NEWS · 07 OCTOBER 2020

Pioneers of revolutionary CRISPR gene editing win chemistry Nobel

Emmanuelle Charpentier and Jennifer Doudna share the award for developing the precise genome-editing technology.

Heidi Ledford & Ewen Callaway

Jennifer Doudna and Emmanuelle Charpentier share the 2020 Nobel chemistry prize for their discovery of a game-changing gene-editing technique. Credit: Alexander Heinel/Picture Alliance/DPA

It's CRISPR. Two scientists who pioneered the revolutionary gene-editing technology are the winners of this year's Nobel Prize in Chemistry.

The Nobel Committee's selection of Emmanuelle Charpentier, now at the Max Planck Unit for the Science of Pathogens in Berlin, and Jennifer Doudna, at the University of California, Berkeley, puts an end to years of speculation about who would be recognized for their work developing the CRISPR–Cas9 gene-editing tools. The technology allows precise edits to the genome and has swept through laboratories worldwide since its inception in the 2010s. It has countless applications: researchers hope to use it to alter human genes to eliminate diseases; create hardier plants; wipe out pathogens and more.

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CRISPR, the disruptor

"The ability to cut DNA where you want has revolutionized the life sciences," said Pernilla Wittung Stafshede, a biophysical chemist and member of the Nobel chemistry committee, at the prize announcement. "The 'genetic scissors' were discovered just eight years ago, but have already benefitted humankind greatly."

Doudna and Charpentier and their colleagues did critical early work characterizing the system, but several other researchers have been cited — and recognized in other high-profile awards — as key contributors in the development of CRISPR. They include Feng Zhang at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, George Church at Harvard Medical School in Boston, Massachusetts, and biochemist Virginijus Siksnys at Vilnius University in Lithuania (see 'CRISPR's many pioneers').

Doudna was "really sound asleep" when her buzzing phone woke her and she took a call from a *Nature* reporter, who broke the news. "I grew up in a small town in Hawaii and I never in a 100 million years would have imagined this happening," says Doudna. "I'm really stunned, I'm just completely in shock."

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"I know so many wonderful scientists who will never receive this, for reasons that have nothing to do with the fact that they are wonderful scientists," Doudna says. "I am really kind of humbled."

Born from bacteria

CRISPR, short for clustered regularly interspaced short palindromic repeats, is a microbial 'immune system' that prokaryotes — bacteria and archaea — use to prevent infection by viruses called phages. At its core, the CRISPR system gives prokaryotes the ability to recognize precise genetic sequences that match a phage or other invaders and target these sequences for destruction using specialized enzymes.

Previous work had identified these enzymes, known as CRISPR-associated proteins (Cas), including one called Cas9. But Charpentier, working first at the University of Vienna and later at the Umeå Centre for Microbial Research in Sweden, identified another key component of the CRISPR system,

an RNA molecule that is involved in recognizing phage sequences, in the bacterium *Streptococcus pyogenes*, which can cause disease in humans.

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Charpentier reported the discovery in 2011 and that year struck up a collaboration with Doudna. In a landmark 2012 paper in *Science*[1], the duo isolated the components of the CRISPR–Cas9 system, adapted them to function in the test tube and showed that the system could be programmed to cut specific sites in isolated DNA. Their programmable gene-editing system has inspired a gold rush of countless applicationsin medicine, agriculture and basic science— and work continues to tweak and improve CRISPR and to identify other gene-editing tools.

"We were hoping that we could really translate this into a technology for rewriting the genetic code of cells and organisms," says Martin Jinek, a biochemist at the University of Zurich who was a postdoc in Doudna's lab and a co-first author on the pivotal *Science* paper. "What we didn't quite appreciate was how quickly the technology would be adopted by others in the field and then pushed forward."

CRISPR'S MANY PIONEERS

There would be no CRISPR without Francisco Mojica. The microbiologist, at the University of Alicante in Spain, helped to give the system its name. In 1993, Mojica identified peculiar repetitive DNA sequences in the genome of the archaeon *Haloferax*. He later showed that similar sequences were widespread in prokaryotes and matched genetic material in phages, viruses that infect bacteria.

