

## How the US CRISPR patent probe will play out

Decision could determine who profits from the gene-editing technique in future.

- [Heidi Ledford](#)

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Emmanuelle Charpentier (left) and Jennifer Doudna (right) seek gene-editing patents.

There is no shortage of optimism about [the scientific potential](#) of CRISPR–Cas9, a technique that can precisely alter the genomes of everything from wheat to elephants. But there is a great deal of confusion over who will benefit financially from its use.

On 10 March, the US Patent and Trademark Office (USPTO) will [begin an investigation](#) into who deserves the patent on using CRISPR–Cas9 to edit genes. This ‘patent interference’ could determine who profits from CRISPR in coming years.

Already, companies have sprung up to take advantage of the technique in agriculture, industrial biotechnology and the treatment of human diseases. One firm, Editas Medicine in Cambridge, Massachusetts, raised US\$94 million when it went public on 2 February, even though it does not expect to enter clinical trials until 2017.

*Nature* takes a look at what the interference proceeding entails and what it could mean for the fate of CRISPR–Cas9.

### Who’s who in the patent interference?

One patent claim comes from a team led by molecular biologist [Jennifer Doudna](#) at the University of California, Berkeley, and microbiologist Emmanuelle Charpentier, now at Umeå University in Sweden and the Max Planck Institute for Infection Biology in Berlin. They published a 2012 paper demonstrating that the Cas9 enzyme can be directed to cut specific sites in isolated DNA ([M. Jinek \*et al.\* \*Science\* 337, 816–821; 2012](#)), and initiated their patent application on 25 May 2012.

Another team, led by [Feng Zhang](#) at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, published a 2013 paper demonstrating the application of CRISPR–Cas9 in mammalian cells ([L. Cong \*et al.\* \*Science\* 339, 819–823; 2013](#)). Zhang’s team began a patent application on 12 December 2012.

Although the Berkeley team filed first, the Broad team submitted its application to an expedited review programme, and was awarded the patent in April 2014. The Berkeley team then requested a patent interference against the initial Broad patent plus 11 related Broad patents. On 11 January, the USPTO granted Berkeley’s request.

### What is a patent interference?

A relic from the past. Until a few years ago, the United States awarded patents to those who could show that they were the first to invent, rather than simply the first to file the patent. Under that system, when competing inventors claimed to have created the same invention first, the USPTO declared an interference proceeding to determine which deserved the patent.

The United States switched to a first-to-file system in March 2013. But several key CRISPR–Cas9 patents were filed before the change.

### What will happen during the patent-interference hearing?

A panel of three USPTO patent judges will hear evidence from both sides to establish which team invented the application of CRISPR–Cas9 for gene editing. Much of the action will be carried out over the telephone or through written documents. But there will probably be some oral arguments, and these could include

testimony from the academic inventors.

Patent interferences can be highly technical, says John Conley, a legal scholar at the University of North Carolina in Chapel Hill. “It’s hard for me to cite anything more convoluted in the law than this,” he says. “It’s mind-boggling.” The USPTO panel will probably try to determine not only which team was the first to use CRISPR–Cas9 for gene editing, but which conceived of the invention first.

The process could be messy. During the era of ‘first-to-invent’ patents, some companies kept ‘inventor’s notebooks’: when someone at the firm thought of a new invention, they were to write it down in the notebook and have the entry notarized in case it came into play during future patent disputes. Few academic labs go to such lengths.

### **When will we find out who has won?**

The law that did away with the United States’ first-to-file policy also introduced changes intended to expedite interferences. But a verdict on the CRISPR patents could still be months, or even years, away. And given the high financial stakes, many expect the losing party to appeal against the USPTO interference decision, further dragging out the process.

### **Will this be the only CRISPR patent interference?**

Not necessarily. In its filings to the Securities and Exchange Commission, Editas Medicine highlighted a potential interference claim by a Seoul company called ToolGen. Having multiple interferences over the same patent is rare, says Conley, but possible.

