atoms. That collective behavior enables a modest number of electrons, shepherded to the right place by an electric field, to radically change the material's behavior, from insulator to conductor to superconductor. Interactions with the supercells also force electrons to slow down and feel each other's presence, which makes it easier for them to pair off, a requirement for superconductivity.

Now, researchers have shown they can dial desired properties into small regions of the sheet by slapping on a pattern of metallic "gates" that subject different areas to varying electric fields. Both groups built devices known as Josephson junctions, in which two superconductors flank a thin layer of nonsuperconducting material, creating a valve for controlling the flow of superconductivity. "Once you have demonstrated that then the world is open," says Klaus Ensslin, a physicist at ETH Zurich, and a co-author on one of the studies, posted to the preprint server arXiv on 30 October. Conventional Josephson junctions serve as the workhorse of superconducting electronics, found in magnetic devices for monitoring electrical activity in the brain, and ultrasensitive magnetometers.

"It's a totally new way of making materials without chemistry."
Eva Andrei, Rutgers University, New Brunswick

The MIT group went further, electrically transforming their Josephson junctions into other submicroscopic gadgets, "just as proof of concept, to show how versatile this is," says lab leader Pablo Jarillo-Herrero, whose group posted its results to arXiv on 4 November. By tuning the carbon into a conductor-insulator-superconductor configuration, they were able to measure how tightly the electron pairs were yoked together—an early clue to the nature of its superconductivity and how it compares with other materials. The team also built a transistor that can control the movement of single electrons; researchers have studied such single-electron switches as a way to shrink circuits and diminish their thirst for energy.

Magic angle graphene devices are unlikely to challenge consumer silicon electronics anytime soon. Graphene itself is easy to make: Sheets of it can be stripped off blocks of graphite with nothing more than Scotch tape. But the devices must be chilled nearly to absolute zero before they can superconduct. And maintaining the precise twist is awkward, as the sheets tend to wrinkle, disrupting the magic angle. Reliably creating smoothly twisted sheets even just 1 micron or two across is still a challenge, and researchers don't yet see a clear path toward mass production. "If you wanted to do a real complex device," Jarillo-Herrero says, "you'd need to create hundreds of thousands of [graphene substrates] and that technology doesn't exist."

Nevertheless, many researchers are excited by the promise of exploring electronic devices without worrying about the constraints of chemistry. Materials scientists typically have to find substances with the right atomic properties and fuse them together. And when the concoction is finished, the different elements may not mesh in the desired way.

In magic angle graphene, in contrast, all the atoms are carbon, eliminating messy boundaries between different materials. And scientists can change the electronic behavior of any given patch at the press of a button. These advantages grant unprecedented control over the material, Ensslin says. "Now, you can play like on a piano."

That control could simplify quantum computers. Those being developed by Google and IBM rely on Josephson junctions with properties that are fixed during fabrication. To operate the finicky qubits, the junctions must be manipulated jointly in cumbersome ways. With twisted graphene, however, qubits could come from single junctions that are smaller and easier to control.

Kin Chung Fong, a Harvard University physicist and member of Raytheon BBN Technologies's quantum computing team, is enthusiastic about another potential use for the material. In April, he and his colleagues proposed a twisted graphene device that could detect a single photon of far infrared light. That could be useful for astronomers probing the faint light of the early universe; their current sensors can spot lone photons only in the visible or nearly visible parts of the spectrum.

The field of twistronics remains in its infancy, and the fussy process of twisting microscopic specks of graphene to the magic position still requires sleight of hand, or at least deft lab work. But regardless of whether twisted graphene finds its way into industrial electronics, it's already profoundly changing the world of materials science, says Eva Andrei, a condensed matter physicist at Rutgers University, New Brunswick, whose lab was one of the earliest to notice twisted graphene's peculiar properties.

"It's a really new era," she says. "It's a totally new way of making materials without chemistry." ■

Charlie Wood is a journalist in New York City.

