NEWS

# Tweak to molecular scissors cuts path to turn on genes

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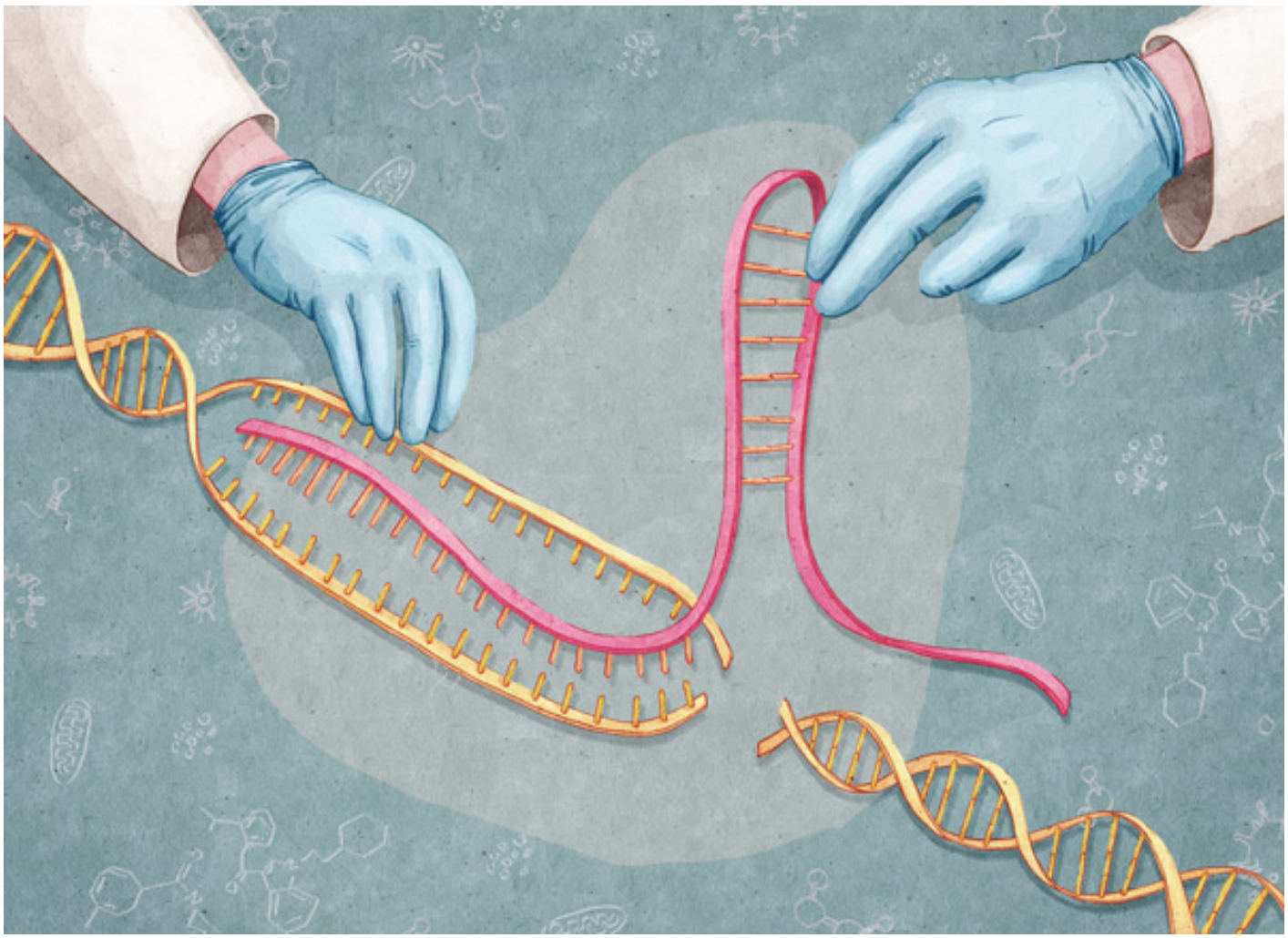
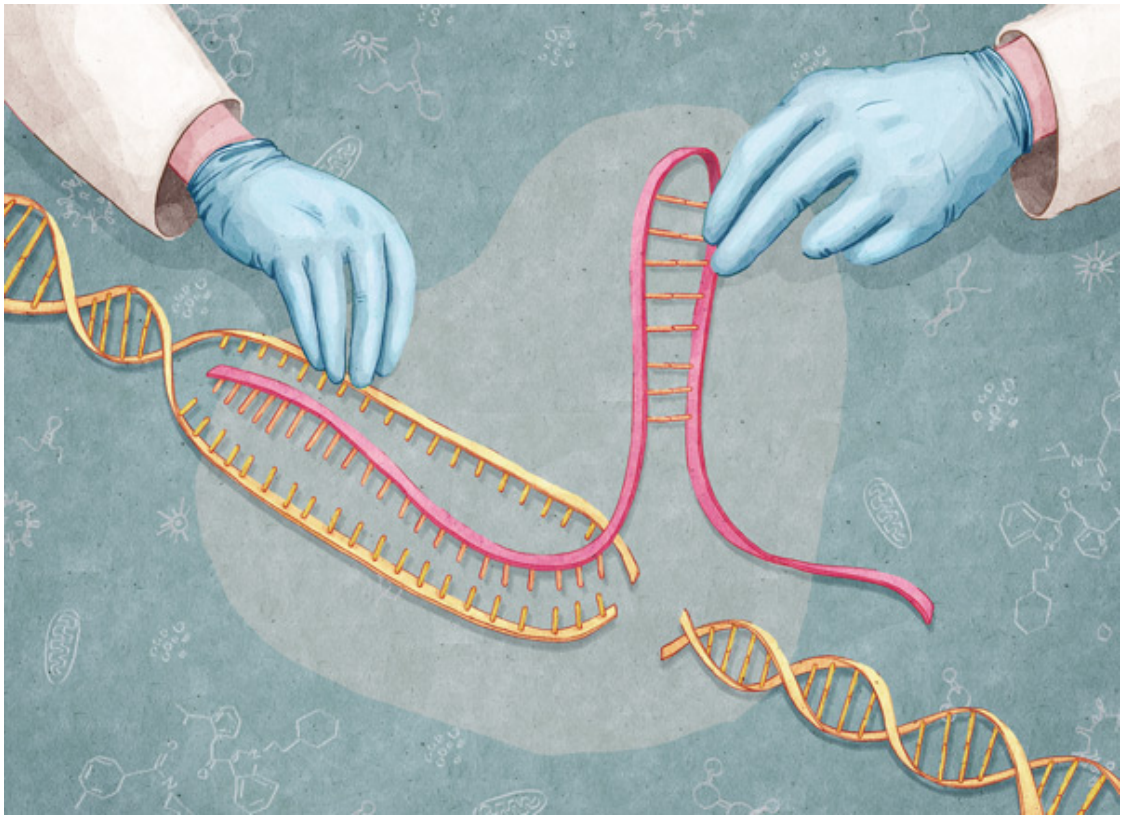




