



Weill Cornell Medicine

Optimized Gene Therapy for Hereditary Angioedema

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Optimized Gene Therapy for Hereditary Angioedema

Background & Unmet Need

- Hereditary Angioedema (HAE) is a genetic disorder in which patients experience acute episodic swelling, often in the face, limbs, GI tract, or airway
- HAE is caused by mutations in the SERPING1 gene, leading to a deficiency in C1 esterase inhibitor (C1EI) or inactive forms of this protein
- Complications of HAE include asphyxiation or death due to swelling of the airway, as well as pain, nausea, vomiting, or unnecessary surgery
- Current treatment for HAE are prophylactic, including infusions of replacement C1EI or related vasodilation inhibitors
- Despite prophylactic treatments, there are more than 20 K emergency department visits annually attributable to HAE
- **Unmet Need:** A one-time treatment eliminating acute swelling episodes from HAE

Technology Overview

- **The Technology:** A novel AAV vector encoding a functional, human C1EI gene for treatment of HAE
- **The Discovery:** The team first created and validated a murine model of HAE by inducing CRISPR-mediated deletions in the SERPING1 gene
- An optimized C1EI gene was generated by removing mRNA instability elements, high and low GC regions, splice signals, and in-sequence translation initiation sequences to increase stability of the gene
- An AAVrh.10hC1EI vector encoding the optimized hC1EI gene under a CAG promoter was generated to restore C1EI activity in deficient mice
- **PoC Data:** Expression of hC1EI in AAVrh.10hC1EI-treated mice persisted for at least 24 weeks
- Vascular permeability, a hallmark of HAE, was significantly reduced ($p < 0.05$) in rear paws and internal organs of AAVrh.10hC1EI-treated mice at 24 weeks (except for lung and intestines in female mice)

Inventors:

Ronald G. Crystal
Odelya Pagovich
Maria Chiuchiolu

Patents:

US Patent 10,214,731
CN Patent CN108025047B
JP Patent 6573991

Issued Patents in AU, IL, SG

Applications Filed in EP, CA, IN, MX, NZ, SG, KR, HK, US, JP, IL, CN, AU

Publications:

Qiu et al. *Allergy*. 2019.

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Technology Applications

- One-time gene therapy for Hereditary Angioedema to prevent episodic swelling and resulting complications

Technology Advantages

- Single dose gene therapy improves patient compliance relative to continuous prophylactic regimens
- Quality of life is improved by one-time treatment regimen compared to burdensome chronic treatments

Supporting Data / Figures

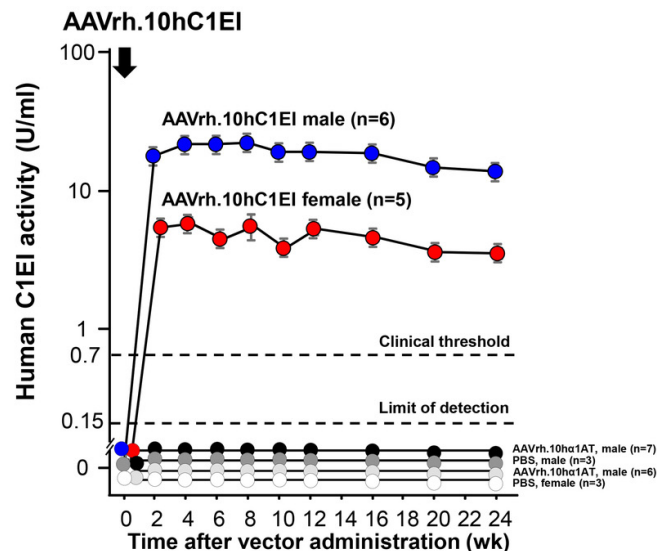


Figure 1: Mice treated with AAVrh.10hC1EI had persistent and high levels of C1EI. Difference between male and female expression is typical for experimental AAV vectors.

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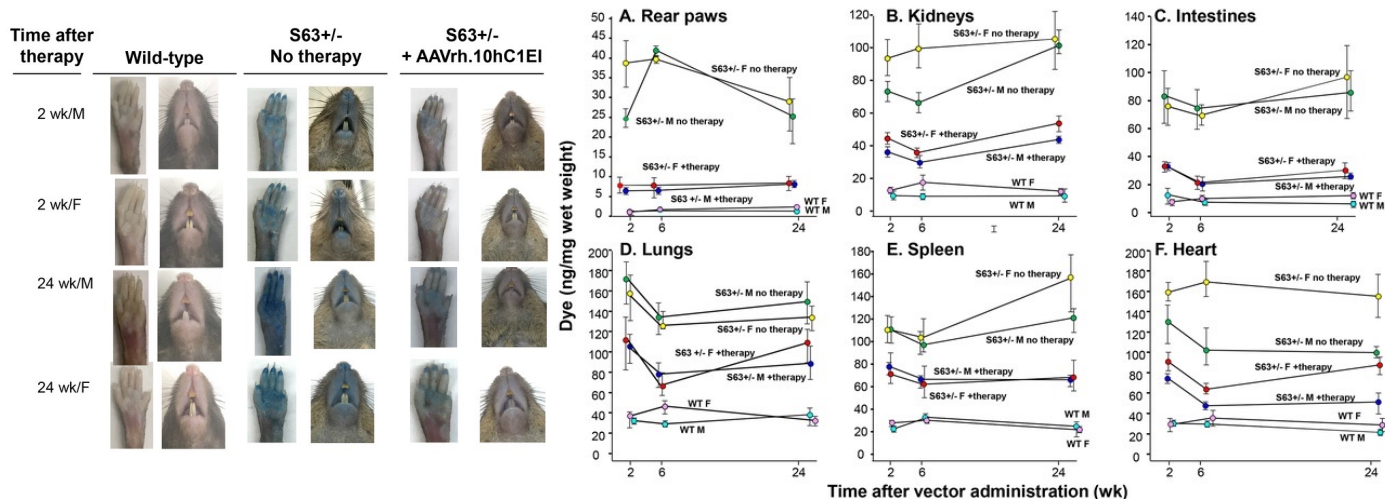


Figure 2: Treated mice have significantly reduced vascular permeability in rear paws and internal organs at 24 weeks (except for lungs and intestines in female mice).

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JP Patent [6573991](#)

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