Broad Institute wins bitter battle over CRISPR patents

The US Patent and Trademark Office issues a verdict in legal tussle over rights to genome-editing technology.

Heidi Ledford 15 February 2017

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In December 2016, lawyers representing the University of California and the Broad Institute participated in oral arguments before a trio of patent-court judges.

The US Patent and Trademark Office (USPTO) has upheld a series of patents granted for CRISPR-Cas9 gene editing to the Broad Institute of MIT and Harvard.

The hotly anticipated decision could conclude a contentious battle between the Broad Institute in Cambridge, Massachusetts, and the University of California over intellectual property rights to the potentially lucrative technology. Although the Broad was awarded its patents first, the University of California was the first of the two to apply for a patent on the technology. The California contingent also argues that its team in

Berkeley had invented the technique before investigators at the Broad.

Lawyers representing the University of California filed for an 'interference' proceeding, in an effort to have the Broad's patents thrown out. But on 15 February, patent judges determined that there was no interference, meaning that the Broad's invention is distinct from that of the University of California's, and the Broad patents will stand. The University of California's patent application will now be referred back to an examiner, but legal challenges could continue.

Outlook hazy

Throughout the interference proceeding, which began in January 2016, the Broad's lawyers argued that the University of California's patent application did not specify how CRISPR-Cas9 editing could be adapted for use in eukaryotic cells — such as those in mice or people. The Broad's patents did make that distinction: as a result, the lawyers argued, the two patent families would not overlap. The strategy would give the Broad control of what are likely to be the most lucrative applications of CRISPR-Cas9 gene editing in plants, livestock and humans.

In the wake of the USPTO decision, however, officials at the University of California said that its patent would nevertheless cover the use of CRISPR-Cas9 in all cells: eukaryotic or otherwise. One of the inventors on that patent, molecular biologist Jennifer Doudna of the University of California in Berkeley, likened the situation to licensing permission to someone who wants to use green tennis balls. "They will have a patent on the green tennis balls," she said, referring to the Broad patents. "We will have a patent on all tennis balls."

Even so, stock in Editas Medicine — a Cambridge, Massachusetts biotechnology firm that has licensed the patents from the Broad Institute — surged shortly after the USPTO verdict was announced. "We are pleased with the USPTO's decision," said Editas president Katrine Bosley in a statement. "This important decision affirms the inventiveness of the Broad's work."

"I think this decision is fair," says Catherine Coombes, a patent lawyer at HGF in York, UK. The University of California's invention would cover the design of the RNA molecule that guides the key step in CRISPR-Cas9 gene editing, directing the Cas9 enzyme to a specific site in the

genome. But getting that system to work in eukaryotes was an additional inventive step, Coombes says.

Double trouble

At a press conference soon after the decision was released, University of California attorney Lynn Pasahow said the team had not yet decided whether it would appeal the patent judges' decision.

The two teams could also still reach a settlement, notes Noonan. The patent battle was unusually fierce given that inventors on both sides worked for academic institutions, and their inability to settle the case before moving to an interference proceeding surprised some.

For now, the USPTO decision creates uncertainty for companies that may want to use CRISPR-Cas9 gene editing in eukaryotic cells, says Kevin Noonan, a partner at the firm McDonnell Boehnen Hulbert & Berghoff in Chicago, Illinois. "Everybody gets to keep their patents," he says. "This is maximum uncertainty for people because you don't know if you have to get licenses from both sides."

If companies are forced to seek licenses from both sides, the cost of commercializing CRISPR-Cas9 gene editing could increase, he adds. "These things should be able to be settled between universities," says Noonan. "This will give a lot of fodder for those who think universities shouldn't be in the patenting business."

At the press conference, Doudna argued that the patent battle had not hampered research, given the speed with which researchers had taken up the technique and companies had rushed to commercialize it.

At the University of Delaware in Newark, technology transfer officer Joy Goswami recently started following the patent case when a large company waivered over whether to license some of his university's patents on applications of CRISPR-Cas9 in agriculture. The uncertainty around the patent landscape likely fueled the hestiation, he says — but such uncertainty is not uncommon in biotechnology, particularly in the first few years after a hot new invention.

"I don't know if this is a big impact," he says. "In general, I can tell that

there has been a sense of cautiousness."

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6 Takeaways from the CRISPR Patent Decision

The landmark ruling will have ripple effects

- By Sharon Begley, STAT on February 16, 2017

Credit: kentoh Getty Images
With the Broad Institute's big win on Wednesday in its battle over key patents on the CRISPR-Cas9 genome editing technology, everything is now crystal clear. Kidding!

The University of California seemed to be the loser, since the patent judges denied its effort to effectively block the Broad's patents. But in a call with reporters, Paul Alivisatos, UC Berkeley's vice chancellor for research, was upbeat that the ruling would allow UC's patent claims to finally "move forward." Berkeley biochemist Jennifer Doudna, whose pioneering CRISPR discoveries UC has been trying to patent, pronounced herself "delighted." Alivisatos dodged a question about why, if UC found the decision so great, it had issued a statement saying it was "considering all of its options," including an appeal.

