Intrastromal delivery of AAV-IDUA for MPS1-associated corneal clouding

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Mucopolysaccharidosis type 1 (MPS1) and corneal blindness

- Caused by mutations in a single gene
- Creates alpha-L-iduronidase (IDUA) deficiency
- Results in severe, progressive multisystem disease
- Rare disease: 1/100,000 patient prevalence
- In the cornea, IDUA clears glycosaminoglycans (GAGs)
- Without IDUA, collagen fibril disruption and fibrosis occurs
- **Corneal clouding results in severe visual impairment**

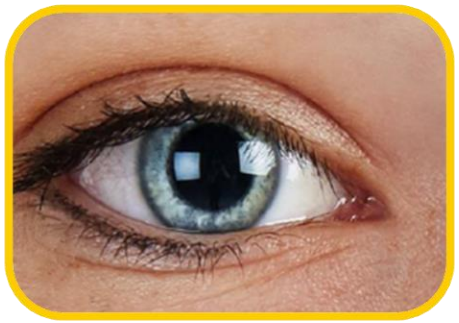
MPS1 Symptoms
Stiffened joints
Skeletal problems
Carpal tunnel syndrome
Heart disease
Upper airway infections
Obstructive sleep apnea
Spinal cord compression
Enlarged liver and spleen
Hernia
Hearing loss
Delayed cognitive development
Coarse facial features
Fluid on the brain
Abnormally shaped teeth
Corneal clouding

Sanofi and Genzyme MPS1 Disease
Huang et al.; Exp Eye Res.; 1996 Apr;62(4):377

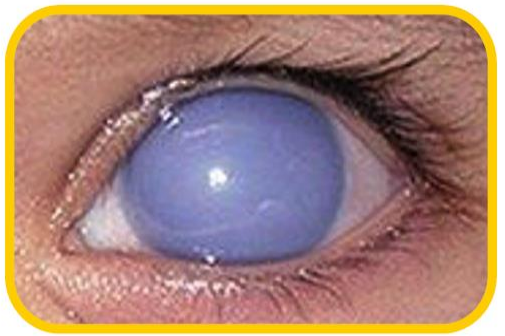
Current standards of care do not treat the cornea

- Current therapies are all systemic:
  1. Enzyme replacement therapy
  2. Hematopoietic Stem Cell Transplants
- Have **no effect** on the cornea
- As a result, MPS1 kids are living longer, *but are going blind*

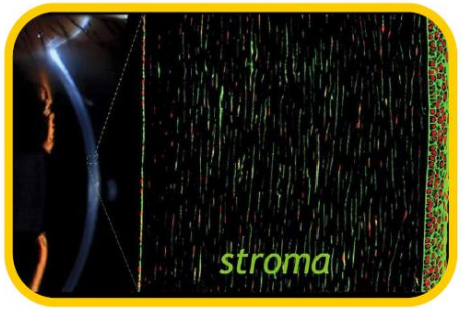
Corneal clouding affects up to 98% of MPS1 patients



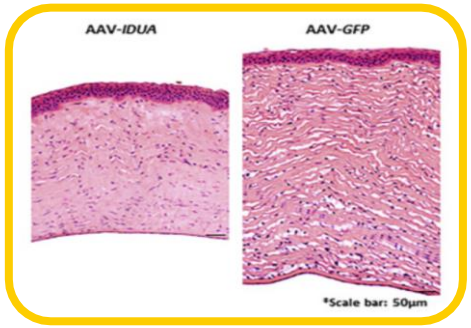
Normal cornea is completely transparent



MPS1 cornea becomes opaque



Normal corneal stroma is transparent with organized fibrils and normal cells



MPS1 corneal stroma has abnormal collagen fibrils, vacuolated stromal cells, and proteoglycan aggregates