### **Is the patent landscape any clearer in Europe?**

No. The Broad and MIT team also fast-tracked several of its applications at the European Patent Office (EPO), and has been awarded several patents so far. Doudna’s single application is pending.

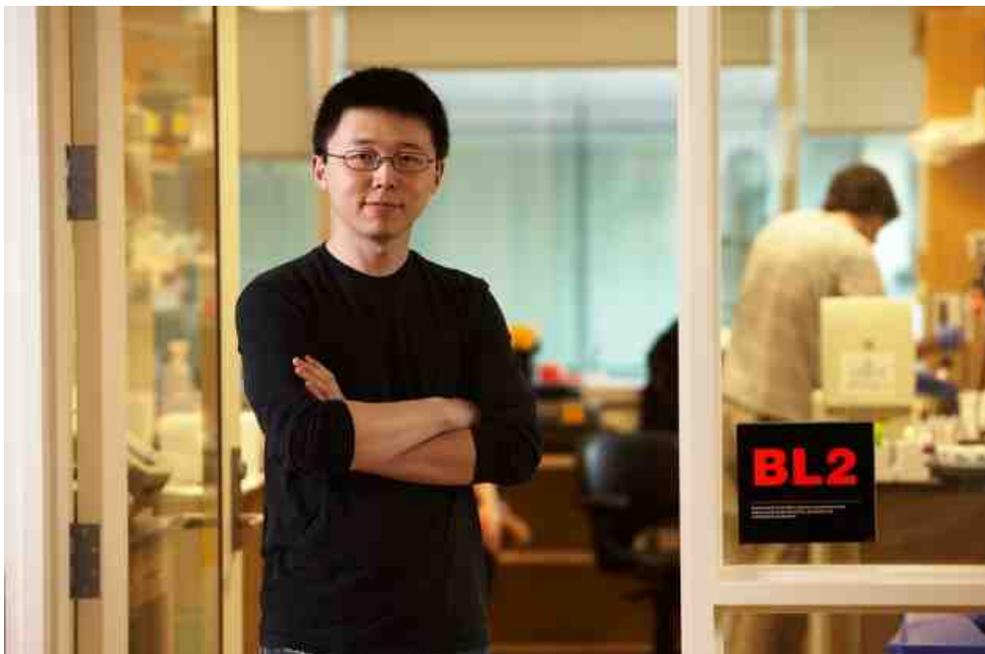
Although the EPO does not have an interference process, outside parties can formally object to a patent. By 11 November 2015, the deadline for objections to the Broad’s first European CRISPR–Cas9 patent, nine parties had come forward — launching an opposition procedure that can take years to resolve.

Once that process is finished, participants can appeal. This adds another four or five years to the clock, says Michael Roberts, a partner at the intellectual-property law firm Reddie & Grose in Cambridge, UK. For this reason, Roberts believes that it will be several years before there is clarity on the earliest CRISPR–Cas9 patents in Europe.

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### **FENG ZHANG: DNA’s master editor**

*Borrowing from bacteria, a biologist helps to create a powerful tool for customizing DNA.*  
By Daniel Cressey



Kent Dayton

With a nip here and a tuck there, a DNA-cutting mechanism that bacteria use to protect themselves from viruses became one of the hottest topics in biomedical research in 2013. And a young neuroscientist with a penchant for developing tools helped to make it happen.

Thirty-two-year-old Feng Zhang of the Massachusetts Institute of Technology in Cambridge is among those leading the charge in using a system called CRISPR/Cas to edit genomes cheaply, easily and precisely. In January, his group showed that the system works in eukaryotic cells — ones with membrane-bound nuclei, including those of all animals and plants. This confirmed its potential for tweaking the genomes of mice, rats and even primates to aid research, improve human-disease modelling and develop treatments ([L. Cong et al. \*Science\* 339, 819–823; 2013](#)).

But as hot as the story has been this year, “the CRISPR craze is likely just starting”, says Rodolphe Barrangou, a microbiologist at North Carolina State University in Raleigh.