In 2005, Mojica hypothesized that these sequences were part of a microbial immune system. With Ruud Jansen at Utrecht University in the Netherlands, Mojica came up with the now-Nobel-prizewinning acronym: CRISPR, short for clustered regularly interspaced short palindromic repeats. For his work on CRISPR, Mojica shared the US$500,000 Albany Medical Center medicine prize in 2017 with Charpentier, Doudna, Feng Zhang, and Luciano Marraffini at Rockefeller University in New York City.

Doudna and Charpentier weren't the only scientists who realized that the CRISPR system could be programmed to cut other pieces of DNA. In 2012 — around the time that the duo published their experiments showing that the CRISPR–Cas9 system could cut isolated DNA — a team led by biochemist Virginijus Šikšnys at Vilnius University in Lithuania, showed how the Cas9 enzyme could be instructed to cut predefined DNA sequences. In 2018, Šikšnys shared the Kavli Prize in Nanoscience with Doudna and Charpentier.

The Nobel Committee's decision not to include Zhang was one of the biggest surprises. The geneticist has been commonly named, with Charpentier and Doudna, as the trio most likely to win a Nobel prize for CRISPR. Zhang's team, in an early 2013 Science paper, modified the CRISPR–Cas9 system to make precise genome cuts in human and mouse cells. Church's team described work cutting DNA human cells around the same time.

Jin-Soo Kim, a genome engineer at the Institute for Basic Science in Daejeon, South Korea, and one of the first to adapt CRISPR for genome editing in a variety of different cells, says that although he is excited about the Nobel prize announcement, he was surprised that biochemist Dana Carroll at the University of Utah in Salt Lake City was overlooked. Carroll developed ways to deploy other enzymes, called zinc-finger nucleases, to edit genomes, well before the days of CRISPR.

Although CRISPR is easier to use than zinc-finger nucleases, Kim says that he considers Carroll to be the founder of the genome-editing field. "No doubt that Doudna and Charpentier deserve the recognition," he says. " But without the demonstration of genome editing via zinc-finger nucleases, not many people could have imagined the use of CRISPR-Cas9 for genome editing."

Race to commercialize

In less than a decade, researchers have used CRISPR-Cas9 to develop genome-edited crops, insects, genetic models and experimental human therapies. Clinical trials are under way to use the technique to treat sickle- cell -anaemia, hereditary blindness and cancer. Doudna, Charpentier and others in the field, have launched a generation of biotechnology companies aimed at developing the technique to achieve these goals.

But the technology has also generated controversy — in particular for its nascent applications in human cells. In November 2018, Chinese biophysicist He Jiankui announced that twin girls had been born from embryos that he and his colleagues had edited using CRISPR–Cas9. The news sparked an outcry: editing embryos raises a host of ethical, social and safety concerns, and many researchers worldwide quickly condemned He's work.

In September, an international panel convened by leading US and UK scientific societies concluded again that the technology is not ready for use in human embryos that are destined for implantation.

The work also sparked a fierce patent battle — chiefly between the Broad Institute and the University of California, Berkeley — that rumbles on to this day over who owns the lucrative intellectual property rights to CRISPR-Cas9 genome editing.

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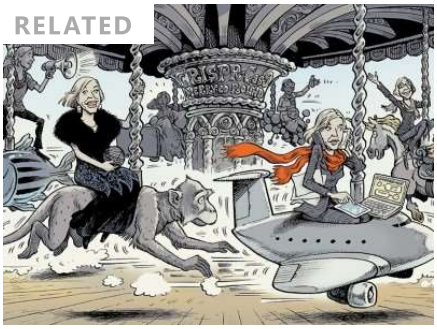

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Still, Church agrees with how the award was divvied up. Although he is proud of the work in his lab and Zhang's lab — which adapted the system to work in mammalian cells, opening the door to modelling and potentially treating human diseases — Church says that this work could be classified as engineering and invention, rather than scientific discovery. "I think it's a great choice," he says.

It is always difficult to single out a discovery for a prize, says Francis Collins, a geneticist and head of the US National Institutes of Health in Bethesda, Maryland. "Virtually nothing comes out of nowhere," he says. "It's hard when you look at any discovery to decide who to pick."

But one unique aspect of CRISPR-Cas9 genome editing has been the ease and versatility of the technique, he adds. "CRISPR-Cas made this so much more readily acceptable," says Collins. "There is no molecular biology laboratory that I know of that hasn't started to work with CRISPR-Cas."

doi: 10.1038/d41586-020-02765-9

Additional reporting by Emma Stoye.

References

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Nature | ISSN 1476-4687 (online)