A Guide to AAV Gene Therapy for MPS I and II
REGENXBIO seeks to understand the diverse perspectives of patients, caregivers and families, and to learn from their experiences in order to guide our work. We are deeply committed to discovering and developing gene therapies that address significant unmet medical needs and improve treatment options for people living with rare, debilitating conditions.
What is MPS?

Mucopolysaccharidoses (MPS) are a group of rare, genetic conditions in which the body is missing a certain enzyme that breaks down sugar molecules known as glycosaminoglycans (GAGs). If these GAGs build up in the body's cells, they can cause progressive damage to many organs, including the brain.

Because available treatments for MPS I and MPS II are not adequately able to treat neurological symptoms, REGENXBIO is developing gene therapies for MPS I and MPS II to address the effects that MPS has on the brain.

**RGX-111** is an investigational, one-time gene therapy for the potential treatment of MPS I. It uses AAV9 to deliver the human α-L-iduronidase (IDUA) gene directly to the central nervous system (CNS, brain and spinal cord). Left untreated, people with severe forms of MPS I, commonly referred to as Hurler Syndrome, typically show symptoms before two years old and have severe cognitive decline after an initial period of normal development.

**RGX-121** is an investigational, one-time gene therapy for the potential treatment of severe MPS II, or Hunter Syndrome. It uses AAV9 to deliver the human iduronate-2-sulfatase (IDS) gene directly to the central nervous system (CNS, brain and spinal cord). In severe forms of MPS II, developmental delays can appear by 18 to 24 months of age and cognitive decline typically begins around six and a half years old. Children may also show severe behavioral symptoms.

To learn more about our clinical trials for MPS I and MPS II, contact us or visit [ClinicalTrials.gov](https://clinicaltrials.gov).
How Does REGENXBIO’s NAV® Technology Work?

**MPS Mechanism of Disease**

**HEALTHY CELL**
- DNA
- Nucleus
- Normal DNA codes for a variety of enzymes that break down GAGs
- Cytoplasm
- Enzymes break down the GAGs

**CELL WITH MPS**
- DNA
- Nucleus
- DNA lacks the code to produce a specific enzyme that breaks down GAGs
- Cytoplasm
- Enzymes only partially break down the GAGs, resulting in a buildup of them within the cell
- Leads to tissue and organ damage, including brain damage, cognitive dysfunction, and multi-system issues

**NAV® Technology**

1. Viral DNA is removed
2. Functional human gene is inserted
3. Treatment is delivered into the central nervous system, guided by CT scan while patient is asleep
4. Vector binds to cell membrane
5. Vector is internalized by cell in a vesicle and transported to nucleus
6. Vector releases functional gene into nucleus
7. Full enzyme complement can now break down GAGs
8. Cell produces missing enzyme from healthy gene
9. Resultant enzyme is secreted and taken up by other cells

**Why are RGX-111 and RGX-121Administered Directly to the Central Nervous System?**

Delivering the gene therapy directly into the central nervous system bypasses the blood-brain barrier. The blood-brain barrier protects the brain from things that can hurt it, but this also prevents some medications from passing through to reach the brain.
**Gene Therapy: What to Know**

- A single, defective (non-working) gene can cause a genetic disorder.
- Genes carry instructions for cells, such as how to make a specific protein that the body needs to work properly. A defective gene can change the message the gene carries, resulting in a non-working protein.
- Adeno associated virus (AAV) gene therapy aims to replace the non-working gene with a functional copy.
- AAV is a virus that is not known to cause disease in humans. The virus’ DNA is removed and the human gene is added in, creating an “AAV vector.”
- Vectors target specific areas or tissues in the body and transfer the working gene into the body’s cells.
- AAV9 has demonstrated that it can target the central nervous system.
- The U.S. Food and Drug Administration (FDA) approved the first AAV-based gene therapy in December 2017 to treat a form of inherited blindness.

**Additional Resources**

- **National Institutes of Health: Genetics Home Reference**
- **National MPS Society**
  - [mpssociety.org](https://mpssociety.org)
REGENXBIO is a leading clinical-stage biotechnology company seeking to improve lives through the curative potential of gene therapy. Our NAV® Technology Platform, a proprietary adeno-associated virus (AAV) gene delivery platform, consists of exclusive rights to more than 100 novel AAV vectors, including AAV7, AAV8, AAV9 and AAVrh10. REGENXBIO’s NAV® Technology is licensed by other leading biotechnology companies that are evaluating its potential across multiple therapeutic areas. REGENXBIO possesses the capabilities to advance therapies from discovery to commercialization, including management and scientific teams that are made up of experienced, passionate leaders in gene therapy.

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