CRISPRs (clustered regularly interspaced palindromic repeats) are DNA sequences that many bacteria and archaea use to defend themselves. They encode RNAs that can specifically recognize a target sequence in a viral genome. The RNAs work in complex with a CRISPR-associated protein, or Cas, which snips the DNA of the invader.

In 2012, Jennifer Doudna of the University of California, Berkeley, Emmanuelle Charpentier, now at the Helmholtz Centre for Infection Research in Braunschweig, Germany, and colleagues showed that they could reprogram a CRISPR system to cut apart potentially any specific DNA target ([M. Jinek \*et al.\* \*Science\* 337, 816–821; 2012](#)). By controlling how the break is repaired, they can edit a gene — adding, switching or removing parts to change the protein it encodes or disable it altogether.

CRISPR is similar to two earlier genome-editing methods: the zinc-finger nuclease (ZFN) and transcription activator-like effector nuclease (TALEN) systems. But both of those locate target sequences using proteins that are often difficult and costly to produce. CRISPRs use RNA, making them easier to design. Zhang says he feels limited only “by what I can imagine is possible”.



*Nature* special: [The year in review](#)

Although Charpentier and Doudna are generally credited with kick-starting the growth of CRISPR editing, Zhang demonstrated its vast potential by showing that it works in eukaryotes, a finding independently confirmed by George Church at Harvard Medical School in Boston, Massachusetts ([P. Mali \*et al.\* \*Science\* 339, 823–826; 2013](#)). Zhang says that he had a head start on many of the teams who jumped in: he had been investigating the technique before it was widely reported, and because his lab had previously fine-tuned ZFNs and TALENs to edit DNA, it had procedures in place for perfecting CRISPRs.

Zhang now says that he feels challenged to be creative with other applications. One particularly ambitious project on his slate is to build a library of CRISPRs that can delete any sequence in an organism’s entire genome in 100–200 base-pair increments. This could make it easier to investigate the function of non-coding DNA.

But he is most interested in using CRISPR to treat neuropsychiatric conditions such as Huntington’s disease and schizophrenia by repairing genes in human tissues. To pursue therapeutic use of the technology, he and other CRISPR pioneers last month launched a company called Editas Medicine, based in Cambridge, that is backed by US\$43 million in venture-capital funding. CRISPR “allows us to start to make corrections in the genome”, says Zhang. “Because it’s easy to program, it will open up the door to addressing mutations that affect few people but are very devastating.”

## CRISPR: gene editing is just the beginning

The real power of the biological tool lies in exploring how genomes work.

Heidi Ledford

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Illustration by Ryan Snook

Molecular biologists are riding a wave of new technologies made possible by CRISPR.

Whenever a paper about CRISPR–Cas9 hits the press, the staff at Addgene quickly find out. The non-profit company is where study authors often deposit molecular tools that they used in their work, and where other scientists immediately turn to get them. It is also where other scientists immediately turn to get their hands on these reagents. “We get calls within minutes of a hot paper publishing,” says Joanne Kamens, executive director of the company in Cambridge, Massachusetts.

Addgene's phones have been ringing a lot since early 2013, when researchers first reported<sup>1, 2, 3</sup> that they had used the CRISPR–Cas9 system to slice the genome in human cells at sites of their choosing. “It was all hands on deck,” Kamens says. Since then, molecular biologists have rushed to adopt the technique, which can be used to alter the genome of almost any organism with unprecedented ease and finesse. Addgene has sent 60,000 CRISPR-related molecular tools — about 17% of its total shipments — to researchers in 83 countries, and the company's CRISPR-related pages were viewed more than one million times in 2015.

Much of the conversation about CRISPR–Cas9 has revolved around its potential for treating disease or editing the genes of human embryos, but researchers say that the real revolution right now is in the lab. What CRISPR offers, and biologists desire, is specificity: the ability to target and study particular DNA sequences in the vast expanse of a genome. And editing DNA is just one trick that it can be used for. Scientists are hacking the tools so that they can send proteins to precise DNA targets to toggle genes on or off, and even engineer entire biological circuits — with the long-term goal of understanding cellular systems and disease.

