



Research Summary

3-METHYLGLUTACONIC ACIDURIA TYPE 1

Triptorelin to treat premature puberty in a 3-MGA-1 patient

The subject of a recently published scientific article is the description of a patient affected by the neurological condition 3-methylglutaconic aciduria type 1 (3-MGA-1) who underwent premature or 'precocious' puberty, at the age of 4.5 years. Premature puberty is sometimes associated with other neurological conditions in children, for example, metachromatic leukodystrophy, Tay-Sachs disease and other diseases which affect the brain's white matter. This might be due to the fact that the conditions cause damage to the part of the brain which regulates the normal onset of puberty. 3-MGA-1 is an exceptionally rare disorder, with around only 40 cases ever previously reported. Patients affected by 3-MGA-1 may experience various neurological symptoms, including speech delay, quadriplegia and movement disorders. It is known that early dietary modifications (restriction of consumption of the amino acid leucine, and supplementation with carnitine), may be an effective symptom-reducing treating for 3-MGA-1 paediatric patients. In this study, the researchers were able to effectively stop puberty in this patient with use of a chemical called triptorelin. Triptorelin acts against gonadotrophin-releasing hormone, a hormone which drives the progression of puberty.

Source: <https://www.sciencedirect.com/science/article/pii/S2214426920301373>

ADRENOLEUKODYSTROPHY

Marketing Authorisation Application submitted to the EU for ALD gene therapy

Gene therapy is a type of medical treatment for conditions that are caused by genetic mutations, such as adenoleukodystrophy. Gene therapies aim to treat a condition by replacing the mutated gene with a 'corrected' version into a person's body. Recently, a Marketing Authorisation Application for a type of gene therapy known as Eli-cel, developed for the treatment of CALD, has been submitted to the European Medicines Agency. Authorisation of this treatment by the EMA would mean that Eli-cel would be allowed to be distributed in the EU. A phase 2/3 clinical trial (a trial combining phase 2, in which correct dosing and basic drug efficacy is demonstrated, and phase 3, in which a new medicine is compared to the best currently available treatment) has shown that the majority of CALD patients treated with Eli-cel retained stable neurological function following treatment. That is, most patients were alive and free from major functional disabilities after more than two years of follow-up.

Alex TLC have recently been involved with the NICE Highly Specially Treatment Appraisal process to ensure this treatment is available for patients in the UK.

Sources: <https://www.medicalbiochemist.com/2020/11/elivaldogene-autotemcel-eli-cel-ald.html>

<https://checkrare.com/gene-therapy-shows-promise-for-cerebral-adrenoleukodystrophy-cald/>

ADRENOMYELONEUROPATHY

Investigation of vitamin B6 in AMN treatment

In order to study both how disease develops in humans and, and to investigate the potential efficacy of new medicines, scientists often create animal models of disease. For example, a mouse model of adenoleukodystrophy (ALD) experiences nerve damage and motor impairment, and later in their lives develop a condition which mirrors adrenomyeloneuropathy (AMN). In this study, researchers have found that treatment of these ALD mice with extremely high doses of vitamin B6 (also known as biotin) for six months was able to eliminate the motor abnormalities and nerve damage. Although translating potential treatments from lab experiments in mice to humans can be very complicated, the authors of this study suggest that in the future, high dose biotin may be a possible treatment option for patients with AMN.

Source: <https://adrenoleukodystrophynews.com/2020/11/18/high-biotin-doses-restore-nerve-cell-health-ald-mouse-model/>

