(SD2017-285) Fully Encodable and Highly Specific CRISPR/Cas Systems, Compositions, and Methods to Achieve Efficient and Reversible Manipulation and Modulation of Target RNA with Simplicity, Reliability and Versatility

Tech ID: 28858 / UC Case 2017-285-0

BACKGROUND

CRISPR-Cas9 technology has revolutionized the field of biological research through the introduction of sequence-specific genomic manipulation at the DNA level. It has also been reported that catalytically-dead Cas9 (dCas9) can successfully be localized to specific mRNAs within live cells. However, no system exists to perform Cas9-mediated sequence editing at the RNA level.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego have patented a programmable method to reversibly alter genetic information with single-nucleotide resolution through targeted RNA editing. This Cas9-directed RNA Editing approach (or CREDIT) provides a means to reversibly alter genetic information in a temporal manner, unlike traditional CRISPR/Cas9 driven genomic engineering which relies on permanently altering DNA sequence.**[click for patent status]**

This invention stems from taking a nuclease-dead version of *Streptococcus pyogenes* Cas9 (dCas9) and generating recombinant proteins with effector enzymes capable of performing ribonucleotide base modification to alter how a sequence of the RNA molecule is recognized by cellular machinery. The inventors have engineered a system that can perform direct conversion of targeted bases on mRNAs of interest and thus alter genetic information at the transcript level.

APPLICATIONS

This RNA editing platform provides a powerful tool for post-transcriptional gene manipulation, as well as a means to further investigate the biological consequences of independent RNA editing events in living systems. Because dCas9 binds with pico-molar affinity to guide RNA scaffold, and because this improved system uses dual guide architecture to increase both target affinity and specificity, researchers can now more efficiently direct RNA editing with fewer potential off-target editing events.

Methods of using CREDIT as a therapeutic for diseases, *e.g.* by using viral or other delivery approaches to deliver CREDIT for *in vivo* RNA editing to treat a disease requiring such editing, such as Hurler's syndrome, Cystic fibrosis, Duchenne muscular dystrophy, multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, alcoholism or alcohol withdrawal and especially over-rapid benzodiazepine withdrawal, and also Huntington's disease.

1) Research tool. Characterize the effects of directed cellular RNA editing on processing and dynamics.

2) Therapeutic for diseases. Viral (AAV) or other delivery approaches to treat: premature termination codon RNA diseases such as Hurler's syndrome, Cystic fibrosis, Duchenne muscular dystrophy, others, as well as diseases associated with deficiencies in RNA editing such as excitotoxic neuronal disorders affiliated with under-editing of the Q/R residue of AMPA subunit GluA2. Excitotoxicity may be involved in spinal cord injury, stroke, traumatic brain injury, hearing loss (through noise overexposure or ototoxicity), and in

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OTHER INFORMATION

KEYWORDS

RNA editing, CRISPR-Cas9 technology, Streptococcus pyogenes Cas9 (dCas9), live cells, ribonucleotide base modification, therapeutics

CATEGORIZED AS

- **Medical**
  - Research Tools
  - Therapeutics
- **Research Tools**
  - Nucleic Acids/DNA/RNA

RELATED CASES

2017-285-0

neurodegenerative diseases of the central nervous system (CNS) such as multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, alcoholism or alcohol withdrawal and especially over-rapid benzodiazepine withdrawal, and also Huntington's disease.

ADVANTAGES

This invention offers advantages over current systems used to directly edit RNA rely either on non encodable components, such as chemical fusion of guide RNAs to an editase moiety (SNAP tag here), or relatively low affinity tethering by fusion of encodable aptamer binding moieties.

dCas9 binds with picomolar affinity to guide RNA scaffold, and because this improved system uses dual guide architecture to increase both target affinity and specificity, researchers can now more efficiently direct RNA editing with fewer potential off-target editing events.

INTELLECTUAL PROPERTY INFO

This patented technology is available for licensing. UCSD has issued patents in the United States and Singapore.

Detailed description of specific embodiments and claim set are available in the published patent application.

Patent No.	Country
11,453,891	UNITED STATES https://patents.google.com/patent/US11453891B2
11201910247Y	SINGAPORE https://patents.google.com/patent/WO2018208998A1

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Published Application	20180334685	11/22/2018	2017-285
Patent Cooperation Treaty	Published Application	2018208998	11/15/2018	2017-285

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