“For the humble molecular biologist, it's really an extraordinarily powerful way to understand how the genome works,” says Daniel Bauer, a haematologist at the Boston Children's Hospital in Massachusetts. “It's really opened the number of questions you can address,” adds Peggy Farnham, a molecular biologist at the University of Southern California, Los Angeles. “It's just so fun.”

Here, *Nature* examines five ways in which CRISPR–Cas9 is changing how biologists can tinker with cells.



**Nature special: CRISPR**

### **Broken scissors**

There are two chief ingredients in the CRISPR–Cas9 system: a Cas9 enzyme that snips through DNA like a pair of molecular scissors, and a small RNA molecule that directs the scissors to a specific sequence of DNA to make the cut. The cell's native DNA repair machinery generally mends the cut — but often makes mistakes.

That alone is a boon to scientists who want to disrupt a gene to learn about what it does. The genetic code is merciless: a minor error introduced during repair can completely alter the sequence of the protein it encodes, or halt its production altogether. As a result, scientists can study what happens to cells or organisms when the protein or gene is hobbled.

But there is also a different repair pathway that sometimes mends the cut according to a DNA template. If researchers provide the template, they can edit the genome with nearly any sequence they desire at nearly any site of their choosing.

In 2012, as laboratories were racing to demonstrate how well these gene-editing tools could cut human DNA, one team decided to take a different approach. “The first thing we did: we broke the scissors,” says Jonathan Weissman, a systems biologist at the University of California, San Francisco (UCSF).

Weissman learned about the approach from Stanley Qi, a synthetic biologist now at Stanford University in California, who mutated the Cas9 enzyme so that it still bound DNA at the site that matched its guide RNA, but no longer sliced it. Instead, the enzyme stalled there and blocked other proteins from transcribing that DNA into RNA. The hacked system allowed them to turn a gene off, but without altering the DNA sequence<sup>4</sup>.

The team then took its 'dead' Cas9 and tried something new: the researchers tethered it to part of another protein, one that activates gene expression. With a few other tweaks, they had built a way to turn genes on and off at will<sup>5</sup>.



**CRISPR, the disruptor**

Several labs have since published variations on this method; many more are racing to harness it for their research<sup>6</sup> (see 'Hacking CRISPR'). One popular application is to rapidly generate hundreds of different cell lines, each containing a different guide RNA that targets a particular gene. Martin Kampmann, another systems biologist at UCSF, hopes to screen such cells to learn whether flipping certain genes on or off affects the survival of neurons exposed to toxic protein aggregates — a mechanism that is thought to underlie several neurodegenerative conditions, including Alzheimer's disease. Kampmann had been carrying out a similar screen with RNA interference (RNAi), a technique that also silences genes and can process lots of molecules at once, but which has its drawbacks. “RNAi is a shotgun with well-known off-target effects,” he says. “CRISPR is the scalpel that allows you to be more specific.”

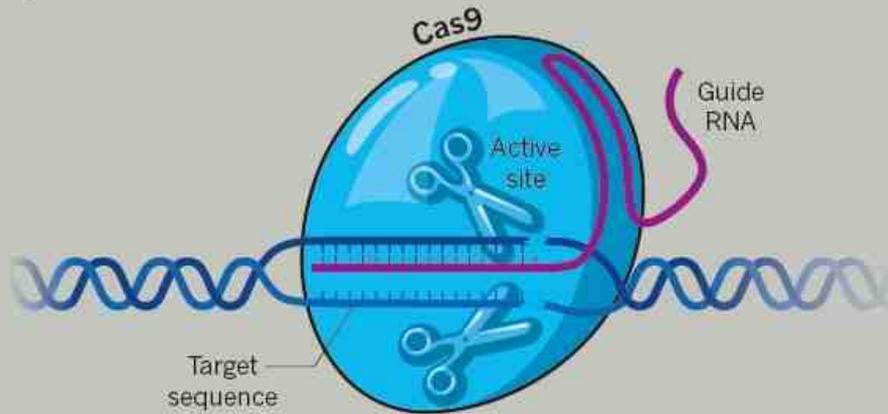
## **HACKING CRISPR**

By modifying the molecular machinery that powers CRISPR–Cas9 gene editing, scientists can probe the functions of genes and gene regulators with

scientists can probe the functions of genes and gene regulators with unprecedented specificity.