CANAVAN DISEASE

Gene therapy as a potential treatment for Canavan Disease

Canavan disease is type of genetic leukodystrophy caused by a mutation in a single gene, which under normal circumstances is responsible for producing a protein known as myelin in the brain. Myelin surrounds all the nerve cells of the body, and acts as a sort of 'insulator' for these cells, increasing the rate at which signals can travel along nerves. Without myelin, nerve impulses slow or stop, causing myriad neurological symptoms. Despite the serious and progressive nature of Canavan disease, the fact that it results due to dysfunction of just one gene means that the condition may be amenable to gene therapy, a type of therapy where a 'corrected' version of the mutated gene is introduced into a patient's body. Within the Cell and Gene Therapy Centre at the Rowan University School in New Jersey, Dr Paola Leone has been working for many years on the development of gene therapy for the treatment of Canavan disease. The rationale of the therapy is that myelin production in a Canavan disease patient may be restored by introducing of a non-mutated version of the gene into a patients' brain. A recent version of the treatment has been tested in a collaborative study between the Cell and Gene Therapy Centre and multiple hospitals across the US. Currently, although gene therapy is still an experimental treatment for Canavan disease, and not yet associated with the complete remission of symptoms, this gene therapy for Canavan disease can result in clinical improvements for patients.

Source: <https://today.rowan.edu/news/2020/11/on-the-cusp-of-a-cure-for-deadly-childhood-disease.html>

GENERAL

Genes responsible for a variety of genetic diseases occur more frequently than thought in a group of individuals from India

A recent study by MedGenome Labs in Bengaluru, India, has established that individuals in India carry mutations associated with rare genetic diseases at a much higher rate than previously thought. Genetic disorders are caused by mutations in an individuals' genes. However, humans have two copies of each one of their genes, and in most cases, in order for a disease to fully manifest, a mutation needs to be present in both copies. This type of genetic disease is known as a recessive condition, and a person who possesses only one copy of a mutated gene but does not have the condition it confers is known as a carrier. If only one mutated gene is needed for a disease to develop, this is known as a dominant condition. This is a very black and white description, and for many recessive conditions, a person may experience symptoms even if they only have one mutated copy of a gene. This is the case in ALD, for example, where a female carrier may have symptoms of the condition without being diagnosed as having overt disease. Other types of recessive genetic disease include cystic fibrosis. Previously, it was thought that fewer individuals in Asian Indian populations were carriers of genes for genetic conditions compared to individuals of white European ethnic descent. However, this study has demonstrated that in fact, in a group of 200 people, 52 (over 1 in 4 people) were carriers of one or more rare genetic disorders. Currently, the only genetic screening that is in done in India is a very limited programme for Thalassaemia and Down Syndrome. This research demonstrates the benefit of having a Genetic Variant Database for the Indian population, so that clinicians may be aware of which genetic mutations are associated with which conditions. This study also demonstrates the importance of screening tests, which can benefit couples planning a family, preventing them discovering that they are carriers of a given potentially life-threatening genetic condition only when they give birth to an affected baby.

Source: <https://www.newindianexpress.com/cities/bengaluru/2020/nov/21/many-carriers-of-genetic-disorders-among-indians-2226084.html>

Orphan Drug and Rare Paediatric Disease status awarded to potential SLC6A1-related epilepsy treatment

SLC6A1-related epilepsy is a disorder caused by mutations in the *SLCA1* gene. Patients whose *SLC6A1* gene does not function correctly usually experience a spectrum of neurological symptoms, including epilepsy and movement disorders. Taysha Gene Therapies have developed a type of gene therapy, known as TSHA-103, for the treatment of conditions caused by *SLCA1* mutation. The therapy involves the introduction of a properly functioning *SLCA1* gene into a patient's body using a viral 'vector', which transports the new version of *SLCA1* directly into a person's cells. TSHA-103 has recently been awarded both Rare Paediatric Disease and Orphan Drug designations by the US Food and Drug Administration. These designations will add momentum to further development of TSHA-103. For example, the Rare Paediatric Disease designation means that TSHA-103 will be eligible to receive a priority review voucher, meaning the therapy might be approved before December 11, 2022. The Orphan Drug designation means that Taysha Gene Therapies may benefit from the Orphan Products Development

Programme, an initiative introduced by the FDA with the aim of incentivising pharmaceutical companies to develop treatments for rare diseases. Whilst SLC6A1 is not a genetic leukodystrophy, TSHA-103 was developed using the same rationale and technology that is used to develop therapies to treat genetic leukodystrophies. The award of a Rare Paediatric Disease and Orphan Drug designation to TSHA-103 demonstrates the real potential and momentum gathering behind the use of gene therapies to treat central nervous system disorders.