Vance, M., Llanga, T., Bennett, W. et al. AAV Gene Therapy for MPS1-associated Corneal Blindness. Sci Rep 6, 22131 (2016). https://doi.org/10.1038/srep22131[2]
Molecular Therapy Volume 28, Issue 6, 3 June 2020, Pages 1455-1463 https://doi.org/10.1016/j.ymthe.2020.04.004

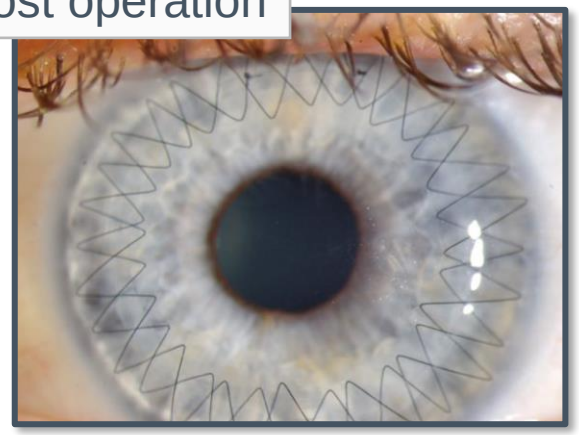
Corneal transplantation is the only treatment available

Key challenges with keratoplasty to treat clouding:

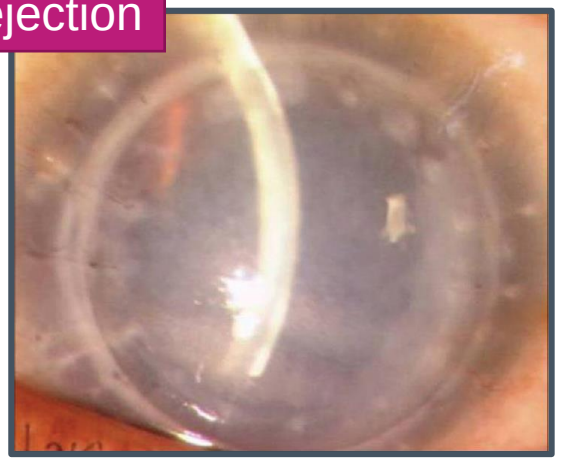
- Surgery is technically difficult
- High post-operative inflammation
- Does not treat disease, requiring multiple surgeries
- Challenging for patients with MPS, high anesthesia risk