### **Snip snip here**

There are two main components of CRISPR–Cas9: the Cas9 enzyme, which cuts DNA, and a snippet of RNA that guides these molecular scissors to the sequence that scientists want to cut.

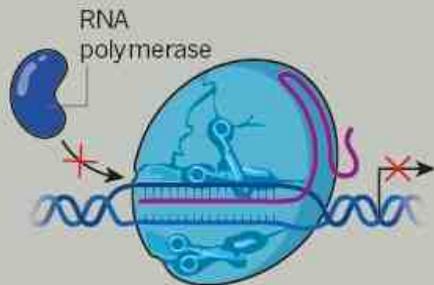


### **Broken scissors**

The Cas9 enzyme can be broken so that it no longer cuts DNA. But with the right guide RNA, it can still attach to specific parts of the genome.

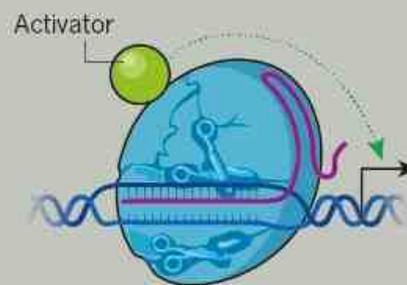
#### **CRISPR inhibition**

A broken, or 'dead', Cas9 enzyme will block the binding of other proteins, such as RNA polymerase, needed to express a gene.



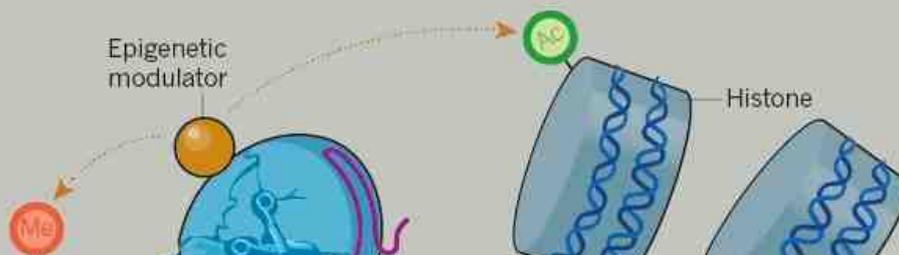
#### **CRISPR activation**

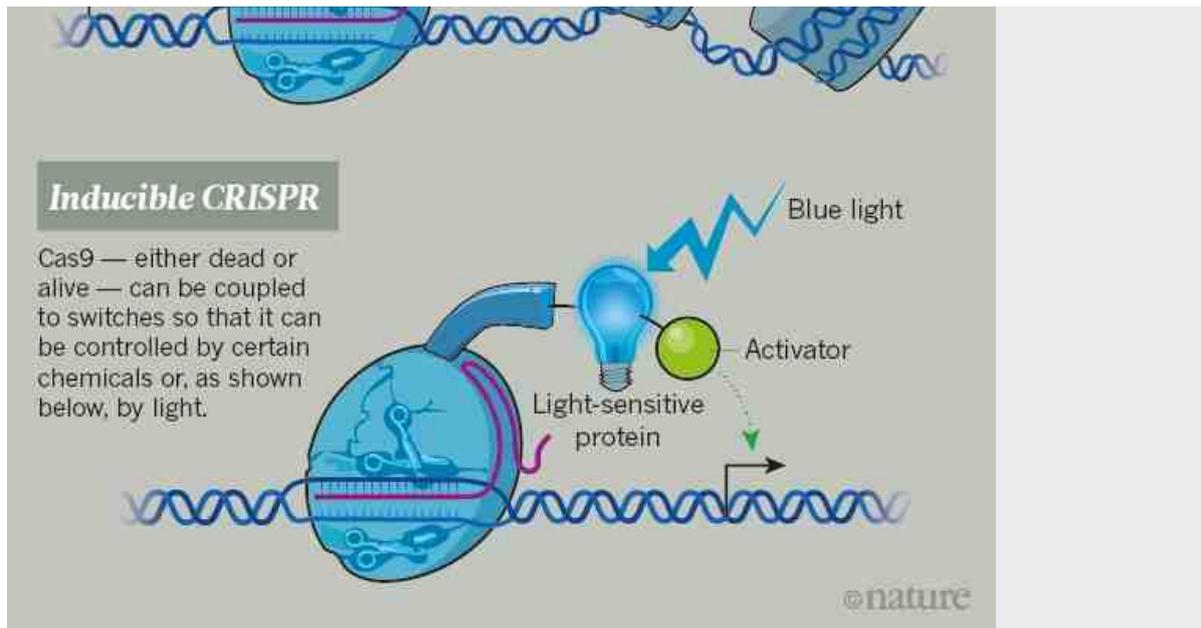
An activating protein can be attached to a dead Cas9 protein to stimulate expression of a specific gene.