Source: <https://www.businesswire.com/news/home/20201203005269/en/Taysha-Gene-Therapies-Receives-Rare-Pediatric-Disease-and-Orphan-Drug-Designations-for-TSHA-103-for-the-Treatment-of-Epilepsy-Caused-by-SLC6A1-Haploinsufficiency>

Launch of a call to the European Commission and EU Member States to introduce a co-ordinated approach to Newborn Screening for Rare Diseases

The European Union has several initiatives designed to promote research in the field of rare diseases. For example, the European Reference Networks provide a virtual platform through which scientists studying rare diseases and clinicians working with affected patients in disparate countries may discuss their work and collaborate. There are also a number of EU-specific grant schemes which provide funds for researchers working on a variety of specific rare diseases. One area still in need of improvement within the EU, however, is the development of a co-ordinated approach to Newborn Screening for Rare Disease (NBS). Although it is known that NBS can have a drastic impact on the lives of patients affected by rare diseases, by, for example, enabling early treatment to be given, generally the uptake of NBS programmes across the EU is very slow. To tackle this problem, several members of the European Parliament, as well as a number of supporting organisations, have launched a call to the European Commission and its Member States demanding that a number of interventions to improve NBS practices are introduced. These interventions include developing and introducing overarching guidelines in the field of NBS for rare diseases and developing an EU-wide platform on NBS for rare diseases. In addition, this group calls on the European Commission to work to position the EU as the central point for data collection and information on rare diseases NBS practices and encourage the exchange between its Member States on best practices. This would allow NBS programmes to be run according to the best existing science and knowledge.

Source: <https://ipopi.org/wp-content/uploads/2020/06/Call-to-Action-NBS-Screen-4-Rare.pdf>

GM1 GANGLIOSIDOSIS

Gene therapy drug for GM1 gangliosidosis in clinical trials

GM1 gangliosidosis is a disease caused by mutations in the gene *GLB1*. This gene gives instructions for the production of a certain protein which helps to break down a number of substances in the brain. When *GLB1* does not function correctly, these substances accumulate to toxic levels, causing damage to the brain and the development of neurological symptoms in the patient. A type of gene therapy for the treatment of types I and II GM1 (otherwise known as infantile and late infantile/juvenile-onset gangliosidosis), known as AXO-AAV-GM1 has been developed by the company Sio Gene Therapies Inc. AXO-AAV-GM1 delivers a 'corrected' version of the *GLB1* gene into a patient via a viral 'vector'. Unlike viruses which cause disease, the virus used by Sio Gene Therapies is harmless, and simply functions as a tool by which the functioning *GLB1* gene can be delivered into the cells of a patient. Recently, Sio Gene Therapies have announced that the first patient has been treated with a new higher dosage of AXO-AAV-GM1 in a Phase 1/2 clinical study (a study combining a phase 1 clinical trial, in which researchers assess if a treatment has the desired effect, and a phase 2 trial, in which dosage regimens and side effects are investigated). A previous group of patients were treated with a lower dose of AXO-AAV-GM1 in mid-2020, and initial results are expected to be announced soon. The introduction of a higher dose regimen was based on promising results from both laboratory research studies and from an expanded access clinical study in which patients received a lower dose of AXO-AAV-GM1.