MICROBIOLOGY

Like CRISPR, mystery gene editor began as a virus fighter

The genetic elements called retrons can only edit single-cell organisms, so far

By **Elizabeth Pennisi**

Seven years ago, an understanding of nature inspired a revolutionary new technology, when researchers turned a defense system used by bacteria to thwart viruses into the gene-editing tool now known as CRISPR. But for another emerging gene editor the understanding has lagged the applications. For several years, researchers have been adapting retrons—mysterious complexes of DNA, RNA, and protein found in some bacteria—into a potentially powerful way to alter genomes of single-cell organisms. Now, biology is catching up, as two groups report evidence that, like CRISPR, retrons are part of the bacterial immune arsenal, protecting the microbes from viruses called phages.

On 5 November in *Cell*, one team described how a specific retron defends bacteria, triggering newly infected cells to self-destruct so the virus can't replicate and spread to others. The *Cell* paper "is the first to concretely determine a natural function for retrons," says Anna Simon, a synthetic biologist at Strand Therapeutics who has studied the bacterial oddities. Another paper, which so far has appeared only as a preprint, reports a similar finding.

The new understanding of retrons' natural function could boost efforts to put them to work. Retrons are "quite efficient tools for accurate and efficient genome editing," says Rotem Sorek, a microbial genomicist at the Weizmann Institute of Science and an author of the *Cell* study. But they don't rival CRISPR yet, in part because the technology hasn't been made to work in mammalian cells.

In the 1980s, researchers studying a soil bacterium were puzzled to find many copies of short sequences of single-stranded DNA littering the cells. The mystery deep-

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ened when they learned each bit of DNA was attached to an RNA with a complementary sequence. Eventually they realized an enzyme called reverse transcriptase had made that DNA from the attached RNA, and that all three molecules—RNA, DNA, and enzyme—form a complex.

Similar constructs, dubbed retrons for the reverse transcriptase, were found in many bacteria. "They really are a remarkable biological entity, yet nobody knew what they were for," says Ilya Finkelstein, a biophysicist at the University of Texas, Austin.

Sorek came upon an early hint of their function when he and his colleagues searched through 38,000 bacterial genomes for genes used to fight off phages. Such genes tend to be close to one another, and his team developed a computer program that searched for new defense systems next to the genes for the CRISPR and other known antiviral constructs. One stretch of DNA stood out to Weizmann graduate student Adi Millman because it included a gene for a reverse transcriptase flanked by stretches of DNA that didn't code for any known bacterial proteins. By chance, she came across a paper about retrons and realized that the mysterious sequences encoded one of their RNA components. "That was a nontrivial leap," Sorek says.

The team then noticed that the DNA encoding retron components often accompanied a protein-coding gene, and the protein varied from retron to retron. The team decided to test a hunch that the cluster of sequences represented a new phage defense. They went on to show that bacteria needed all three components— the DNA-RNA hybrid, reverse transcriptase, and the second protein—to defeat a variety of viruses.

For a retron called Ec48, Sorek and colleagues showed the associated protein delivers the coup de grâce by homing in on a bacterium's outer membrane and altering its permeability. The researchers concluded in the *Cell* report that the retron somehow "guards" another molecular complex called RecBCD that is the bacterium's first line of antiviral defense. Some phages deactivate the complex, which triggers the retron to unleash the membrane-destroying protein and kill the infected cell, the team found.

A second group has reached similar conclusions. Led by Athanasios Typas, a microbiologist at the European Molecular Biology Laboratory (EMBL), Heidelberg, the group realized that next to the genes coding for a retron in a *Salmonella* bacterium was a gene for a protein toxic to *Salmonella*. The team discovered the retron normally keeps the toxin under wraps, but activates it in the presence of phage proteins.

The two groups met at an EMBL meeting in the summer of 2019. "It was refreshing to see how complementary and converging our work was," Typas says. The teams simultaneously posted preprints on their work in June on bioRxiv. (The second group's paper is under review.)

Even before these discoveries, other researchers had taken advantage of retrons' then-mysterious features to devise new gene editors. CRISPR easily targets and binds to or cuts desired regions of the genome, but so far it isn't very adept at introducing new code in the target DNA. Retrons, combined with elements of CRISPR, seem able to do better thanks to their reverse transcriptases: They can manufacture lots of copies of a desired sequence, which can be spliced efficiently into the host genome. "Because CRISPR-based systems and retrons have different strengths, combining them is a highly promising strategy," Simon says.

