RNA-targeting CRISPR could yield treatments for Huntington's, ALS

by *Amirah Al Idrus* | Aug 10, 2017 2:20pm

UC San Diego researchers are using CRISPR-Cas9 to target RNA, which could lead treatments for genetic diseases that have no cure.

Researchers from the University of California, San Diego have **used** a new version of the gene editing technology CRISPR to fix problems in RNA, rather than to change DNA, a promising step for a group of diseases, including Huntington's and amyotrophic lateral sclerosis, that have no cure.

CRISPR uses the Cas9 enzyme and a "guide" RNA to snip out mutations in DNA, but until recently, it has not been used to target RNA. After using the method to **track RNA** in live cells last year, the UC San Diego team is now correcting mistakes in RNA that lead to microsatellite repeat expansion diseases. In these disorders, too many repeats in RNA sequences causes RNA to clump together in cells, preventing them from producing essential proteins.

The team tested their RNA-targeted Cas9 (RCas9) system on laboratory models and found that the method cleared 95% or more of the RNA clumps—called foci—related to myotonic dystrophy, one type of ALS and Huntington's disease. It also eliminated 95% of errant repeat RNAs in cells taken from patients with myotonic dystrophy. The findings are published in Cell.

"We are really excited about this work because we not only defined a new potential therapeutic mechanism for CRISPR-Cas9, we demonstrated how it could be used to treat an entire class of conditions for which there are no successful treatment options," said David Nelles, co-first author of the study and a postdoctoral researcher in the laboratory of Gene Yeo, a professor of cellular and molecular medicine at the UC San Diego School of Medicine.

Various companies and institutions are working on CRISPR treatments for a range of diseases, including **Duchenne muscular dystrophy** and **sickle cell disease**. A main concern is the chance of off-target mutations,

where the system makes unwanted gene edits and causes harmful side effects. Multiple teams are working on adding anti-CRISPR proteins to a CRISPR-Cas9 molecule to act as an “off switch” for off-target edits.

Yeo and his team at UC San Diego believe their work could lead to gene therapies for more than 20 diseases that have no cure, though the technique needs to be refined before it reaches the clinic. Gene therapy is typically delivered via adeno-associated viruses, which are too small to hold Cas9, so Yeo’s team deleted the parts of the enzyme that aren’t needed to modify RNA.

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"The main thing we don't know yet is whether or not the viral vectors that deliver RCas9 to cells would [elicit] an immune response," Yeo said. "Before this could be tested in humans, we would need to test it in animal models, determine potential toxicities and evaluate long-term exposure."

To that end, Yeo and some of his colleagues have launched a company, Locana, to bring RCas9 from the lab to the clinic.

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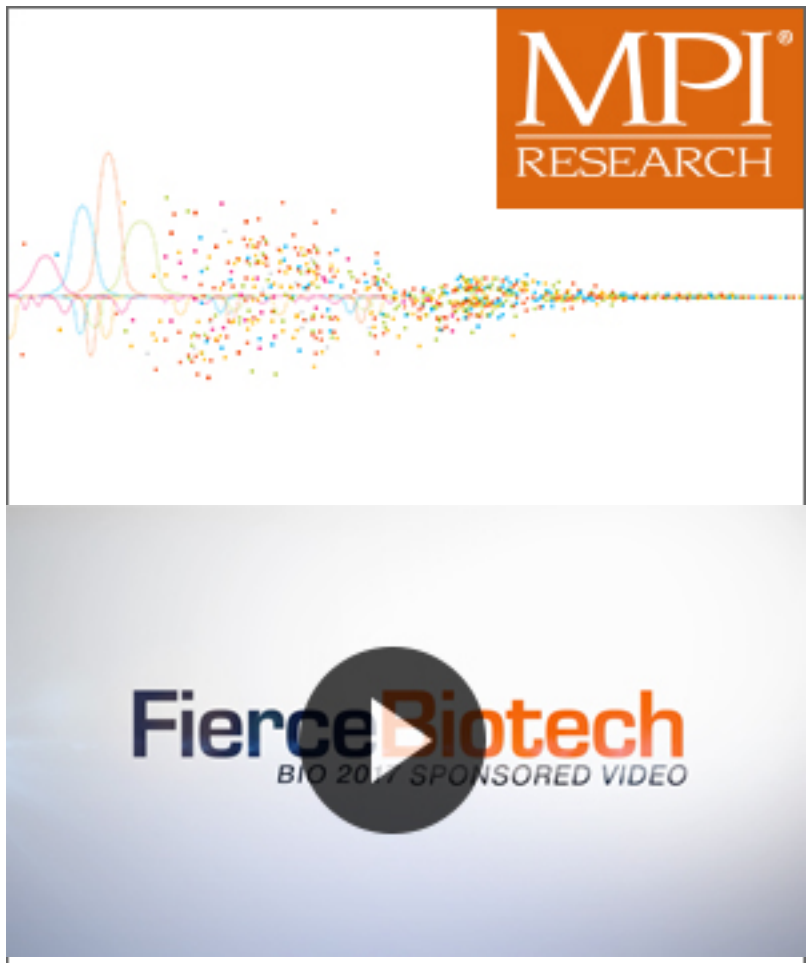

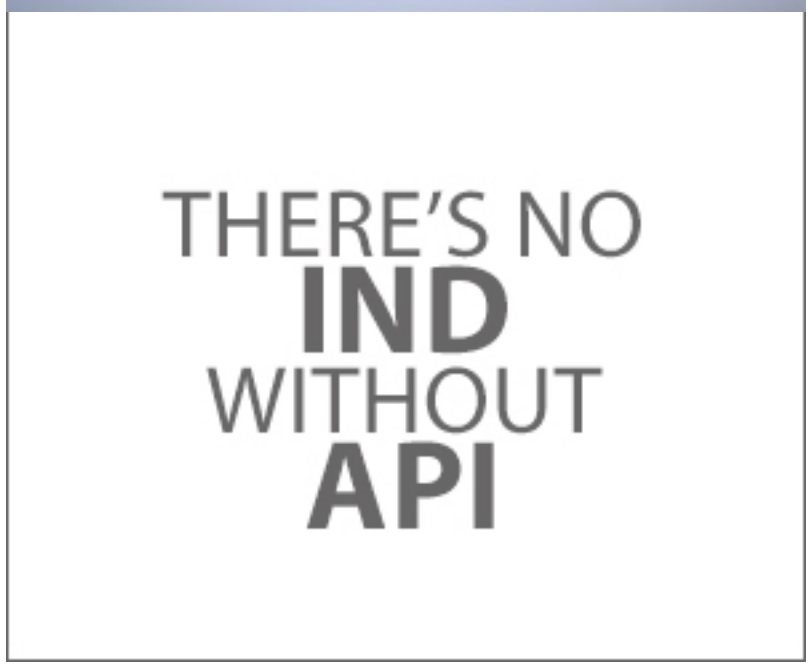

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About the Author

Amirah Al Idrus

Editor