Source: <https://www.biospace.com/article/releases/sio-gene-therapies-announces-first-patient-dosed-in-high-dose-cohort-of-axo-aav-gm1-clinical-trial-in-patients-with-gm1-gangliosidosis/>

GM2 GANGLIOSIDOSIS

Orphan Drug and Rare Paediatric Disease status awarded to potential GM2 gangliosidosis treatment

The GM2 gangliosidoses are a group of three related diseases, otherwise known by their individual names: Sandhoff disease, AB variant and Tay-Sachs disease. They are caused by mutations in a gene which carries instructions for the production of a certain protein responsible for the breakdown of another class of molecules in the brain. When this gene does not function correctly, these molecules accumulate to toxic levels, resulting in the neurological symptoms associated with GM2 gangliosidosis. A new type of therapy for the treatment for GM2 gangliosidosis, known as PLX-300, has been developed by the pharmaceutical company Polaryx Therapeutics Inc. In contrast to many new treatments for genetic leukodystrophies, PLX-300 is not a type of gene therapy, but rather a more conventional type of drug initially derived from a chemical found in plants. Polaryx Therapeutics have recently announced that PLX-300 has received both Rare Paediatric Disease and Orphan Drug designations from the US Food and Drug Administration (FDA). Orphan Drug designation means that Polaryx Therapeutics will receive several benefits from the FDA, including tax credits, eligibility for market exclusivity and a waiver of a new drug application. The Orphan Drug Designation programme was introduced to encourage pharmaceutical companies to develop therapies for rare diseases. The Rare Paediatric Disease designation means that Polaryx Therapeutics will receive a priority review voucher, meaning that, if pre-clinical and clinical studies are successful, PLX-300 will be eligible for expedited review, and so will come to market quicker. PLX-300 is currently still undergoing pre-clinical studies, but Polaryx Therapeutics hope that the treatment will move into Phase 1/2 clinical studies shortly.

Source: <https://www.prnewswire.com/news-releases/polaryx-therapeutics-receives-both-rare-pediatric-disease-and-orphan-drug-designations-for-the-treatment-of-gm2-gangliosidosis-with-plx-300-301180296.html>

HYPOMYELINATING LEUKODYSTROPHY

De novo stop-loss variants in *CLDN11* cause hypomyelinating leukodystrophy

Hypomyelinating leukodystrophy is a type of genetic disease in which myelin is lost from nerve cell fibres. Myelin is the principal component of the white matter in the brain, and is crucial for nerves cells to be able to correctly signal to one another. Hypomyelinating leukodystrophy may be caused by mutations in a variety of genes, and disease severity varies according to in which gene and where in that gene the responsible mutation has occurred. In a recent article, published in the neurology journal 'Brain', researchers describe how they have discovered a new gene to be associated with hypomyelinating leukodystrophy. This gene, *CLDN11*, contains the instructions to make the protein claudin-11, a protein found in the myelin of the central nervous system (i.e. the brain and the spinal cord). Thanks to this work, future researchers and clinicians will know to check for mutations in *CLDN11* in patients experiencing symptoms of a genetic leukodystrophy, including movement disorders and problems with speech. The identification of a disease-causing mutation in these patients will allow these patients and their families to receive more pragmatic genetic counselling, and the association of the protein claudin-11 dysfunction with hypomyelinating leukodystrophy opens the door to research into disease-modifying therapies.

Source: <https://www.sciencedirect.com/science/article/pii/S2214426920301373>

METACHROMATIC LEUKODYSTROPHY

Investigational New Drug status application submitted to the FDA for MLD gene therapy

An Investigational New Drug (IND) application for a type of gene therapy has been submitted to the Food and Drug Administration (FDA) by the pharmaceutical company Orchard Therapeutics. The treatment is known as OTL-200 (or Libmeldy), and was developed for the treatment of metachromatic leukodystrophy (MLD). In effect, this therapy aims to introduce a 'corrected' version of the mutant gene responsible for MLD into patients. In order to receive IND status, Orchard Therapeutics supplied information to the FDA on 39 patients treated over the past eight years with OTL-200 as part of clinical studies and compassionate use programmes demonstrating that OTL-200 was safe for use in humans and was able to reduce MLD disease progression. IND status means that Orchard Therapeutics can proceed further down the path towards achieving regulatory approval for the use of OTL-200 to treat MLD patients in the US, as they will now be able to transport OTL-200 across state lines to various clinical investigators, facilitating clinical trials and further studies. Encouragingly, Orchard Therapeutics have also received market authorisation for OTL-200 from the European Commission, which means that Orchard Therapeutics will have the right to market a medicine in one, several or all EU Union Member States.

