Novel CRISPR Gene Therapy for Haploinsufficiency

Tech ID: 30127 / UC Case 2017-040-0

INVENTION NOVELTY

This technology presents a way to treat human genetic disease caused by haploinsufficiency and reduced protein production. The method employs the use of adeno-associated viral (AAV) vectors for the *in vivo* delivery of a CRISPR-based gene expression activator (CRISPRa) that boosts transcription from the existing functional copy of the affected gene.

VALUE PROPOSITION

Haploinsufficiency – having only one functional copy of a gene due to gene deletion or other gene-inactivating mutations, is the basis of many human genetic disorders caused by the insufficient amounts of product generated by the affected gene. Attempts to treat such developmentally-predetermined conditions have relied on gene therapy and the re-introduction of a second functioning gene copy. However, this therapeutic approach has been hampered by a series of confounding factors including gene size, mutations caused by gene or vector insertion, and inability to target specific cells or deliver specific doses of the gene. A unique merit of this novel technology is the use of non-pathogenic and non-integrating AAV vector to deliver a CRISPRa, which is targeted to the enhancer or promoter region of a gene. In the case of low gene dosage-based conditions, this allows for inducing transcription from the existing copy of the gene without creating any changes in the patient's DNA. Furthermore, as the AAV vector will not be carrying the actual missing gene copy, this method circumvents common limitations to using AAV for effective delivery in patients.

TECHNOLOGY DESCRIPTION

Gene transcription is increased by a nuclease defective Cas9 (dCas9) fused to a transcriptional activation domain combined with a unique guide RNA construct targeted to the regulatory (promoter and/or enhancer) regions of a gene. Thus, this CRISPRa complex does not cause nicks or breaks in the DNA, can be easily packaged in an AAV vector for *in vivo* delivery, and cell/tissue-specificity is determined by the targeted cis-regulatory regions. The inventors have demonstrated successful *in vivo* use of the technology by curing obesity in *Sim1* and *Mc4r* mouse haploinsufficiency models, which as is the case in humans, results in defects in the leptin pathway and hyperphagic obesity.

LOOKING FOR PARTNERS

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OTHER INFORMATION

KEYWORDS

Haploinsufficiency, Gene therapy, CRISPR

CATEGORIZED AS

- **Medical**
  - Disease: Genetic Diseases and Dysmorphic Syndromes
  - Gene Therapy

RELATED CASES

2017-040-0

To develop & commercialize the technology as a gene therapy tool for the treatment of human disease based on genetic haploinsufficiency.

STAGE OF DEVELOPMENT

Pre-clinical / Proof of concept

RELATED MATERIALS

- Matharu, N., Rattanasopha, S., Tamura, S., Maliskova, L., Wang, Y., Bernard, A., ... & Ahituv, N. (2019). CRISPR-mediated activation of a promoter or enhancer rescues obesity caused by haploinsufficiency. Science, 363(6424), eaau0629.

OTHER INFORMATION

Commentary: Montefiori, L. E., & Nobrega, M. A. (2019). Gene therapy for pathologic gene expression. *Science*, *363*(6424), 231-232.

DATA AVAILABILITY

Under CDA / NDA

PATENT STATUS

Country	Type	Number	Dated	Case
Australia	Issued Patent	2018218280	01/30/2025	2017-040
China	Issued Patent	ZL201880023129.0	03/26/2024	2017-040
United States Of America	Issued Patent	11,730,828	08/22/2023	2017-040
European Patent Office	Published Application	3579858	12/18/2019	2017-040
Japan	Published Application			2017-040

Additional Patents Pending

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