MeuSIX Partners

- *Fondazione Telethon, Italy*
- *ReGenX Biosciences, USA*
- *GenoSafe SAS, France*
- *Federico II University of Naples, Italy*
- *Hacettepe University, Turkey*
- *Erasmus University, The Netherlands*
- *Bicocca University of Milan, Italy*
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MeuSIX

Clinical Trial of Gene Therapy for Mucopolysaccharidosis type VI - a severe lysosomal storage disorder

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MPS VI
a severe lysosomal storage disorder

MPS VI, also known as Mucopolysaccharidosis VI or Maroteaux-Lamy syndrome, belongs to a group of rare inherited diseases called lysosomal storage disorders.

Most lysosomal storage disorders are due to a genetic deficiency of an enzyme in subcellular organelles called lysosomes. When the enzyme is missing, lysosomes cannot break down a specific kind of material that accumulates and causes all of the problems seen in lysosomal storage disorders.

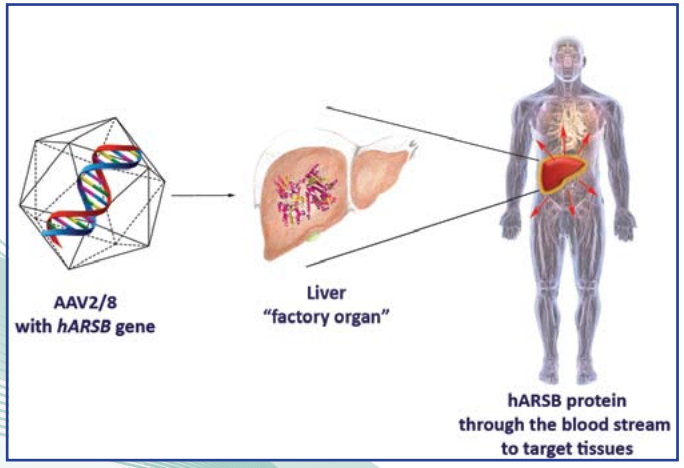
MPS VI is caused by a deficiency of the ARSB enzyme, which results in intra-lysosomal storage and increased urinary excretion of partially degraded glycosaminoglycans (GAGs), previously known as mucopolysaccharides.

No single symptom defines MPS VI. A patient with MPS VI may develop a cluster of several symptoms affecting various body systems, with the exception of the central nervous system. Symptoms of MPS VI are not usually evident at birth, but show up later as GAGs build up. However the rate at which symptoms appear and worsen varies widely. Some affected individuals have a rapidly advancing form of MPS VI and may start showing symptoms as early as 6 to 24 months of age. Others have a more slowly progressing form of MPS VI and may not show significant symptoms until much later. MPS VI often produces a range of recognizable changes in physical appearance, as the thickening of nose, lips, and tongue that occurs as GAGs build up in tissues. MPS VI individuals may have a large head, a protruding abdomen, and short stature.

At the moment, the recommended therapy for MPS VI is Enzyme Replacement Therapy (ERT): it consists of weekly intravenous infusions with recombinant ARSB, which last few hours.

Gene therapy
a single administration treatment

Gene therapy has the potential to convert the liver into a factory and a “depot” for the sustained systemic release of the enzyme ARSB.



Pre-clinical studies have demonstrated that a single intravascular administration of an adeno-associated virus (AAV) encoding ARSB results in levels of expression of therapeutic ARSB for at least 4 years post-injection and significant improvement in biochemical, visceral, and skeletal features.

Based on encouraging pre-clinical results, the MeuSIX consortium plans to conduct a Phase I/II clinical trial to investigate the safety and efficacy of AAV-mediated gene therapy in patients with MPS VI.

Orphan Drug Designations (ODDs) have been obtained from both the European Medicinal Agency and the US Food and Drug Administration for the MPS VI therapeutic AAV vector.

Objectives of
gene therapy MPS VI clinical trial

To achieve this important goal, we have established the following roadmap:
- to produce Good Manufacturing Practice (GMP) clinical-grade vector for gene therapy in humans;
- to perform pre-clinical toxicological studies in animals using the GMP vector;
- to design a Phase I/II clinical trial;
- to produce and file the documents required to obtain authorization to perform the clinical trial;
- to perform the Phase I/II clinical trial to investigate the safety and efficacy of gene therapy for MPS VI.

Positive results from this Phase I/II study will support the licensure of the AAV vector for the treatment of MPS VI. If successful, this therapeutic strategy may overcome the limitations of ERT, which include limited efficacy and the need for multiple intravenous administrations.

	ERT	Gene therapy
Frequency of treatment	Multiple infusions with several side effects	Single infusion in a life-time
Efficacy	Not effective on some MPS VI features	Potentially effective on almost all MPS VI features
Cost	Highly costly	More cost effective

The MPS VI gene therapy trial will be the first gene therapy clinical trial for a metabolic disease using AAV2/8 and may pave the way towards clinical trials for other diseases due to lysosomal enzyme deficiency, as well as inborn errors of liver metabolism in general. The results of this trial may demonstrate the clinical potential of AAV-mediated liver gene therapy as a strategy for the treatment of other rare diseases requiring sustained systemic release of therapeutic proteins.