Sources: <https://www.onenewspage.com/n/Press+Releases/1zluml1ss6/Orchard-Therapeutics-Announces-FDA-Clearance-of-IND-Application.htm>

<https://www.globenewswire.com/news-release/2020/12/21/2148486/0/en/Orchard-Therapeutics-Receives-EC-Approval-for-Libmeldy-for-the-Treatment-of-Early-Onset-Metachromatic-Leukodystrophy-MLD.html>

LEIGH SYNDROME

Grants awarded to two cell-science researchers at the Institute of Neurosciences in Barcelona for research into Leigh and Lesch-Nyhan syndrome

Leigh syndrome is a rare and serious genetic disorder characterised by the progressive onset of serious neurological symptoms. Leigh syndrome is known to be caused by dysfunction of a mitochondria, a component of every human cell which are responsible for generating energy. As the brain and nervous system require the most amount of energy, these are the tissues which are most affected when genetic mutations affect the function of mitochondria. Recently, a researcher named Albert Quintana, based at the Institute of Neuroscience in Barcelona, was awarded a grant to study the effect on cannabidiol (CBD) on cellular processes known to be disrupted in patients affected by Leigh syndrome. Also at the Institute of Neuroscience is Francesc Xavier Soriano Zaragoza, who has recently been awarded a grant to facilitate his study of Lesch-Nyhan syndrome. Lesch-Nyhan syndrome is caused by mutations in the gene *HPRT1*. It is known that *HPRT* dysfunction is associated with accumulation of a chemical known as ZMP, which Soriano-Zaragoza and his team believe is toxic may be contributing to the development of the neurological symptoms associated with Lesch-Nyhan syndrome. Using the funds awarded by this grant, the team of researchers plan to investigate two different methods for reducing levels of ZMP and reducing its toxic effects on cells. The first involves using very high levels of folic acid, a vitamin commonly prescribed for pregnant women due to its role in preventing birth defects such as spina bifida, and the second using a type of molecule derived from bacteria. These studies remain at the pre-clinical stage, i.e., the researchers will be conducting their experiments in cell culture and animal models of disease rather than on patients. However, these type of laboratory studies are extremely important for understanding what causes a given disease. Establishing the mechanism of disease at a subcellular level will potentially allow researchers in the future to develop targeted therapeutics.

Source: <https://www.miragenews.com/uab-researchers-awarded-la-marat-grants-to-study-rare-diseases/>

Leigh syndrome associated with TRMU gene mutations

Leigh syndrome is a rare genetic leukodystrophy characterised by the gradual onset of a variety of neurological symptoms, including motor problems, seizures and muscle weakness. In a recent scientific paper, published in the journal 'Molecular Genetics and Metabolism Reports', a group of researchers describe how they have found mutations in the gene *TRMU* in patients who have both the symptoms of Leigh syndrome and liver disease. Mutations in this gene have previously known to cause acute liver disease. However, this is the first time they have been associated with neurological symptoms. Likewise, Leigh syndrome is rarely associated with liver malfunction. However, this paper provides evidence that when looking for a genetic diagnosis in a patient with Leigh syndrome, the gene *TRMU* should be sequenced to look for mutations. This may allow for a more accurate genetic diagnosis, which permits more effective and pragmatic genetic counselling to be given to patients and their families.