As a result of challenges with keratoplasty, a high unmet medical need remains

Post operation



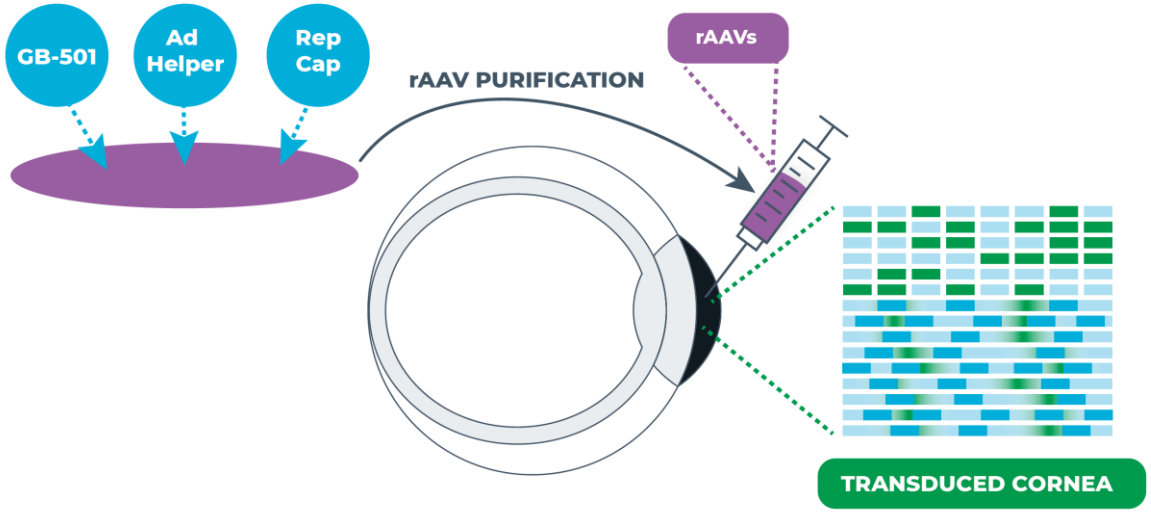
Rejection



GB-501 is designed to reverse and prevent corneal blindness

Corneal Administration of IDUA

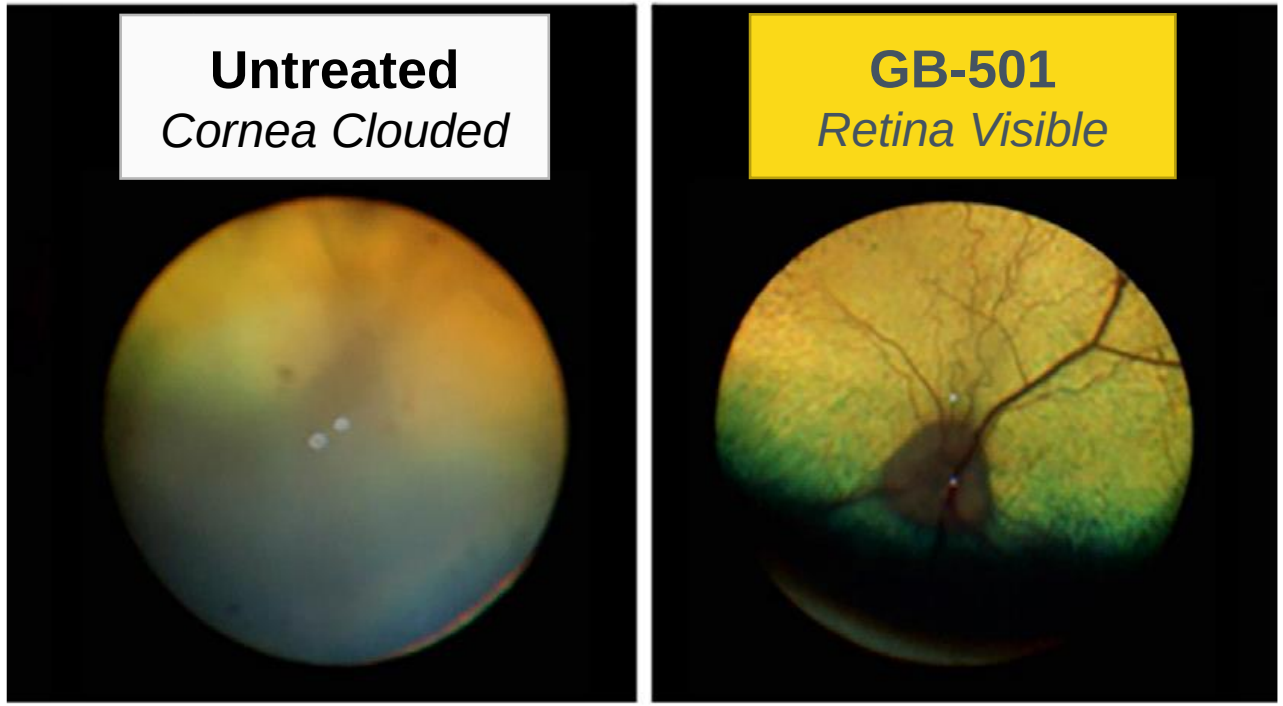
- ✓ **Readily accessible external organ**
  - Corneal injections are common
  - Easily transduced at low titers
- ✓ **Particles restricted to the eye**
  - Drug remains in cornea
  - Immune privileged, avascular
- ✓ **Stromal cells are non-dividing**
  - Low-dose, small-volume treatment
  - Durable cure



