

A new 'mini-CRISPR' flexes its editing power in monkey muscles

The downsized DNA-slicing machinery may reach more tissues to take aim at more diseases

31 JAN 2025 • 3:50 PM ET • BY [JENNIFER COUZIN-FRANKEL](#)



A miniaturized CRISPR system can edit DNA in monkey muscle, according to a new preprint. TRAFFIC_ANALYZER/GETTY IMAGES

SHARE:



A version of this story appeared in Science, Vol 387, Issue 6734.



In the years since the gene-editing strategy CRISPR burst onto the scene, it’s run into a big limitation: The classic CRISPR system is too unwieldy to get into many of the body’s tissues and do its slicing and dicing. Now, researchers from a company co-founded by Jennifer Doudna of the University of California, Berkeley, who won the [2020 Nobel Prize](#) for helping develop CRISPR, are reporting what they hope will be a significant step forward. In a preprint posted last night, the team describes a “mini-CRISPR” successfully shipped into [muscle cells in mice and monkeys](#), where it efficiently edited a gene linked to neuromuscular disorders.

What’s reported is “truly impressive,” says Nic Bengtsson, who studies gene editing in neuromuscular diseases at the University of Washington and wasn’t involved in the work. The mini–gene editor, carried into cells by a virus commonly used in gene therapy, looks promising as a kind of “off-the-shelf system, ready to use” for a variety of conditions, he says. Still, he cautions, questions and hurdles remain before the strategy can be tested in people.

CRISPR, which originally evolved in bacteria as part of their immune system, is akin to a set of molecular scissors that cleaves DNA at precise locations, allowing it to excise a problem portion of a gene with help from a strand of RNA that guides it into location. In December 2023, U.S. regulators approved the first CRISPR-based therapy, to treat sickle cell disease. That treatment involves extracting a patient’s blood stem cells and using CRISPR to fix them before reinfusing them into the body.

SIGN UP FOR THE AWARD-WINNING SCIENCEADVISER NEWSLETTER

The latest news, commentary, and research, free to your inbox daily

SIGN UP >

Clinical trials are ongoing for treatments that deliver CRISPR’s editing machinery directly into the bloodstream, where it has [successfully edited genes in liver cells](#). But that approach, which packaged CRISPR proteins into fat particles, hasn’t yet worked in other tissues because few lipid particles reach them. Researchers instead would like to ferry in DNA encoding CRISPR using the well-studied adeno-associated virus, or AAV, often used for delivery of gene therapy. Doing so is challenging, however, in part because the CRISPR’s components are bulky—in particular the enzyme Cas9 that cuts DNA, which typically includes more than 1300 amino acids. That’s too much DNA to squeeze into a single AAV, so researchers have instead tried delivering CRISPR and its guide RNA using two or more AAVs. But so far, it hasn’t worked very well.

Multiple research teams have been working to craft miniaturized CRISPR systems that are still effective at editing but can be packed into just one AAV vector. Among these is the team at Mammoth Biosciences—which may have hit on success. Its scientists began by sifting through genetic sequence data from all sorts of CRISPR varieties that turn up in microbes. They put an initial 176 candidates through “a barrage of tests,” and found “that needle in the haystack,” says Lucas Harrington, the company’s chief scientific officer and co-founder and a former student of Doudna’s. They named that top pick NanoCas; it has 425 amino acids, making it about one-third the length of Cas9. Harrington and his colleagues engineered it so it could effectively slice mammalian DNA.

That slimdown allowed the DNA for the editing system to fit inside a single AAV vector. The group showed NanoCas could edit DNA in various mammalian cells in the lab, then moved into mice. When they used it to shut off a cholesterol gene called *PCSK9* in the liver, NanoCas successfully edited about 60% of cells, a performance at least as good as Cas9.

Then they turned to a tougher target for traditional CRISPR: muscle. They tested whether NanoCas could target a gene in muscle cells called dystrophin, which encodes a key scaffolding protein. People with Duchenne muscular dystrophy, a devastating muscle wasting disease that typically surfaces in early childhood, have a mutation in that gene and aren’t able to make any or enough functional protein.