### **CRISPR epigenetics**

A broken Cas9 enzyme can be coupled to epigenetic modifiers, such as those that add methyl groups (Me) to DNA or acetyl groups (Ac) to histone proteins. This will allow researchers to study how precisely placed modifications affect gene expression and DNA dynamics.





Nik Spencer/Nature

Weissman and his colleagues, including UCSF systems biologist Wendell Lim, further tweaked the method so that it relied on a longer guide RNA, with motifs that bound to different proteins. This allowed them to activate or inhibit genes at three different sites all in one experiment<sup>7</sup>. Lim thinks that the system can handle up to five operations at once. The limit, he says, may be in how many guide RNAs and proteins can be stuffed into a cell. “Ultimately, it’s about payload.”

That combinatorial power has drawn Ron Weiss, a synthetic biologist at the Massachusetts Institute of Technology (MIT) in Cambridge, into the CRISPR–Cas9 frenzy. Weiss and his colleagues have also created multiple gene tweaks in a single experiment<sup>8</sup>, making it faster and easier to build complicated biological circuits that could, for example, convert a cell’s metabolic machinery into a biofuel factory. “The most important goal of synthetic biology is to be able to program complex behaviour via the creation of these sophisticated circuits,” he says.

### CRISPR epigenetics

When geneticist Marianne Rots began her career, she wanted to unearth new medical cures. She studied gene therapy, which targets genes mutated in disease. But after a few years, she decided to change tack. “I reasoned that many more diseases are due to disturbed gene-expression profiles, not so much the single genetic mutations I had been focused on,” says Rots, at the University Medical Center Groningen in the Netherlands. The best way to control gene activity, she thought, was to adjust the epigenome, rather than the genome itself.



### Epigenome: The symphony in your cells

The epigenome is the constellation of chemical compounds tacked onto DNA and the DNA-packaging proteins called histones. These can govern access to DNA, opening it up or closing it off to the proteins needed for gene expression. The marks change over time: they are added and removed as an organism develops and its environment shifts.

In the past few years, millions of dollars have been poured into cataloguing these epigenetic marks in different human cells, and their patterns have been correlated with everything from brain activity to tumour growth. But without the ability to alter the marks at specific sites, researchers are unable to determine whether they cause biological changes. “The field has met a lot of resistance because we haven’t had the kinds of tools that geneticists have had, where they can go in and directly test the function of a gene,” says Jeremy Day, a neuroscientist at the University of Alabama at

Birmingham.

CRISPR–Cas9 could turn things around. In April 2015, Charles Gersbach, a bioengineer at Duke University in Durham, North Carolina, and his colleagues published<sup>9</sup> a system for adding acetyl groups — one type of epigenetic mark — to histones using the broken scissors to carry enzymes to specific spots in the genome.

