Who owns gene editing?

Patents in the time of CRISPR

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New gene-editing technologies, like CRISPR, promise revolutionary advances in biology and medicine. However, several patent disputes in the USA and UK may have complicated who can use CRISPR. What does this mean for the future of gene editing?

Precisely editing the genetic code of living organisms has long been a supreme ambition of biologists. Editing the genome has the potential to cure genetic diseases, revive extinct species and combat public health crises, among other advances. The potential for the technology seems limited only by the human imagination. Previous efforts in the area, however, have proven less than satisfactory .

A recent advance in one gene-editing technology, Clustered Regularly Interspaced Short Palindromic Repeats—better known as CRISPR—may bring biologists' ambitions to fruition. This precision-editing system has so far lived up to its hype: CRISPR has been demonstrated to work in virtually every cell type attempted and appears almost infinitely flexible in modification .

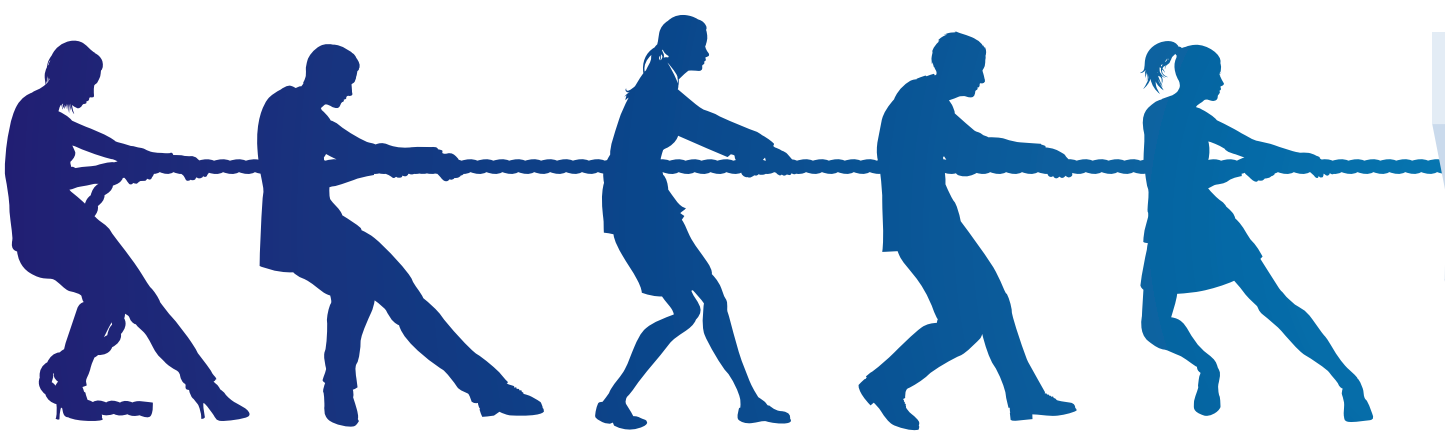
But the promise of the technology has generated a patent dispute among the technologies' creators: Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, now at the Max Planck Institute for Infection Biology in Berlin, on one side, and Feng Zhang of the Broad Institute, on the other. Resolving the patent dispute may ultimately decide who owns the rights to this crucial piece of biotechnology. This article outlines the law surrounding patents on biotechnology and explains the contours and effects of the current CRISPR patent disputes.

Patents

Broadly speaking, inventions present an informational paradox: often, costly and burdensome research is required to bring them to fruition, but once developed the invention becomes known to the public. Without some law restricting the copying of these inventions, many researchers may not have the incentive to engage in foundational research in the first instance.

Since at least the fifteenth century, the solution to this problem has been some form of patents: government issued rights to inventors—rights that allow inventors, for a limited period of time, to prevent others from copying their inventions. To be clear, patents are not inventors' rights to use and develop their own inventions; they are rights only to exclude others from copying them. Patents, consequently, are viewed as "limited rights, for a limited time". Nonetheless, this limited right can be tremendously valuable. Many pharmaceutical patents, for example, are worth billions of dollars.

Not all inventions deserve patent protection. Precisely because patents can be so valuable—and because patentees can essentially exclude others from developing certain areas of technology—patent laws throughout the world have established certain standards in an effort to ensure that only significant advances in science and technology receive patent protection. Today,



in the USA and UK, patents may be granted only for inventions that are new, useful and "inventive" or "non obvious." In addition, patentees must sufficiently disclose their inventions to the public—enough to enable others to make and use the invention. To meet these twin aims, patents, as documents, contain two parts: a written description of the invention, known as the specification, and the claims, short statements identifying the "metes and bounds" of the invention. The claims, in essence, define the patented invention.

In this way, the current system of patents ideally does double-duty in breaking the informational paradox of inventions. It encourages researchers to invest in expensive research by holding up the reward of a patent if they are successful. And it also requires inventors to disclose the fruits of that research to the public. Today, for better or worse, patents form an integral part of the research and development lifecycle for a host of industries.

The CRISPR patent dispute

Patent law has long faced the problem of contemporaneous invention: what to do when two inventors contemporaneously invent the same or a similar invention and each file competing patent applications? In much of the world, administrative efficiency dictates that the patent should be awarded to the first person to file. But, up until 2013 in the USA, the USA Patent and Trademark Office (PTO) awarded the patent to the first inventor . This presented several problems for the PTO—especially where, because of quirks of timing at the Patent Office, a later inventor but earlier filer was awarded the first patent. Through a restrictive reading of the patent statute, this circumstance potentially blocked the first inventor's patent application from being awarded.