In mice with a human version of the mutated dystrophin gene, the NanoCas strategy seemed to work well, editing 10% to 40% of the cells across a range of muscle types, including heart and calf muscle. (These engineered mice don’t get sick like people with the mutation, so the team couldn’t assess potential effects on Duchenne symptoms.)

Finally, a big test came in three healthy macaque monkeys. The researchers injected an AAV carrying DNA for the CRISPR-containing viral vector and its guide RNA into the animals’ bloodstreams. They monitored liver function, as liver damage can be a risk of AAV therapy; that and other health measures stayed in normal range, they found. Depending on muscle type, NanoCas edited the dystrophin gene in up to 30% of the monkeys’ skeletal muscle cells; the number was somewhat lower in heart muscle, about 15%.

Those levels are “certainly in a range you would expect to be clinically meaningful,” says Terence Flotte, a gene therapist and dean of the University of Massachusetts T.H. Chan School of Medicine.

But he and others note it’s early days. There’s no information yet on whether the strategy can help a sick animal get better. AAV also comes with risks, including immune reactions and potential “off-target” effects, in which healthy DNA is affected by accident. “Their preliminary data is encouraging,” but “limited,” says Mark Kay, a gene therapist at Stanford University. Still, he’s heartened by how easily this miniature CRISPR can slip into an AAV vector, which opens up a raft of new tissue targets, including for Duchenne—a condition in dire need of new treatments, he notes.

Harrington acknowledges the challenges, including concerns about AAVs, but is hopeful about what’s to come. “The fact that we can now very efficiently edit with a single AAV” makes delivering CRISPR into the body and editing previously inaccessible tissues “not just theoretical,” he says. Harrington says Mammoth will continue to work on Duchenne and send its NanoCas system after targets relevant to other muscle disorders as well as brain diseases. “We are really trying to think, ‘What can we do as quickly as possible?’”

doi: 10.1126/science.zarx6ub

RELEVANT TAGS:

- BIOLOGY
- HEALTH

ABOUT THE AUTHOR

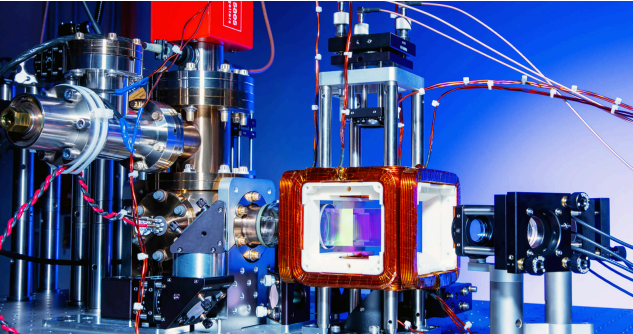


Jennifer Couzin-Frankel

Author

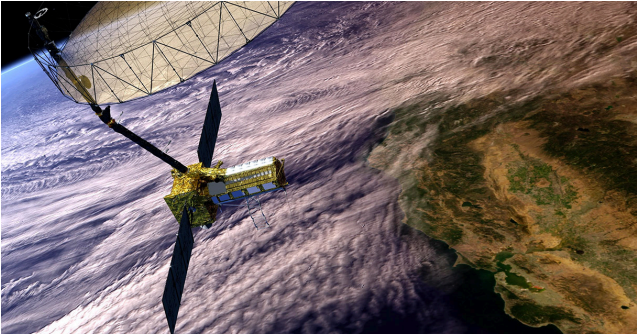
Jennifer Couzin-Frankel is a reporter at *Science*, covering biomedical research.

MORE FROM NEWS



10 JUL 2025
Quantum computers made of individual atoms leap to the fore

BY ADRIAN CHO



10 JUL 2025
Giant radar satellite set to probe Earth’s shifts and shudders

BY MICHAEL GRESHKO



9 JUL 2025
Pterosaur died with belly full of plants—a fossil first

BY TAYLOR MITCHELL BROWN

[VIEW MORE >](#)

Got a tip for Science's news department?

