Who Owns CRISPR?

With one US patent awarded and many other applications under consideration for the popular genome-editing technology, companies are adopting multiple strategies to navigate the complex intellectual property landscape.

By Jenny Rood | April 3, 2015

NISHIMASU ET AL.On April 15, 2014, the US Patent and Trademark Office (USPTO) awarded the first patent for use the CRISPR/Cas system to edit eukaryotic genomes to Feng Zhang of the Broad Institute and MIT. Originally a bacterial or archaeal defense system that uses viral DNA inserted into the genome (CRISPR) as a guide to cut the genomic material of invading viruses with a CRISPR-associated enzyme (Cas), researchers have found many ways to turn the system into a potent and quick way to edit specific genetic sequences. Although there are a handful of other CRISPR-related patents, covering everything from the system's use in yogurt production to a potential treatment for Huntington's disease, Zhang's patent was the first to be granted that covers the technology itself as a platform for a wide array of applications.

However, a patent application filed by Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, currently at the Helmholtz Center for Infection Research in Germany, predates Zhang's by seven months. Zhang's was most likely granted first because he applied for a fast-track patent, which awarded his intellectual property (IP) six months after he applied. "I think without Zhang fast-tracking his application, the PTO would have flagged it for being in conflict with Doudna's earlier application," Jacob Sherkow of the New York Law School wrote in an e-mail to *The Scientist*. Had his application not been expedited, "we may have been living in a world where there were no issued CRISPR patents" until 2017, he added. The Doudna/Charpentier patent application, assigned to the University of California and the University of Vienna, claims much of the same technology as the Zhang patent, and could be read to cover genome-editing either solely in prokaryotes or in both prokaryotes and eukaryotes. "It's hard to reconcile 100 percent of both of them," said Sherkow.

With Zhang's patent already on the books, the Doudna/Charpentier application may only be granted with significant revisions limiting its scope. Alternatively, the patent still under review could be granted, invalidating some of Zhang's claims and upending his current advantage. A final "nuclear option" if the Doudna/Charpentier application is not granted, Sherkow said, would be a patent dispute in court that could potentially leave both parties empty-handed. He estimates it could be three to five years before the CRISPR IP landscape will be fully settled. In the meantime, researchers and companies are employing a variety of strategies to make use of the hot technology now.

Taconic, a company that specializes in creating specialized rodent models for researchers, has licensed Zhang's patent. Although the company's rights under the license are quite broad, it plans only to edit the genomes of mouse and eventually rat models using CRISPR/Cas, said Taconic Vice President and General Counsel Gretchen Rice. Since May 2014, the company has offered researchers CRISPR-generated constitutive knockout and point-mutation knock-in mice, which take 12 weeks to deliver and cost one-third of what a traditional mouse generated by homologous recombination might, according to James Vitale, Taconic's director of product management. As Taconic continues to develop CRISPR products, including CRISPR-edited rats, Rice said the firm is actively monitoring the status of other patent applications. "Our intention would be to get a license to any patent that issues," she said.

Other companies, too, have decided not to wait. Horizon Discovery, a biotechnology company that makes genome-edited cell lines and animals, has licensed not only Zhang's patent, but also a previous application from George Church at Harvard and, via ERS Genomics, Charpentier's IP. "The ERS portfolio is more of a fundamental patent, and the Broad and Harvard IP are a little more application-specific," said Eric Rhodes, Horizon's chief technology officer. "We want to provide our customers with the feeling that when they're purchasing reagents from us, that they really couldn't have more comprehensive coverage right now than what we've got," he added. Licensing patents that have yet to be granted can be difficult, however. "What finally gets granted is very often different from what that initial filing might have been," Rhodes said.

Another option for smaller companies is to create their own, more specific IP. ToolGen, a South Korean genome-editing company, has licensed its international Patent Cooperation Treaty (PCT) patent, which covers CRISPR as a platform as well as a method for modifying the guide RNA to improve cell specificity, to a plant-breeding company and to Thermo Fischer for research applications. Seokjoong Kim, a research director at ToolGen, said he hopes that the Thermo license will make other companies aware of ToolGen's offerings and open opportunities for further commercial collaborations. "The complexity of the IP situation is making it hard for customers," said Kim, noting that some might hesitate to enter the CRISPR field because of the uncertainty surrounding the related patents.

Caribou Biosciences, a platform technology company founded by Doudna and her colleagues to develop CRISPR for research, therapeutic, agricultural, and industrial use, has also generated its own IP in addition to the exclusive license from the University of California and University of Vienna to the Doudna/Charpentier patent currently under review. It has licensed IP from other universities, and is developing Cas proteins other than Cas9, the most commonly used variant, according to Caribou Chief Executive Officer Rachel Haurwitz.

As more and more patents related to CRISPR/Cas are filed, and as more companies make use of the technology, many hope that the IP confusion will be resolved, possibly with an agreement among the different applicants and holders. For example, IP battles related to short interfering RNA (siRNA) technology were resolved by allowing academic researchers to use the technology for free, granting nonexclusive licenses to companies selling products that use the technology, and granting an exclusive license to one company, Alnylam, for therapeutic

applications. However, the CRISPR situation is further complicated by the existence of three startups that aim to develop gene-editing therapeutics: Editas Medicine, cofounded by Zhang; CRISPR Therapeutics, cofounded by Charpentier; and Intellia Therapeutics, cofounded by Doudna's Caribou Biosciences.

Intellia Chief Executive Officer Nessan Bermingham said it is hard to say how his company's strategy differs from that of Editas and CRISPR Therapeutics because they have yet to disclose their plans, but Intellia is currently focused on ex vivo modification of cells through a partnership with Novartis which will use the Doudna/Charpentier IP, if granted, to develop CRISPR-based applications for oncology, chimeric antigen receptor (CAR) T-cell therapies, and hematopoetic stem cells. In addition to licenses for the CRISPR/Cas9 technology, Bermingham said that a therapeutic application of the technology also requires IP in targeting and delivery of the edited genomes into patients. "We all need to be pragmatic and understand that our priority here is patients," Bermingham said. "We're not here to fight about IP."

Because therapeutic technologies take years to develop, the IP situation is less pressing for drug developers than for companies that wish to make use of the technology for research purposes now, Rhodes of Horizon Discovery said. If the experience of cross-licensing siRNA technology is any guide, that extra time may allow the scientists that currently appear to be in conflict to come to an agreement.

"It is not impossible that despite the business complexities that the parties are facing that they will still be able to work out an agreement amongst themselves," Sherkow said. "The technology seems so powerful, the technology seems so profitable, and the intellectual property issues seem so irreconcilable that it's a big mystery as to what's going to happen."