nervous system, causing a cascade of symptoms such as toxicity, inflammation, and general cell dysfunction. Scientists are currently trying to find a treatment using a variant of the ABCD1 gene known as ABCD2 gene. The gene can act by replacing the action of ABCD1 gene and produce the transport protein responsible for the metabolism of VLCFA. However, for the gene to be activated, a molecule called 4-Phenylbutyrate (4PBA) is necessary. Combining the 4PBA treatment with other chemical structures will allow for lower doses and better delivery of the drug. Studies made in mice compared the efficacy of the drug in both early and late onset of the symptoms of the disease. In the first study, mice treated with the treatment before or early on the onset of the symptoms revealed significant improvements in the cells by reducing their VLCFA quantity. In a second study, treatment after the appearance of symptoms resulted in a behavioral improvement whilst no difference in the VLCFA levels was seen. Overall, early 4PBA combination treatment can allow for the amelioration of symptoms, which can possibly alter the progression of the disease and allow for a better life quality for the patient.

AMN (Adrenomyeloneuropathy)

Adrenomyeloneuropathy in a subacute combined degeneration suspect: a diagnostic dilemma
https://www.ijmedicine.com/index.php/ijam/article/view/3583/2398

Selection of clinical doses for SBT101, an AAV9-hABCD1 vector for the treatment of Adrenomyeloneuropathy
https://www.mdsabstracts.org/abstract/selection-of-clinical-doses-for-sbt101-an-aav9-habcd1-vector-for-the-treatment-of-adrenomyeloneuropathy/
In this abstract, an overview of SBT101 doses' efficacy and safety is demonstrated when treating Adrenomyeloneuropathy (AMN). AMN is an adult on-set genetic neurodegenerative disease, characterized by slow and progressive spinal cord abnormalities, resulting in loss of mobility and multiple neurological impairments. AMN is caused by mutations in the ABCD1 gene responsible for producing a protein that transfers very long chain fatty acids (VLCFAs) to the mitochondria which are organelles able to metabolize them. As there is no treatment available, scientists developed an innovative treatment using an AAV9-hABCD1 vector. The SBT101 drug allows the insertion of a functional ABCD1 gene via the AAV9-hABCD1 vector. Studies showed an increased success rate when demonstrating the safety and efficacy of the drug's dose in mice allowing for the development of the appropriate dose for human patients. Overall, SBT101 could be a possible treatment as it was proven safe and successful, allowing human trials to take place.

Alexander Disease

Identification of a novel de novo pathogenic variant in GFAP in an Iranian family with Alexander disease by whole-exome sequencing
https://pubmed.ncbi.nlm.nih.gov/36088400/

Canavan Disease

BridgeBio Pharma Presents Updated Positive Data from its BBP-812 Canavan Disease Gene Therapy Program at the 51st Annual Meeting of the Child Neurology Society
https://bridgebio.com/news/bridgebio-pharma-presents-updated-positive-data-from-its-bbp-812-canavan-disease-gene-therapy-program-at-the-51st-annual-meeting-of-the-child-neurology-society/

Myrtelle Completes Dosing of 8 Patients with Canavan Disease in Its Phase 1/2 Clinical Trial of the Investigational Gene Therapy rAAV-Olig001-ASPA
https://myrtellegtx.com/myrtelle-completes-dosing-of-8-patients-with-canavan-disease-in-its-phase-1-2-clinical-trial-of-the-investigational-gene-therapy-raav-olig001-aspa/
This article reviews the data generated by the completion of Myrtelle's investigational gene therapy rAAV-Olig001-ASPA for treating Canavan disease (CD). The underlying cause of CD is mutations in the Aspartoacylase gene (ASPA) interrupting therefore the normal production of the enzyme Aspartoacylase (ASPA) in oligodendrocytes (neural cells). This results in the impaired metabolism of a substance known as N-Acetylaspartate (NAA), leading to its accumulation in the brain and affecting the cell's function. Myrtelle was able to develop a gene therapy, using a virus to target oligodendrocytes and restore the normal function of ASPA and the metabolism of NAA. The drug is currently in Phase1/2 meaning that clinical trials in patients are now possible due to encouraging data and limited adverse effects. Three patients receiving the treatment, showed after six months, functional improvement and an increment of the white matter in the brain alongside an increment of myelin. In total, 8 patients received the treatment so far, allowing for the generation of scientific data including both the safety and the efficacy of the drug. Adverse discussions must be made by the authorities and the regulatory agencies to ensure the final phase of the clinical approval for rAAV-Olig001-ASPA. The approval of the drug will allow the treatment of the condition and halt the progression of the disease.

Krabbe Disease

Forge Biologics Announces Updated Positive Clinical Data in RESKUE, a Novel Phase 1/2 Gene Therapy Trial for Patients with Krabbe Disease
https://www.forgebiologics.com/2022/10/11/forge-biologics-announces-updated-positive-clinical-data-in-reskue-a-novel-phase-1-2-gene-therapy-trial-for-patients-with-krabbe-disease/
This article refers to the positive clinical data released by Forge Biologics for the drug FBX-101 to treat Krabbe disease. There are treatments available that can be successful in delaying the progression of the condition when performed before symptom onset. Studies showed that late treatment is not successful, as progressive loss of motor skills occurs and eventually results in loss of life. Forge Biologics was able to develop a drug known as FBX-101 which delivers a functional strand of the GALC gene in cells of the central and peripheral system, allowing motor skills improvement and prolonging the lives of patients. The drug is currently under development and in Phase 1/2 to

investigate both its efficacy and safety, in combination with the already existent treatment to increase its success. Data generated on the clinical trials, also known as RESKUE, indicate an increase of GALC enzyme activity in the blood, normal brain development, and improved motor skills. Moreover, the drug was well tolerated with minor side effects. Overall, FBX-101 could allow the treatment of Krabbe's disease and alter the progression of the disease.