The team found that adding acetyl groups to proteins that associate with DNA was enough to send the expression of targeted genes soaring, confirming that the system worked and that, at this location, the epigenetic marks had an effect. When he published the work, Gersbach deposited his enzyme with Addgene so that other research groups could use it — and they quickly did. Gersbach predicts that a wave of upcoming papers will show a synergistic effect when multiple epigenetic markers are manipulated at once.

The tools need to be refined. Dozens of enzymes can create or erase an epigenetic mark on DNA, and not all of them have been amenable to the broken-scissors approach. “It turned out to be harder than a lot of people were expecting,” says Gersbach. “You attach a lot of things to a dead Cas9 and they don’t happen to work.” Sometimes it is difficult to work out whether an unexpected result arose because a method did not work well, or because the epigenetic mark simply doesn’t matter in that particular cell or environment.



#### Where in the world could the first CRISPR baby be born?

Rots has explored the function of epigenetic marks on cancer-related genes using older editing tools called zinc-finger proteins, and is now adopting CRISPR–Cas9. The new tools have democratized the field, she says, and that has already had a broad impact. People used to say that the correlations were coincidental, Rots says — that if you rewrite the epigenetics it will have no effect on gene expression. “But now that it’s not that difficult to test, a lot of people are joining the field.”

#### CRISPR code cracking

Epigenetic marks on DNA are not the only genomic code that is yet to be broken. More than 98% of the human genome does not code for proteins. But researchers think that a fair chunk of this DNA is doing something important, and they are adopting CRISPR–Cas9 to work out what that is.

Some of it codes for RNA molecules — such as microRNAs and long non-coding RNAs — that are thought to have functions apart from making proteins. Other sequences are ‘enhancers’ that amplify the expression of the genes under their command. Most of the DNA sequences linked to the risk of common diseases lie in regions of the genome that contain non-coding RNA and enhancers. But before CRISPR–Cas9, it was difficult for researchers to work out what those sequences do. “We didn’t have a good way to functionally annotate the non-coding genome,” says Bauer. “Now our experiments are much more sophisticated.”

Farnham and her colleagues are using CRISPR–Cas9 to delete enhancer regions that are found to be mutated in genomic studies of prostate and colon cancer. The results have sometimes surprised her. In one unpublished experiment, her team deleted an enhancer that was thought to be important, yet no gene within one million bases of it changed expression. “How we normally classify the strength of a regulatory element is not corresponding with what happens when you delete that element,” she says.

#### “I wish I had had this technology sooner. My postdoc would have been a lot shorter.”

More surprises may be in store as researchers harness CRISPR–Cas9 to probe large stretches of regulatory DNA. Groups led by geneticists David Gifford at MIT and Richard Sherwood at the Brigham and Women’s Hospital in Boston used the technique to create mutations across a 40,000-letter sequence, and then examined whether each change had an effect on the activity of a nearby gene that made a fluorescent protein<sup>10</sup>. The result was a map of DNA sequences

that enhanced gene expression, including several that had not been predicted on the basis of gene regulatory features such as chromatin modifications.

Delving into this dark matter has its challenges, even with CRISPR–Cas9. The Cas9 enzyme will cut where the guide RNA tells it to, but only if a specific but common DNA sequence is present near the cut site. This poses little difficulty for researchers who want to silence a gene, because the key sequences almost always exist somewhere within it. But for those who want to make very specific changes to short, non-coding RNAs, the options can be limited. “We cannot take just any sequence,” says Reuven Agami, a researcher at the Netherlands Cancer Institute in Amsterdam.

Researchers are scouring the bacterial kingdom for [relatives of the Cas9 enzyme that recognize different sequences](#). Last year, the lab of Feng Zhang, a bioengineer at the Broad Institute of MIT and Harvard in Cambridge, characterized a family of enzymes called Cpf1 that work similarly to Cas9 and could expand sequence options<sup>11</sup>. But Agami notes that few alternative enzymes found so far work as well as the most popular Cas9. In the future, he hopes to have a whole collection of enzymes that can be targeted to any site in the genome. “We’re not there yet,” he says.