Julia Yellow Gene editor: A revolutionary technique, CRISPR, allows researchers to mutate or delete genes; the new method allows them to activate genes.

A new technique allows scientists to turn on the expression of any gene, giving them the unprecedented ability to explore the function of every gene in the human genome.

“You can now look at every gene in the genome and turn it on or turn it off and see whether or not it plays a role in a given disease or biological process,” says lead researcher **Feng Zhang**, assistant professor of brain and cognitive sciences at the Massachusetts Institute of Technology.

The technique, described 10 December in *Nature*, is a modified version of a method called CRISPR. Two years ago, CRISPR wowed researchers by allowing them to ‘edit’ — delete or insert mutations into — any gene they wanted.

Like CRISPR, the new method gives researchers an invaluable tool to study autism-linked genes. For example, researchers could activate genes, one at a time or simultaneously, in large duplications and deletions of DNA linked to autism, says **Michael Talkowski**, assistant professor of

neurology at Harvard Medical School.

“For a long time we have been continuously coming up with methods to knock down gene expression, but there have not been really good, reliable methods to activate gene expression,” he says. “The uses of this technology are just innumerable.”

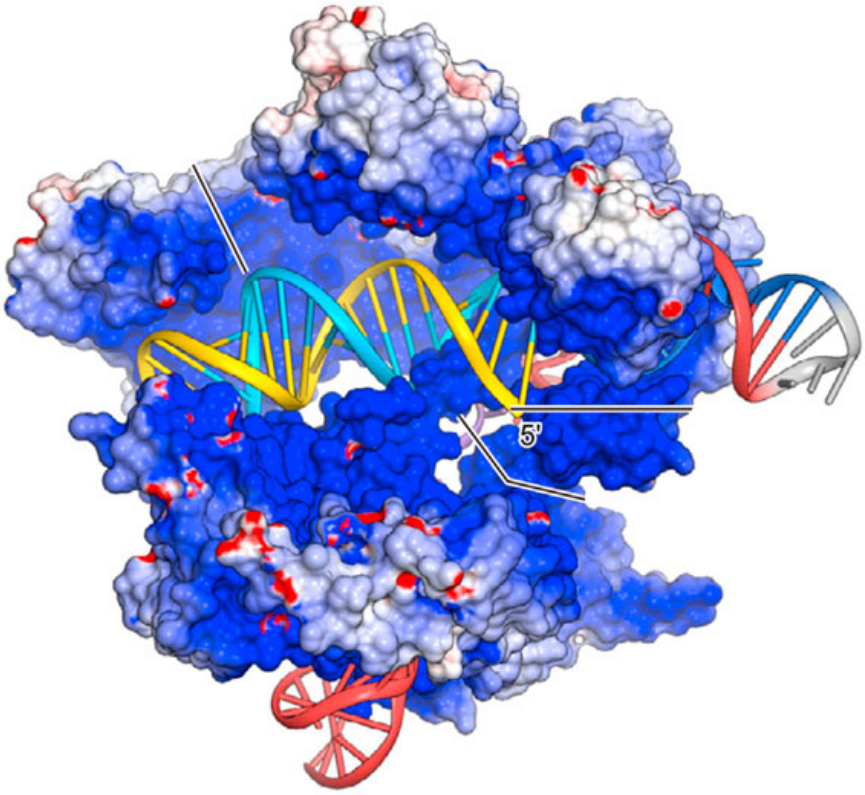
The technique is restricted to cultured cells, including neurons made from stem cells of people with autism, but researchers are trying to adapt it for use in animal models and, potentially, people.

Autism-linked mutations **typically affect only one of two gene copies**, and the new method may allow researchers to boost activity of the ‘healthy’ gene to normal levels, says **Guoping Feng**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology, who was not involved in the new study. “It will be potentially therapeutic.”

## Scissor switch:

CRISPR works by allowing researchers to place an enzyme called CRISPR-CAS9, which has a scissorlike domain, anywhere in the genome they choose. The new technique replaces the scissors with ‘activators’ that act as landing strips for the cellular machinery that triggers gene expression.

The study is not the first to harness this approach, but earlier efforts to link activators to CRISPR-CAS9 worked only some of the time. In a study published last year, Zhang and his team analyzed the structure of CRISPR-CAS9 when bound to DNA and found that the bulky complex may sit between the activators and DNA[2].




Tricky tether: Studying the structure of the gene-editing complex when bound to DNA allowed the researchers to boost the technique's efficiency.

In the new study, they instead placed the activators on the small, synthetic RNA molecules that guide CRISPR-CAS9 to specific points in the DNA. They also used multiple activators instead of a single one.

The new method works every time, and the researchers were able to use it to boost the expression of 12 genes that could not efficiently be activated by previous methods.

The researchers created an open-access library of guide RNAs that turn on every gene in the human genome. As a proof of concept, they used the library to activate each of the 20,000 human genes in skin cancer cells**.** This revealed genes that confer resistance to certain forms of chemotherapy.

The same process could reveal genes that have compensatory effects in autism, Zhang says. "The new method provides a way to discover genes that, if they are turned on, provide an advantage."

In another study, posted 20 December on the biology preprint server bioRxiv, researchers used **multiple activators bound to CRISPR** to turn on two developmental genes in induced pluripotent stem cells. This allowed them to consistently transform the cells into neurons in just four days, besting the efficiency of the standard technique.

Both techniques lead to higher levels of gene expression than can be achieved with standard methods, says **George Church**, professor of genetics at Harvard Medical School and lead researcher on the stem cell study. This is crucial for screening large numbers of genes and finding their links to conditions such as autism, he says. “In practice, you’re going to want to get as high activation as possible.”

Before the technique can be applied to animals, researchers need to control the expression levels of the activated genes and target specific organs, such as the brain.

“That’s the ultimate goal,” says Zhang. “We’re working on it, because I really would like to be able to use this system to study the brain. Hopefully, other people will help out, too, to make it quicker.”

## References:

1: Konermann S. *et al. Nature* Epub ahead of print (2014) **PubMed**

2: Nishimasu H. *et al. Cell* **156**, 935-949 (2014) **PubMed**