That was right before the discussion turned to green tennis balls. (More on that below.) What inquiring minds want to know:

How can UC be happy?

When it filed for patents based on a 2012 discovery by Doudna and her chief collaborator, Emmanuelle Charpentier, it reached for the moon, asking for patents covering CRISPR genome editing "in any setting, including eukaryotic cells and other cell types." Eukaryotic cells are those with a nucleus, like animal and plant cells — including, of course, human cells. But the 2012 experiments showed only that CRISPR can cut DNA that's floating in a test tube; they didn't demonstrate such editing in cells. "It is undisputed that [Doudna's 2012 paper] does not report the results of experiments using the CRISPR-Cas9 system in a eukaryotic cell," the patent judges wrote in their ruling.

Editing of eukaryotic cells is what scientists led by the Broad's Feng Zhang (and separately, George Church of Harvard Medical School and his team) did.

Nevertheless, UC is putting a brave face on its prospects. "The patent the Broad received is for the use of CRISPR genome-editing technology in eukaryotic cells," Doudna told reporters after the patent decision. "Ours is for its use in all cells." (By "ours," she means the patents that UC filed for in 2012 but which had been held up by the legal proceeding.) The patent judges' opinion offered UC reason to hope: An "earlier disclosure of a genus does not

necessarily prevent patenting a species member of the genus," it wrote, suggesting that a larger category of something can be patented separately from a subset of it.

What will that mean for licensees of CRISPR patents?

UC believes that any company that wants to use CRISPR to develop human therapies — we're looking at you, Editas Medicine — will need to license not only the Broad's patents on eukaryotic cells but also those UC expects to receive on all kinds of cells. "It looks to me as if someone wanting to use the Broad patent would also have to license the UC patent," agreed law professor Hank Greely of Stanford University. "The UC patent (if granted) would be on any use; the Broad would be on use in eukaryotes. I think someone who wanted to do this in eukaryotes would need to have licenses to both."

That's where green tennis balls come in. "It is possible in patent law to get a patent on all tennis balls and for someone else to get a patent on green tennis balls," said UC attorney Lynn Pasahow. For "all tennis balls," read "all cells." For "green tennis balls," read "eukaryotic cells."

What sank UC's chance to invalidate the Broad's patents?

The judges' decision that there was no "interference in fact" meant that the CRISPR patents issued to the Broad covered different inventions than those in the patents UC applied for. And crucially, it was not "obvious" how to go from Doudna's work (CRISPRing free-floating DNA) to Zhang's (CRISPRing human cells). If the judges found that Zhang's achievement was "obvious," given what Doudna did, then it might not be patentable. UC tried with all its might to argue that extending Doudna's work in this way was obvious.

But the judges extensively cited Doudna's own statements, mostly to reporters, in concluding otherwise. "We weren't sure if CRISPR/Cas9 would work in eukaryotes — plant and animal cells," she said. Her team had experienced "many frustrations" getting CRISPR to work in human cells. Genetic "techniques for making these modifications in animals and humans have been a huge bottleneck in both research and the development of human therapeutics," she cautioned. The patent judges concluded that "the inventors themselves were uncertain" about making CRISPR work in human cells.

That could send a terrible message to scientists, said Dr. Robert Cook-Deegan of Arizona State University, an expert on legal and ethical issues surrounding biotechnology. "I hope this does not become the poster child that patent offices use to coach scientists not to be honest about uncertainties about their discoveries," he said. "The fact that Doudna's quotes were used by the judges mainly tells me Doudna was being honest. I hope scientists will continue to be honest and not succumb to being told they can't say things that might undermine a broad patenting strategy."

Please, is it almost over?

Legal experts told STAT that they expect UC to appeal to a circuit court, and Alivisatos kept the door to that wide open. But with the legal meter ticking — it passed $15 million for both sides last summer — patent experts offered a glimmer of hope for an end game. "This is the scenario that should most strongly drive the parties toward some kind of bargain," said law

professor Jorge Contreras of the University of Utah. Once Berkeley gets its patent or patents, “we’ll see whether their patents are required for commercial implementation of CRISPR. If so, companies could need something from both Broad and UC.” That recognition might pave the way to a settlement.

If so, it could and should have happened sooner, experts said. The Broad and UC “should have done a cross-licensing deal,” said Cook-Deegan. “Everyone could have kept more money in their pockets with much [less] scientific rivalry and animus, and they could still have divvied up the rewards.” The result “really is too bad,” he added, “because UC could use the money a whole lot more than the Broad.”

Might this be less momentous than it seems?

Yes.CRISPR-Cas9is unlikely to be the last genome-editing technology ever discovered. In 2015, Zhang and his colleagues discovered a version called Cpf1, which they’ve now patented and licensed to Editas. “I continue to think the possibility of inventing around the [CRISPR] patents seems very likely,” said Stanford’s Greely. Bacteria “have certainly come up with other ways to reach the same end [of genome editing], ways that aren’t covered by UC’s or the Broad’s claims. That could make either of these patents ultimately of little importance … especially if the licensing conditions give people a strong incentive to come up with invent-arounds.” Science will march on.