NEWS

CRISPR goes wild, and scientists debate its fidelity

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The gene-editing tool CRISPR may cause thousands of unintended mutations, but critics say it's way too soon to accuse it of infidelity[1].

A two-page study, published 30 May in *Nature Methods*, put **biology's hottest technique** in the crosshairs, questioning its ability to rewrite DNA with the precision necessary for medicine. The paper's findings quickly dominated social media conversations on biology. And the stocks of biotech companies with CRISPR-based projects dipped by as much as 15 percent.

But some researchers are loath to end their love affair with CRISPR. Reports of the method's infidelity, they say, are greatly exaggerated. One reason, they note, is that the study is small — just

two mice for CRISPR and a single control mouse.

“I think it’s an important finding that we really need to follow up, but it’s really hard to judge why there are so many [mutations],” says **Guoping Feng**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology. He says another enzyme the team used may in fact have caused the errant mutations.

Two weeks after the paper’s publication, *Nature Methods* editors **added a note to the paper**, saying they are considering the criticism of the results and plan to respond soon.

Wandering scalpel:

CRISPR is a molecular scalpel that cuts DNA. It can home in on a specific spot on the molecule using a piece of RNA as a guide. The tool holds significant medical promise because it could help **modify or fix genes** that cause medical conditions.

In 2016, **Alexander Bassuk**’s team reported injecting mouse embryos with CRISPR fused to its usual protein partner, CAS9, which binds to DNA. The researchers targeted a gene called PDE6B that is involved in vision. The experiment was designed to correct a mutation that causes blindness in the mice[2]. It did.

For the new study, Bassuk and his collaborators looked for off-target effects of the treatment. They sequenced the whole genomes of the two mice and the control mouse. They compared the results from the edited mice against a database that includes genomes of 36 mouse strains.

CRISPR-CAS9 introduced more than 100 unintended mutations and more than 1,600 one-letter swaps in the code of DNA, the researchers found.

None of these changes had any obvious consequences. “As far as we can tell, it hasn’t affected the mice,” says Bassuk, professor of pediatric neurology at the University of Iowa in Iowa City. But the researchers tested only the mice’s vision and do not know if the mutations affected the animals’ behavior or perception.

This was not the first time that CRISPR had caused accidental mutations, though previous reports found far fewer mutations[3].

“It’s always been a concern for everyone in the field that this is not a completely clean method,” says **Anis Contractor**, associate professor of physiology at Northwestern University in Chicago. Contractor was not involved in the research but uses CRISPR to make mouse models. “This is a big red flag.”

Contractor and others say the findings may prompt a change in best practices when using the

method. Scientists may need to sequence the genomes of their models — an expensive task — to uncover any unexpected mutations.

Rushed job:

Others, however, are downplaying the results.

“I don’t think this paper has any merit for CRISPR research,” says **George Church**, professor of genetics at Harvard University. “I think it’s a negative example that we can use as a cautionary tale.” Church is co-founder of **Editas Medicine**, a biotechnology company that is using the technique to develop gene-editing therapies. The company lost 12 percent of its value the day the study was published. (Its stock has since gone up, surpassing its previous value.)

Church and the company’s other executives wrote to *Nature Methods* with a laundry list of **concerns about the paper**. Their biggest beef, says Church: The study’s control mouse likely wasn’t genetically identical to the ones that had been edited with CRISPR, so it’s impossible to know whether the mutations resulted from the method.

Instead, Church argues, it’s possible that the mutations represent natural genetic variance between the animals. Church stops short of saying the paper should be retracted but calls it a “rushed job.” Another gene-editing company, **Intellia Therapeutics**, voiced **similar complaints**.

The team also used an unusual version of the editing system, says Feng, who is using CRISPR to create animal models of autism. He says the use of extra nickase, an enzyme that can cause breaks in a strand of DNA, could have caused the mutations.

“I couldn’t figure out what reason you’d need to do it this way,” he says.

Bassuk points out that the team did the editing work in 2015, early in CRISPR’s use.

“We used what was available at the time,” Bassuk says. “It’s obviously not what people are using in 2017.” He says he is not sure whether the editing system made a difference in the results.

In the past three months, researchers have debuted the first two mouse models of autism created using CRISPR. No one has yet published work on using CRISPR to correct genes in animal models of the condition.

In the short term, the findings “will definitely temper the enthusiasm for CRISPR models,” says **J. Tiago Gonçalves**, assistant professor of neuroscience at Albert Einstein College of Medicine in New York, who was not involved in the research. “But in the end, I’m confident the problems will be solved and we’ll figure out what’s happening.”

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