Hunter Syndrome (MPS II)

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Gene Therapy in Action is a digital publication casting an important spotlight on rare diseases and cancers. This series highlights the increasingly critical role of genetic engineering (also called "gene therapy" or "gene transfer") in the clinical landscape with respect to developing novel and effective therapeutics for the treatment of life-threatening conditions with an urgent unmet medical need. This blog is for educational purposes only and is not intended to replace the advice of your doctor or other health care provider.

What is Hunter Syndrome?

Hunter syndrome, also known as mucopolysaccharidosis type II (MPS II), is a rare genetic lysosomal storage disorder (LSD) that affects the metabolism of carbohydrates, leading to an accumulation of large complex sugar molecules in multiple body systems. Hunter syndrome is caused by the absent or deficient activity of the lysosomal enzyme, iduronate 2-sulfatase (I2S). The National MPS Society estimates that Hunter syndrome affects approximately 1 in 100,000 to 1 in 170,000 individuals worldwide, almost exclusively males.

Hunter syndrome is a permanent, progressive disease that affects physical appearance, mental development, organ function, and physical abilities. The disease presents with a variety of phenotypes and is traditionally categorized as non-neuronopathic or neuronopathic, with the neuronopathic form of the disease typically including central nervous system (CNS) symptoms. Diagnosis of Hunter syndrome generally occurs between ages 2 and 4 years, when symptoms become more apparent. Children develop physically and cognitively until between ages 2 and 5 and then regress, leading to a number of potential symptoms such as joint mobility limitations, coarsening of facial features, hearing loss, enlargement of liver and spleen, cardiac disease, short stature, and intellectual disabilities. Individuals with the neuronopathic form of Hunter syndrome have a life expectancy of 10 to 20 years, while individuals with non-neuronopathic Hunter syndrome typically live into adulthood, though with a shortened lifespan.

What Causes Hunter Syndrome?

Hunter syndrome is caused by mutations in the IDS gene located on the X-chromosome. The IDS gene instructs cells to produce the enzyme iduronate-2-sulfatase (I2S), which normally breaks down large sugar molecules known as mucopolysaccharides or glycosaminoglycans (GAGs).

Since the body cannot break down GAGs in individuals with dysfunctional I2S, the GAGs accumulate inside storage compartments (lysosomes) in cells, leading to the development of systemic pathologic symptoms over time. Hunter syndrome is an X-linked recessive disorder, meaning the IDS gene's location on the X-chromosome leads to development of disease primarily in males, who inherit just one X-chromosome, from their mothers (and a Y-chromosome from their fathers). Though cases have been documented in females, occurrence of Hunter syndrome is even rarer in females, who would need to inherit X-chromosomes with the IDS mutation from both parents.

More than 300 mutations in the IDS gene have been found to cause Hunter syndrome.

Treatments for Hunter Syndrome

Enzyme replacement therapy (ERT) is the standard treatment for Hunter syndrome. Currently, the only ERT approved in the United States by the Food and Drug Administration (FDA) for the treatment of Hunter syndrome is idursulfase (Elaprase™), a purified form of the I2S enzyme, typically given weekly as an intravenous injection. Idursulfase can stabilize the physical symptoms of Hunter syndrome, but cannot cross the blood-brain barrier, and is therefore unable to prevent cognitive regression.

In addition to ERT, a multidisciplinary approach to addressing symptoms of Hunter syndrome is also recommended to manage challenges associated with the condition and improve quality of life. Interventions include developmental, occupational, and physical therapies. Surgeries may be necessary to address physical symptoms such as breathing issues, hernias, or heart complications.

Gene Therapy Highlights for Hunter Syndrome

Given the association between mutations in the IDS gene and the development of Hunter syndrome, gene therapy presents an attractive approach for development of therapeutic strategies for treating the disease. In general, gene therapy, or gene transfer, is the process of introducing genetic material into the body for one of several purposes: to introduce a functional copy of a dysfunctional gene, to silence ("turn-off") the expression of a harmful or toxic gene, to introduce gene editing components to correct the disease-causing mutation, or to introduce new or modified genes into the body to help treat a disease. Below we highlight just a few ongoing clinical trials in which various gene therapy approaches are being investigated for the potential treatment of Hunter syndrome. A common therapeutic approach currently used in clinical trials is to replace the mutated form of the I2S enzyme with a fully functional copy. The information provided below is from publicly available sources and is not intended to reflect as advertising or endorsement of any clinical trial Sponsor. The status of each trial was accurate at the time of publication.

