# Scientists tinker with gene-mapping device to make DNA editing safe

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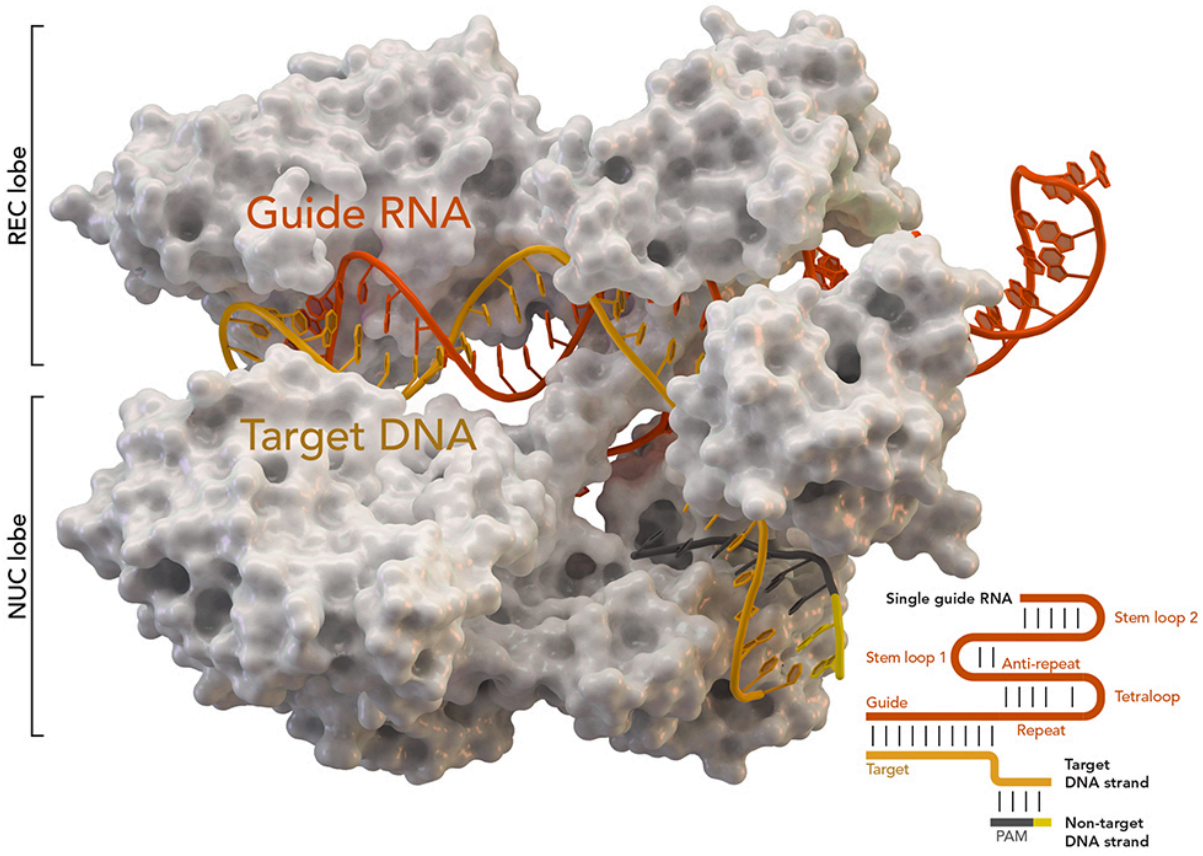


CRISPR-associated protein Cas9 (white) from Staphylococcus aureus based on Protein Database ID 5AXW. Credit: Thomas Splettstoesser (Wikipedia, CC BY-SA 4.0)

Ilya Finkelstein chuckles when recounting the origins of the project that landed the University of Texas scientist and his colleagues in the prestigious academic journal *Cell*.

According to a peer-reviewed article, they found a way for scientists to more safely use a new kind of gene editing technique called CRISPR - a technology that has embroiled much of the scientific world in seemingly fantastic debates, such as whether creating mushrooms that don't brown in supermarkets could lead to people creating new animals or ordering babies with designer DNA.

Thanks to CRISPR, the debates are no longer abstract arguments inspired by science-fiction films. Those CRISPR-modified mushrooms made the shelves of stores. Chinese scientists in 2015 left much of the world aghast by using CRISPR to manipulate human embryos, an experiment that failed in the way many scientists feared it would. Only two years later, with the ethical and legal implications of CRISPR only marginally clearer, more than a dozen clinical trials are using the technology on human cells, with a study on human embryos garnering international headlines earlier this month.

Finkelstein and his colleagues have developed a technique that basically makes CRISPR less likely to scramble the genes it modifies, according to their paper. They say their work could enable scientists to cure a disease such as diabetes while significantly reducing the risk of a side effect such as cancer.

The breakthrough was the result of collaboration that sounds like the setup for a joke about a mismatched set of people walking into a bar - a mechanical engineer, a mathematician, a biochemist and an astrophysicist. And it started with a humble plea:

"Does anyone want to earn a Ph.D. digging through the garbage?"

Finkelstein began making the offer in 2014. As an assistant professor in the Department of Molecular Biosciences - and someone whose lab is dedicated to studying the how the human genome is linked to aging - he had been looking for an opportunity to work with CRISPR.

The technology - whose name is short for "clustered regularly interspaced short palindromic repeats" - was discovered by scientists performing experiments on yogurt cultures. They found that bacteria have immune systems that fight viruses quite effectively. Other scientists expanded on the idea; eventually came CRISPR, which exploits the system that bacteria use to protect themselves. It allows researchers to use proteins to cut out selected segments of DNA and, if needed, insert new ones.