The current CRISPR dispute involves similar difficulties. Doudna and Charpentier filed an early patent application covering a limited form of the CRISPR technology in May 2012. Zhang filed a similar application seven months later, in December 2012. But Zhang's attorneys requested that the PTO "fast-track" his application: a procedure allowed—for a fee—on shorter, less contentious applications. Zhang's attorneys' strategy worked and, as a result, Zhang was awarded his first patent in April 2014 and over a dozen more by the following year. During this time, however, Doudna and Charpentier's application suffered numerous technical difficulties at the PTO. And through much of 2014, it appeared that Zhang's issued patents would block their applications, even though the duo had good claims as both the first inventors and first filers.

In April 2015, with the CRISPR patent race slipping away from them, Doudna's attorneys requested that the PTO declare an interference proceeding: a trial, within the PTO, to determine the first inventor of a disputed technology. After receiving a recommendation from the patent examiner responsible for Doudna and Charpentier's application, the PTO formally instituted an interference proceeding in January 2016 .

At its core, the interference proceeding is designed to answer who invented what, first. To do that, a three-judge panel at the PTO will receive evidence concerning what Doudna, Charpentier and Zhang did in their laboratories, what they disclosed in their original patent applications and how an average molecular biologist would have viewed this information as the technology progressed through 2012. In addition, the panel must determine exactly which parts of Doudna and Charpentier's application overlap with Zhang's patents. To aid them in that determination, the panel drafts a "count," a hypothetical patent claim that covers both sets of technologies. Moving forward, the scientists' attorneys will file several sets of motions arguing that the count does or does not cover the technology in dispute, or that the count needs to be rewritten or broken up into several pieces to cover the contested inventions. In

addition, the attorneys will also file motions arguing that their respective clients were, in fact, the first to invent the CRISPR technology. The panel's ruling on these motions should come in January 2017 if not earlier.

Outside of the USA, however, no analogue to interference proceedings exists. European patent offices faced with the contemporaneous invention problem simply award the patent to the first filer. But there are other procedures to contest already issued patents at their respective patent offices. At the European Patent Office, for example, anyone may file an opposition to a patent issued within nine months, arguing that the granted patent fails the novelty, inventive step or disclosure requirements. This has, in fact, happened with the CRISPR technology, where, to date, nine entities—including one company, CRISPR Therapeutics, founded by Charpentier—have filed oppositions to one of Zhang's European patents. Decisions in those cases are not expected until the end of 2017, at the earliest. These disputes—both in the USA and elsewhere—concerning control of the CRISPR technology suggest that ownership over the CRISPR patents will take years to unravel, and will result in a complicated system of patent rights throughout the world.

The future of CRISPR research

The patent disputes over CRISPR will likely have significant impact over the future of research in the area. First and foremost, the disputes may very well affect the funding of companies currently engaged in CRISPR research. A recent Bloomberg report by Caroline Chen and Doni Bloomfield noted that several drug manufacturers have entered into funding arrangements with various CRISPR start-ups, some worth hundreds of millions of dollars. The companies currently developing CRISPR either have a direct stake in the outcome of the current patent dispute or could be affected if the ultimate victor decides to enforce its patents against them. As a consequence, the patent dispute may shape which companies are allowed to commercially develop the CRISPR technology.

Second, the patent dispute may also alter which research institutions continue to study CRISPR as a gene-editing technology. Well-heeled research

institutions that cannot come to a license agreement with the eventual owner of the CRISPR patents may find themselves on the outside, looking in. This is important to mention—especially in the USA—because, contrary to popular belief, there is no "research exemption" for patent infringement. In Europe, however, such research exemptions do exist under the national laws of each country, but may be limited where academic institutions partner with commercial developers.

Third, the CRISPR patent dispute, no matter which way it turns, may signal a fundamental shift in the litigation and enforcement of foundational biotechnology. Most revolutions in molecular biology—like recombinant DNA, PCR and RNAi—have been patented. And almost without exception, those technologies have been subject to free and easy licenses. But the CRISPR patent dispute appears to be shaping up to something different. It may very well signal a culture shift in academic research institutions from pure and translational research into profit-maximizing commercialization. While this is not altogether bad, it's likely to conflict with universities' broader educational missions to the public. As a result, which aspects of CRISPR will become subject to research, and by whom, may turn on those universities' financial interests in developing certain CRISPR technologies rather than their scientific or therapeutic importance.

Taken together, these shifts may complicate the future of gene editing. It may be difficult, for example, simply to determine whether one is infringing one of the variety of patents covering gene-editing technology. And even if the CRISPR patent disputes produce a clear winner, it is unclear how the victor will deploy licenses, to whom and at what price. Furthermore, gene editing, and CRISPR in particular, is progressing so rapidly that is unclear whether new developments will be covered by the current landscape. As one example, the count at issue in the USA interference proceeding requires the "hybridization" of a guide RNA and a tracrRNA . But it's unclear whether this allows the RNAs to exist in two separate pieces or if they need to be linked, covalently or by sequence, somehow.

To both of their credits, Doudna and Zhang have supported some "open science" protocols by making CRISPR constructs available through an online repository called AddGene. In that way, the scientists are engaging in that most noble of scientific practices: the sharing of results. But it remains unclear how their benevolence jibes with their patents and the current patent dispute. It is likely that the litigation will need to be resolved first.

Gene editing, and CRISPR in particular, heralds a foundational advance in molecular biology. Like previous advances in biotechnology, CRISPR is subject to several patents and is at the centre of a current wide-ranging patent dispute. But the current patent dispute surrounding CRISPR seems quite different from past cases. Even with a clear winner, the CRISPR patent dispute may ultimately complicate who can practise the technology going forward. It seems, then, that the development of CRISPR as a technology is a study as much of law as science. ■

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