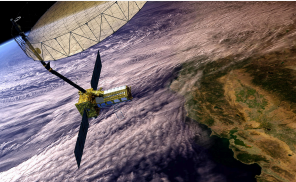
[CONNECT >](#)

Sign up for ScienceAdviser

Get *Science*’s award-winning newsletter with the latest news, commentary, and research, free to your inbox daily.

[SUBSCRIBE >](#)

SCIENCEINSIDER

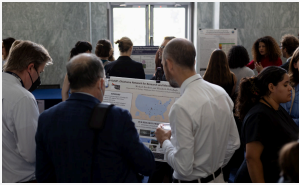


10 JUL 2025 | BY MICHAEL GRESHKO
Giant radar satellite set to probe Earth’s shifts and shudders



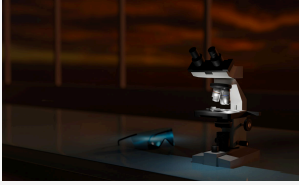
8 JUL 2025 | BY SOFIA MOUTINHO

AI challenge to find lost Amazonian civilizations draws critics



8 JUL 2025 | BY JEFFREY MERVIS, NAZEEFA AHMED

Democrats stage a science fair of canceled grants to show what’s been lost



7 JUL 2025 | BY KATIE LANGIN

‘It’s a nightmare.’ U.S. funding cuts threaten academic science jobs at all levels

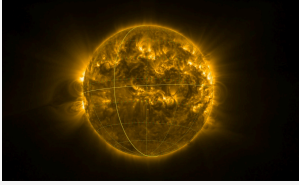
[VIEW MORE](#) >

SIFTER



17 JUN 2025 | BY JON COHEN

Videos of bat-munching animals may show how viruses spread



13 JUN 2025 | BY CHRISTIE WILCOX

Human eyes have never seen the Sun’s south pole—until now



9 JUN 2025 | BY RODRIGO PÉREZ ORTEGA

Long-necked dinosaur found with its last meal still inside



22 MAY 2025 | BY PHIE JACOBS

Penguin poop could be driving Antarctic cloud formation

[VIEW MORE](#) >

Science

Science
Advances

Science
Immunology

Science
Robotics

Science
Signaling

FOLLOW US



GET OUR NEWSLETTER

NEWS

- [All News](#)
- [ScienceInsider](#)
- [News Features](#)
- [Subscribe to News from Science](#)
- [News from Science FAQ](#)
- [About News from Science](#)
- [Donate to News](#)

COMMENTARY

- [Opinion](#)
- [Analysis](#)
- [Blogs](#)

AUTHORS & REVIEWERS

- [Information for Authors](#)
- [Information for Reviewers](#)

ADVERTISERS

- [Advertising Kits](#)
- [Custom Publishing Info](#)
- [Post a Job](#)

ABOUT US

- [Leadership](#)
- [Work at AAAS](#)
- [Prizes and Awards](#)

CAREERS

- [Careers Articles](#)
- [Find Jobs](#)
- [Employer Hubs](#)

JOURNALS

- [Science](#)
- [Science Advances](#)
- [Science Immunology](#)
- [Science Robotics](#)
- [Science Signaling](#)
- [Science Translational Medicine](#)
- [Science Partner Journals](#)

LIBRARIANS

- [Manage Your Institutional Subscription](#)
- [Library Admin Portal](#)
- [Request a Quote](#)
- [Librarian FAQs](#)

RELATED SITES

- [AAAS.org](#)
- [AAAS Communities](#)
- [EurekAlert!](#)
- [Science in the Classroom](#)

HELP

- [FAQs](#)
- [Access and Subscriptions](#)
- [Order a Single Issue](#)
- [Reprints and Permissions](#)
- [TOC Alerts and RSS Feeds](#)
- [Contact Us](#)



© 2025 American Association for the Advancement of Science. All rights reserved. AAAS is a partner of HINARI, AGORA, OARE, CHORUS, CLOCKSS, CrossRef and COUNTER.