CRISPR is fast enough that experiments that used to take months or years can be finished in days, accelerating the pace of scientific advancement. The technique has spread so quickly that no one at the University of Texas is sure how many of its scientists are using CRISPR in their experiments.

Scientists are still determining the various ways CRISPR molecules interact with various types of DNA. A key question: how accurate are CRISPR molecules? Do they sometimes confuse one sequence of DNA for another, snipping one instead of the other? How do you test for that?

Finkelstein is among the scientists excited about what the technique can do for humanity by, for instance, improving crop yields. But he cautions that the technology is nowhere near ready for the mind-bogglingly complex task of modifying the DNA of each cell in an adult, and is still not ready for use in human embryos.

"That said, no one is listening to me," he told the Austin American-Statesman. "So why not try to make this safer?"

The idea started with an expensive DNA sequencer that researchers on the floor above Finkelstein's lab have been using to analyze peoples' genes. The DNA is loaded onto special slides before being placed in the machine, which uses a chemical process to analyze the DNA. Once used, those slides were thrown away - complete with the DNA. Finkelstein saw a ready source of genetic material on which to test CRISPR.

The problem: Finkelstein had trouble finding people interested in joining the project.

"I guess the moral of the story is, a) don't try to sell a project by telling people they will be digging through trash, and b) find someone who is too fearless or naive to know what they're doing," he said.

Wry observations aside, what scientists are doing with CRISP goes beyond evolution. Finkelstein notes that people can now use a jellyfish gene to make green corn - something that would never have naturally evolved.

"Essentially, we're short-circuiting evolution. Now we can do things evolution can never do," Finkelstein said. "We're at the 'Gattaca' moment," he added, referencing the 1997 sci-fi film about genetic manipulation, "I really think that."

As Finkelstein was looking for people to help make the "moment" safer, Cagri Savran happened to be looking for a project on which to work.

Savran is a professor of mechanical and biomedical engineering at Purdue University. His lab makes medical equipment, such as sensors that test for blood impurities. He had collaborated with UT professor Andy Ellington in the past and, when the opportunity for a sabbatical in 2014-15 arose, Ellington persuaded Savran to spend it in Austin.

Savran wanted to branch out from the world of engineering by partnering with people who practice "fundamental science." He thought he might bring over one of his projects from Purdue. Instead, Ellington walked Savran across the hallway and introduced him to Finkelstein. Maybe, Ellington suggested, Savran could build a machine to conduct experiments using the DNA slides Finkelstein had noticed were sitting in a trash bin one floor up.

Savran agreed. He was not aware that the project had a shortage of scientists.

"I'm an engineer," he told the Statesman. "I love gadgets, finding gadgets and tearing them apart and putting them together, even if I have to pull parts out of the trash."

The team working on the project eventually grew so large that three people are listed as lead authors on the paper, with another 10 as co-authors. Team members say the project worked largely because they could meld different skill sets, mentalities and approaches. Finkelstein, who is listed as the principle investigator, said his contribution boiled down to two main jobs: "One, to help them talk to one another, and two, to keep the lights on."

The fundamental challenge the team faced: compiling the mind-boggling amount of data needed to really know if CRISPR can be trusted to accomplish what its proponents say it can. To that end, Savran built a machine mounted on a high-resolution microscope. To use it, scientists load the slides created by DNA sequencer and then squirt them with a solution that includes CRISPR proteins. The contraption then tracks the various proteins and their interactions with various sections of DNA.

It essentially performs many mini-experiments at once.

The machine's design and software are open source. That means that, in theory, anyone with the funds can build one and run it. Savran said his challenges included making the machine simple enough that any biology student could use it, sturdy enough that no one would break it, and reliable enough that "you don't have it leaking all over a really expensive microscope."

Other challenges called for other specialties. For instance, human cells are mostly empty space, with the DNA in those cells so small and far apart that mapping them is akin to mapping the cosmos. So Finkelstein recruited William Press, a UT astrophysicist who has branched out into computer science and "computational biology." Press and his team helped write the software to track what was happening on the slides - a system based on ones used to chart the far reaches of the universe.

The UT team hopes the work will form the basis for all sorts of CRISPR tests around the world.

This is where the ethics debate meets the realities of human progress.

In a study published earlier this month in the journal *Nature*, scientists explained how they successfully edited genes in human embryos to repair a common serious mutation that causes fatal heart conditions. As a *New York Times* article noted, "The research marks a major milestone and, while a long way from clinical use, it raises the prospect that gene editing may one day protect babies from a variety of hereditary conditions."

The article added: "The achievement is also an example of human genetic engineering, once feared and unthinkable, and is sure to renew ethical concerns that some might try to design babies with certain traits, like greater intelligence or athleticism."

The UT researchers envision their work being used to help prevent or cure sickness - tailoring individual gene therapies for people, as opposed to tailoring new kinds of people. The hypothetical question du jour at UT asks: What if scientists can discover whether a particular CRISPR protein will cure a case of diabetes but also cause cancer?

Finkelstein argues that if they can, they should - even if they cannot make the technology perfect.

"Whenever you look at this precision cutting, you always worry about cutting in the wrong place," Finkelstein said. "Nothing is going to be perfect. The question is whether we can live with the risk."

Savran uses a more Austin-specific line of argument.

"One thing I had to get used to was the traffic in the Austin area," he said. "I had to take extra care to drive as safely as possible. Even then there was risk. But the benefit, at least for me, was worth the risk."