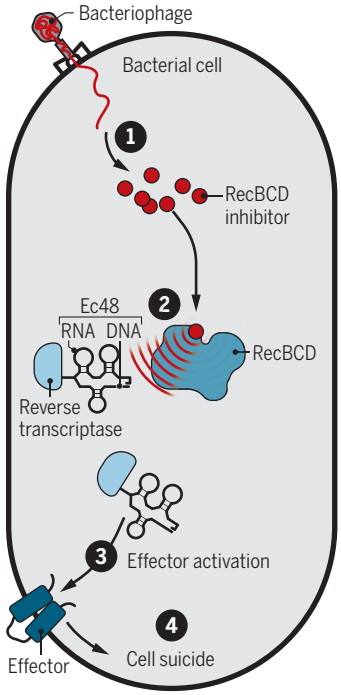
In 2018, researchers in Hunter Fraser's Stanford University lab introduced a retron-derived base editor, dubbed CRISPEY (Cas9 retron precise parallel editing via homology). First, they made retrons whose RNA matched yeast genes, but with one base mutated. They combined them with CRISPR's "guide RNA," which homes in on the targeted DNA, and the Cas9 enzyme that acts as CRISPR's molecular scissors. Once Cas9 cut the DNA, the cell's DNA repair mechanisms replaced the yeast gene with the DNA generated by the retron's reverse transcriptase.

CRISPEY enabled Stanford graduate student Shi-An Anderson Chen and his colleagues to efficiently make tens of thousands of yeast mutants, each different by just one base. That let them determine, for example, which bases were essential for yeast to thrive in glucose. "CRISPEY is very cool and extremely powerful," says Harmit Malik, an evolutionary biologist at the Fred Hutchinson Cancer Research Center. This year, two other teams—led by geneticist George Church at Harvard University and Massachusetts Institute of Technology synthetic biologist Timothy Lu—described similar feats in bacteria in bioRxiv preprints.

Researchers are excited about retrons, but caution they have a lot more to learn about how to turn these bacterial swords into plowshares. "It could be that retrons will be as revolutionary as CRISPR has been," Simon says. "But until we understand more about the natural biology and synthetic behavior of retrons, it is difficult to say." ■

How bacteria fight back

Genetic elements called retrons defend bacteria against viruses called bacteriophages (bottom). Retrons work by sensing viral invasion, then triggering the infected cell to self-destruct (graphic).

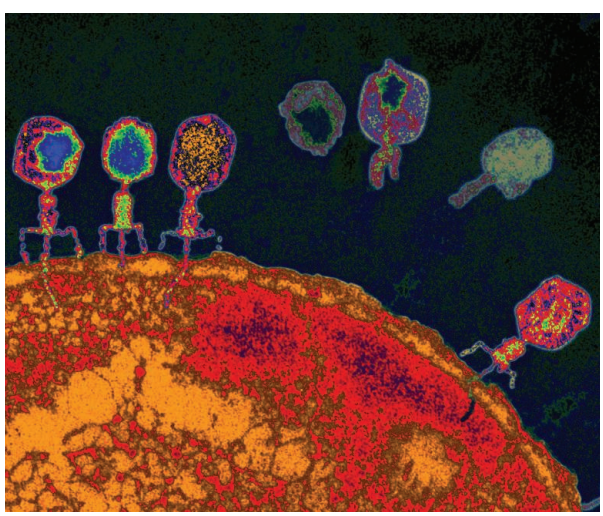


1 Many invading bacteriophages carry genes for proteins that inhibit RecBCD, the bacterium's first line of defense against viruses.

2 The Ec48 retron guards RecBCD. When it senses this defense system has been disarmed, the retron mounts a backup response.

3 Each retron is associated with a protein—called an effector—that can be toxic to the cell. When backup is needed, the retron activates this toxin.

4 Ec48's activated effector digs into and disrupts the cell membrane, so the cell dies before the virus has a chance to replicate.



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Science

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Elizabeth Pennisi

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