Source: <https://www.sciencedirect.com/science/article/pii/S2214426920301361>

New drug molecules hold promise for treating rare inherited terminal childhood disease

Leigh syndrome is a type of genetic leukodystrophy which is caused by mutations in mitochondrial DNA. Most of the DNA within cells is harboured within the nucleus of a cell. However, a small amount of DNA, containing a limited number of genes, may be found within mitochondria. Mitochondria are small sub-cellular structures responsible for producing the energy required by the cell, and in line with this function, the genes within mitochondrial DNA carry the instructions for proteins needed to carry out this energy-producing function. Recently, researchers at the University of Exeter in the UK have found a way to re-programme mitochondria carrying genetic mutations associated with defective energy production and Leigh syndrome in *C.elegans*, a type of microscopic worm commonly used by biologists as a model organism. The scientists found that a group of new drugs normalise energy production in the mitochondria harbouring these mutations, keeping the worms healthy. The team hope to test these drugs on patients affected by mitochondrial disorders in the near future and are in the process of looking for commercial partners that could help them to do this work.

Source: <https://www.sciencedirect.com/science/article/pii/S2214426920301361>

VANISHING WHITE MATTER DISEASE

A drug reverses age-related cognitive decline

A recent study by researchers at the University of California at San Francisco (UCSF) has shown that a new experimental drug is able to reverse age-related cognitive decline in mice. Age-related cognitive decline includes a reduced ability to make new short-term memories and reduced 'mental flexibility', i.e., becoming 'stuck in your ways'. This new drug, known as ISRIB, is thought to improve brain function by restoring the function of nerve and immune cells within the central nervous system (the brain and spinal cord). Only a few doses of ISRIB are required for this remarkable effect, a fact which has led the researchers to suggest that the cognitive decline that occurs with age is due to a 'reversible blockage' in brain cell function, rather than by cell degradation and loss. ISRIB works by acting against a type of cell stress response, called the ISR, which can be activated by various cellular stressors. ISR is a normal cellular pathway. However, over a person's life, cellular stress accumulates, due to, for example, viral infections and chemical exposure, leading the ISR to become chronically activated. When this happens in the central nervous system, cells lose their ability to function properly, leading to the development of various neurological symptoms. ISRIB 'resets' the system, shutting off the abnormally activated ISR and allowing the cell to function normally again. Interestingly, chronic ISR activation occurs in a wide variety of neurological conditions, including Alzheimer's Disease, Amyotrophic Lateral Sclerosis (Motor Neurone Disease) and Vanishing White Matter Disease, a type of genetic leukodystrophy. Although the study of ISRIB and its potential uses remains in the pre-clinical stage, and many challenges are associated with translating the use of a drug in the lab to the treatment of patients, ISRIB is a promising potential drug for the treatment of both age-related cognitive decline and a number of neurological conditions.

Source: <https://www.sciencecodex.com/drug-reverses-age-related-cognitive-decline-within-days-662328>

Vanishing white matter disease expression of truncated EIF2B5 activated induced stress response

Vanishing white matter disease (VWM) is a type of genetic leukodystrophy caused by mutations in the gene *E1F2B1*. This gene carries instructions for the protein eIF2B, which is responsible for promoting the production of a large and diverse range of other cellular proteins. Precisely why mutations in *E1F2B1* so severely affect the production of myelin (a protein which helps nerve cells to function correctly and makes up a large component of the white matter in the brain) is unknown. In order to study how genetic diseases develop, and to test potential therapies, researchers often use animal models. In a recent paper published in the scientific journal 'eLife', researchers describe the development of a VWM disease model in zebrafish, a small fish species commonly used by scientists in the study of embryonic development and gene function. In this article, scientists demonstrate that mutation of the zebrafish equivalent to *E1F2B1* gene in zebrafish causes a variety of neurological symptoms often seen in VWM patients, including defects in myelin production, death of nerve cells in the central nervous system and motor problems. In addition, the researchers found that the mutated *E1F2B* gene in zebrafish caused the activation of a cellular stress response known to be present in human VWM patients. Previously, the available animal models of VWM did not fully recapitulate the type of disease seen in humans. Thanks to this study, future researchers will now be able to study the development of VWM more accurately and have more reliable indications of if potential therapies are working. In addition, this work has contributed more to the understanding of how cell stress pathways become chronically activated in VWM patients, an avenue which is currently under intense study in regard to the development of VWM drug treatments.

Source: <https://elifesciences.org/articles/56319>