IDUA is secreted: single injection results in ***complete corneal clearing***

Restoration of corneal clarity following single intrastromal injection

GB-501 demonstrated *complete* and *sustained* corneal clearing within 3 weeks



Clearing observed in **all MPS1 dogs**, regardless of severity, in as little as **one week** post-injection

***All** corneas remained clear for **two-year** study duration*

Miyadera, K., et al. (2020). "Intrastromal Gene Therapy Prevents and Reverses Advanced Corneal Clouding in a Canine Model of Mucopolysaccharidosis I." Mol Ther 28(6): 1455-1463.

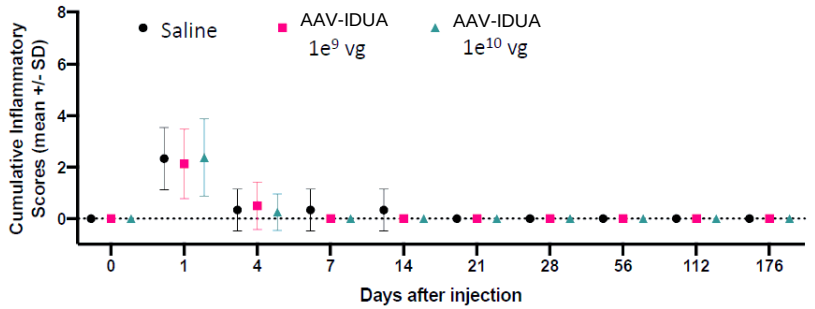
Excellent safety profile in rabbits

Six-month safety and tolerability study

Intrastromal injection 50 µL
Groups:

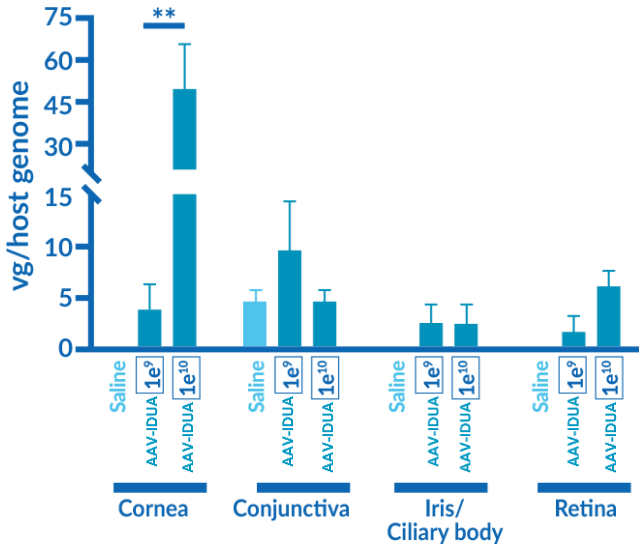
Saline (6 rabbits)
AAV-IDUA 1e^{9}/cornea (8 rabbits)
AAV-IDUA 1e^{10}/cornea (16 rabbits)

Cumulative ocular examination scores (Hackett-McDonald)



Safe and well-tolerated in rabbits with no dose-limiting events

Biodistribution in rabbits shows high corneal levels



No adverse effects following GB-501 injection:

- ✓ Intraocular pressure
- ✓ Corneal thickness
- ✓ Endothelial cell counts
- ✓ Blood chemistry and other body parameters

Phase 1/2a clinical safety and activity data readout anticipated in 4Q23

GB-501: minimally invasive, high safety margins, rapid clinical results

- Novel, first-in-class corneal gene therapy
- Rapid, sustained clearing with single injection of GB-501 observed in animal model
- Small, focused clinical trials, with patients identified from MPS registries
- All components of GB-501 have been previously tested in humans
  - Safety and biodistribution studies demonstrated corneal compartment ideal for gene therapy
- Potential platform for treating other corneal opacities/dystrophies