### **CRISPR sees the light**

Gersbach’s lab is using gene-editing tools as part of an effort to understand cell fate and how to manipulate it: the team hopes one day to grow tissues in a dish for drug screening and cell therapies. But CRISPR–Cas9’s effects are permanent, and Gersbach’s team needed to turn genes on and off transiently, and in very specific locations in the tissue. “Patterning a blood vessel demands a high degree of control,” he says.



#### **Should you edit your children’s genes?**

Gersbach and his colleagues took their broken, modified scissors — the Cas9 that could now activate genes — and added proteins that are activated by blue light. The resulting system triggers gene expression when cells are exposed to the light, and stops it when the light is flicked off<sup>12</sup>. A group led by chemical biologist Moritoshi Sato of the University of Tokyo rigged a similar system<sup>13</sup>, and also made an active Cas9 that edited the genome only after it was hit with blue light<sup>14</sup>.

Others have achieved similar ends by combining CRISPR with a chemical switch. Lukas Dow, a cancer geneticist at Weill Cornell Medical College in New York City, wanted to mutate cancer-related genes in adult mice, to reproduce mutations that have been identified in human colorectal cancers. His team engineered a CRISPR–Cas9 system in which a dose of the compound doxycycline activates Cas9, allowing it to cut its targets<sup>15</sup>.

The tools are another step towards gaining fine control over genome editing. Gersbach’s team has not patterned its blood vessels just yet: for now, the researchers are working on making their light-inducible system more efficient. “It’s a first-generation tool,” says Gersbach.

### **Model CRISPR**

Cancer researcher Wen Xue spent the first years of his postdoc career making a transgenic mouse that bore a mutation found in some human liver cancers. He slogged away, making the tools necessary for gene targeting, injecting them into embryonic stem cells and then trying to derive mice with the mutation. The cost: a year and US\$20,000. “It was the rate-limiting step in studying disease genes,” he says.

A few years later, just as he was about to embark on another transgenic-mouse experiment, his mentor suggested that he give CRISPR–Cas9 a try. This time, Xue just ordered the tools, injected them into single-celled mouse embryos and, a few weeks later — *voilà*. “We had the mouse in one month,” says Xue. “I wish I had had this technology sooner. My

postdoc would have been a lot shorter.”

Researchers who study everything from cancer to neurodegeneration are embracing CRISPR-Cas9 to create animal models of the diseases (see page 160). It lets them engineer more animals, in more complex ways, and in a wider range of species. Xue, who now runs his own lab at the University of Massachusetts Medical School in Worcester, is systematically sifting through data from tumour genomes, using CRISPR-Cas9 to model the mutations in cells grown in culture and in animals.

Researchers are hoping to mix and match the new CRISPR-Cas9 tools to precisely manipulate the genome and epigenome in animal models. “The real power is going to be the integration of those systems,” says Dow. This may allow scientists to capture and understand some of the complexity of common human diseases.



#### Genome editing: 7 facts about a revolutionary technology

Take tumours, which can bear dozens of mutations that potentially contribute to cancer development. “They’re probably not all important in terms of modelling a tumour,” says Dow. “But it’s very clear that you’re going to need two or three or four mutations to really model aggressive disease and get closer to modelling human cancer.” Introducing all of those mutations into a mouse the old-fashioned way would have been costly and time-consuming, he adds.

Bioengineer Patrick Hsu started his lab at the Salk Institute for Biological Studies in La Jolla, California, in 2015; he aims to use gene editing to model neurodegenerative conditions such as Alzheimer’s disease and Parkinson’s disease in cell cultures and marmoset monkeys. That could recapitulate human behaviours and progression of disease more effectively than mouse models, but would have been unthinkable expensive and slow before CRISPR-Cas9.

Even as he designs experiments to genetically engineer his first CRISPR-Cas9 marmosets, Hsu is aware that this approach may be only a stepping stone to the next. “Technologies come and go. You can’t get married to one,” he says. “You need to always think about what biological problems need to be solved.”

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