Editas Medicine Co-founders Present Novel Methods for Improving Genome Editing Specificity in Two Nature Biotechnology Papers

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Findings Advance Therapeutic Potential for CRISPR/Cas9 Technology

Cambridge, Mass., April 25, 2014 – Editas Medicine, a transformative genome editing company, today announced the publication of new data highlighting novel approaches to improve the specificity of CRISPR/Cas9 genome editing technology. The data are presented in two papers independently co-authored by company co-founders Keith Joung, M.D., Ph.D. and David Liu, Ph.D. in the current online edition of *Nature Biotechnology*. [1,2]

"Our understanding of CRISPR/Cas9 genome editing technology and how it may be applied for therapeutic use continues to mature, and together, these findings highlight critical advances that improve the specificity of the CRISPR/Cas9 system," said Kevin Bitterman, Ph.D., interim president, Editas Medicine. "Each scientific advance contributes to Editas' mission of refining and translating genome editing technology into therapeutics that will make a meaningful difference for patients."

The paper co-authored by Dr. Joung, associate chief of pathology for research and associate pathologist at Massachusetts General Hospital and associate professor of pathology at Harvard Medical School, characterizes the development and optimization of a next-generation, dimerization-dependent CRISPR-based nuclease technology platform that shows substantially improved genomic specificities. The cleavage activity of dimeric RNA-guided dead Cas9 (dCas9)-FokI Nucleases, named RFNs, depends on the binding of two guide RNAs (gRNAs) to DNA with a defined spacing and orientation. The published findings show robust activities compared to monomeric wild-type Cas9 nucleases and nickases, in addition to improved genomic specificities with no evidence of unwanted mutagenesis at off-target sites.

The paper co-authored by Dr. Liu, Howard Hughes Medical Institute investigator and professor of chemistry and chemical biology at Harvard University, presents a similar approach to engineering a dimerization-dependent Cas9-FokI nuclease fusion, named fCas9, with improved specificity. The fusion protein requires the simultaneous DNA binding and association of two FokI-dCas9 monomers to cleave DNA. The results show that the engineered FokI-dCas9 modified target DNA sites with efficiency comparable to that of nickases, but with greater than 140-fold higher specificity than wild-type Cas9 in human cells. The specificity of fCas9 was at least four-fold higher than that of paired nickases at human genome loci with highly similar off-target sites elsewhere in the genome. Additionally, unwanted binding was reduced further by the requirement that only sites flanked by two gRNAs approximately 15 or 25 base pairs apart are cleaved.

About Genome Editing

Following an explosion of high-profile publications on CRISPR/Cas9 and TALENs, genome editing has emerged as one of the most exciting new areas of scientific research. These recent advances have made it possible to modify, in a targeted way, almost any gene in the human body with the ability to directly turn on, turn off or edit disease-causing genes. Editas Medicine's five founders have published much of the foundational work that has elevated genome editing technology to a level where it can now be optimized and developed for therapeutic use.

CRISPR (clustered, regularly interspaced short palindromic repeats)/Cas9 (CRISPR-associated protein 9) and TALENs (transcription activator-like effector nucleases) comprise novel gene editing methods that overcome the challenges associated with previous technologies. Early published research on CRISPR/Cas9, coupled with a growing body of work on TALENs, suggests the potential to pursue therapeutic indications that have previously been intractable to traditional gene therapy, gene knock-down or other genome modification techniques. The CRISPR/Cas9 system, the most recent and exciting approach to emerge, acts by a mechanism in which the Cas9 protein binds to specific RNA molecules. The RNA molecules guide the Cas9 complex to the exact location in the genome that requires repair. CRISPR/Cas9 uniquely enables highly efficient knock-out, knock-down or selective editing of defective genes in the context of their natural promoters, unlocking the ability to treat the root cause of a broad range of diseases.

About Editas Medicine

Editas Medicine is a transformative genome editing company founded by five world leaders in the fields of genome editing, protein engineering, and molecular and structural biology, with specific expertise in CRISPR/Cas9 and TALENs technologies. The company's mission is to translate its genome editing technology into a novel class of human therapeutics that enable precise and corrective molecular modification to treat the underlying cause of a broad range of diseases at the genetic level. Editas Medicine was launched in November 2013 with funding from Flagship Ventures, Polaris Partners and Third Rock Ventures with participation from Partners Innovation Fund. For more information, visit www.editasmedicine.com.

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1. Tsai, S.Q., et al. Dimeric CRISPR RNA-guided FokI nucleases for highly specific genome editing. *Nature Biotechnology*, 2014 Apr 25; doi: 10.1038/nbt.2908. [Epub ahead of print]

2. Guilinger, J.P., et al. Fusion of Inactivated Cas9 to FokI Nuclease Improves Genome Modification Specificity. *Nature Biotechnology*, 2014 Apr 25; doi:10.1038/nbt.2909. [Epub ahead of print]