Therapeutics & Vaccines

Gene Correction of Pompe Disease and Other Autosomal Recessive Disorders via CRISPR and other RNA-Guided Nucleases

View U.S. Patent No. 11,739,320 in PDF format.

WARF: P190021US02

Inventors: Krishanu Saha, Jared Carlson-Stevermer, Lucille Kohlenberg

The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in improving gene editing interventions against Pompe disease and other autosomal recessive disorders. UW–Madison researchers have developed a complexed CRISPR-Cas gene editing approach for treating Pompe disease.

Overview

Pompe disease is a rare autosomal recessive genetic disease (mutations from both parent carriers have to be inherited by the offspring to see symptoms) that typically affects children during development, but can also present as an adult. Pompe disease is characterized by a lack of functional acid alpha-glucosidase (GAA) enzyme. The lack of GAA leads to a glycogen buildup in cells throughout the body, which results in muscular weakness and wasting. Newborns in which the disease is misdiagnosed rarely survive past one year. Currently, children suffering from the disease are provided with GAA enzyme via biweekly intravenous (IV) infusions, but not all children respond to the treatment.

Gene therapy is an attractive alternative to enzyme replacement treatment for Pompe disease. However, most conventional gene therapy strategies focus on adding extra copies of the normal gene without correcting the preexisting mutations within the cells of the patient. Correcting the preexisting mutation preserves the natural regulation of the gene and can lead to more durable and efficacious treatments with less toxicity from adding extra copies of the gene. Almost 400 mutations to the gene have been identified, complicating gene therapy approaches. Inventors at UW-Madison explored the possibility of correcting mutations on both mutant alleles using CRISPR-Cas to determine whether there was any advantage to that strategy.

The Invention

UW–Madison researchers have developed a complexed CRISPR-Cas system (S1mplex; P170309US01) for treating patients with inherited autosomal recessive conditions. The work focuses on Pompe disease. The inventors identified new guide RNA target sites and repair templates that could be used for gene therapy strategies and cell therapeutic strategies.

The inventors demonstrated successful editing of fibroblast and induced pluripotent stem cells from three Pompe patients at UW Hospital having heterozygous mutations (each allele containing a different mutation, both leading to loss of function of the enzyme). Using their complexed CRISPR-Cas technology markedly increased editing precision (18.4-fold) in two different cell lines (HEK and hPSC), easing concerns about off-target effects. Importantly, rapid glycogen processing improvements were observed after gene correction – 24 hours and 96 hours, respectively.

Applications

- Gene editing of deleterious mutations found in Pompe disease cells

Key Benefits

- Paired with complexed CRISPR-Cas (S1mplex), precise-to-imprecise editing ratios were improved 18.4-fold.
- Intervention utilizing multiple gene correction within the same human cell is possible.
- Rapid improvements in glycogen processing is observed (as short as 24 hours).

Additional Information

For More Information About the Inventors

- Krishanu Saha

Related Technologies

- See WARF reference number P170309US01: S1mplex Precision Gene Editing.

Publications

- Carlson-Stevermer J., Abdeen,A.A., Kohlenberg L. et al. 2017. Assembly of CRISPR Ribonucleoproteins with Biotinylated Oligonucleotides via an RNA Aptamer for Precise Gene Editing. Nat Commun 8, 1711.

Tech Fields

- Therapeutics & Vaccines : Other therapeutic technologies

For current licensing status, please contact Jennifer Gottwald at jennifer@warf.org or 608-960-9854