Highlight #1:

Trial Title: A Phase 1/2/3 Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamics of RGX-121 in Pediatric Subjects with MPS II (Hunter Syndrome)

ClinicalTrials.gov Identifier: NCT03566043 **Status:** Current recruiting participants

Intervention/treatment: Genetic – RGX-121

Trial Summary: This Phase I/II/III study is an experimental gene therapy study designed to assess the safety and efficacy of a recombinant, replication-defective adeno-associated virus (AAV) vector designed to produce ("express") cDNA encoding the human gene for iduronate-2-sulfatase (IDS) in male children 4 months to 5 years of age with neuronopathic Hunter syndrome. This virus, modified in the laboratory so that it cannot reproduce once introduced into the body, acts as an efficient delivery system ("vector") to introduce genetic material into the body to use for the production of the iduronate-2-sulfatase (I2S) enzyme. The study agent, RGX-121, is administered as a one-time intracisternal injection directly into the cerebrospinal fluid (CSF), with the goal of producing therapeutic amounts of I2S in the central nervous system (CNS). Use of an AAV vector for gene transfer would allow for long-term production of I2S that may prevent or stabilize cognitive regression in affected children.

Highlight #2:

Trial Title: A Phase 1 Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of HMI-203 in ERT-Treated Adults With Mucopolysaccharidosis Type II (MPS II) (juMPStart Trial)

ClinicalTrials.gov Identifier: NCT05238324 **Status:** Current recruiting participants

Intervention/treatment: Biological: Genetic – HMI-203

Trial Summary: This Phase I clinical trial is an experimental gene therapy study designed to assess the safety and efficacy of a human hematopoietic stem cell-derived recombinant, replication-defective adeno-associated virus vector (AAVHSC) designed to deliver functional copies of the IDS gene to multiple organs where there are missing or mutated copies of the gene in adult males with Hunter syndrome currently being treated with enzyme replacement therapy (ERT). The study agent, HMI-203, is delivered as a single intravenous injection developed to enable the long-term production of the I2S enzyme throughout the body. The Phase I dose-escalation portion of the trial is designed to evaluate three doses of HMI-203 to potentially determine the optimal dose(s) for a future trial.

Highlight #3:

Trial Title: A Phase I/II, Study of Autologous CD34+ Hematopoietic Stem Cells Transduced ex Vivo With CD11B Lentiviral Vector Encoding Human IDS Tagged With ApoEII in Patients With Neuronopathic Mucopolysaccharidosis Type II (nMPS II, Hunters Syndrome)

ClinicalTrials.gov Identifier: NCT05665166 **Status:** Not yet recruiting participants

Intervention/treatment: Genetic – Autologous CD34+ HSCs transduced ex vivo with CD11B LV encoding human IDS tagged with ApoEII

Trial Summary: This Phase I/II study is a gene therapy study designed to assess the safety, tolerability, and efficacy of the treatment of neuronopathic Hunter syndrome with the patient's own cells (autologous CD34+ hematopoietic stem cells) genetically modified with a self-inactivating lentiviral vector encoding human IDS tagged with ApoEII in pediatric males aged 3 to 12 months. Cells are removed from the study subject and genetically altered with the lentiviral vector ex vivo (outside the body) before being returned to the subject via infusion. This investigational gene therapy includes CNS-targeted gene expression due to the APOEII tag and is intended to express supra-physiological levels of I2S enzyme in transduced cells with the objective of correcting both systemic and neurological manifestations of Hunter syndrome.

Gene Therapy in Action
A digital series from Sabai Global

Hunter Syndrome

For Patients, Family Members and Caregivers

Looking for resources on Hunter Syndrome?

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=MPS+II&term=&cntry=&state=&city=&dist=)
- Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/diseases/6675/mucopolysaccharidosis-type-ii)
- Hunter Patients (https://www.hunterpatients.com/)
- National MPS Society (https://mpssociety.org/)
- National Organization for Rare Diseases (NORD) (https://rarediseases.org/rare-diseases/mucopolysaccharidosis-type-ii-2/?filter=ovr-ds-resources)
- Project Alive (https://projectalive.org/)

For Sponsors, CROs and Institutions

Interested in hearing how our extensive in-house staff of subject-matter experts can facilitate an accelerated, compliant Institutional Review Board (IRB) or Institutional Biosafety Committee (IBC) review of your gene transfer/gene therapy clinical trials?

Contact us at info@sabai.com or call 1-888-442-2472 to set up a call with our team.