

PERSPECTIVE

The CRISPR-Cas9 Patent Appeal: Where Do We Go From Here?

Jacob S. Sherkow^{1-3,*}

Abstract

An appellate court in the United States affirmed the Patent Office's finding that the Broad Institute's patents covering eukaryotic applications of CRISPR-Cas9 was separately patentable over the University of California's (UC) earlier patent application. This does not bode well for future negotiations between UC and the Broad Institute, even as nuclease technology continues to eclipse the original dispute. This perspective explores the appellate decision, where UC goes from here, and what this all means for scientists in the future.

Introduction

On September 10, 2018, the U.S. Court of Appeals for the Federal Circuit announced its decision in the eagerly awaited CRISPR*-Cas9 patent appeal.¹ The court affirmed the U.S. Patent Trial and Appeal Board's (PTAB) decision that there was “no interference-in-fact” between the University of California's (UC) now famous patent application and a dozen of the Broad Institute's patents for eukaryotic applications of the technology.[†] In sum, the court concluded that using CRISPR-Cas9 in eukaryotic cells—at least, when the Broad Institute's patent application was filed in late 2012—was patentability distinct from UC's earlier disclosures of the technology *in vitro*.

There has been a considerable amount of ink spilled—some of it mine—on the merits of the decision itself.^{2,3} But it bears repeating that the decision, while likely *legally* correct, does not altogether mesh with the way research science is actually practiced. It is one of an increasing number of instances where science and patent law seem misaligned.

There are now perhaps four things to think about following the decision: (1) where UC goes from here; (2) what this means for UC's currently pending patent appli-

cation; (3) what this means for future negotiations between UC and the Broad Institute; and (4) what this all means for scientists and commercial developers using CRISPR technology.

1. Where Does UC Go from Here?

The Federal Circuit's affirmation of the U.S. PTAB decision stands as a “loss” in the UC's win-loss column. UC wanted the interference—it petitioned for it—so the PTAB's “no interference in fact” decision at least cut against UC's professed desire. The Federal Circuit's affirmation was in favor of the Broad, which argued from the beginning that it was engaged in different work. To that end, UC could ask for two forms of appeal: either a rehearing from the Federal Circuit but with a full panel of 12 judges, not simply the original three who decided the immediate case (a rehearing *en banc* in legal parlance), or a petition to the Supreme Court of the United States to hear the case.

Either form of appeal is unlikely to proceed. For a rehearing *en banc*, the Federal Circuit, writ large, agrees to hear such cases either where the original panel got its facts wrong or where the larger issue is of such importance to an understanding of patent law *doctrine* that a hearing from the entire court is needed. This simply isn't likely here. As noted in Judge Moore's Federal Circuit decision, this case was simply a straightforward application of deferring to the PTAB's findings.¹ The PTAB, in other words, may have gotten things wrong,

*Clustered Regularly Interspaced Short Palindromic Repeats.

[†]The University of California's application listed Jennifer Doudna as an inventor, as well as Emmanuelle Charpentier, then University of Umeå, Sweden, and other researchers from the University of Vienna. The Broad Institute's patents listed Feng Zhang, among others.

¹Innovation Center for Law and Technology, New York Law School, New York, New York; ²Department of Health Policy and Management, Columbia University Mailman School of Public Health, New York, New York; ³Center for Advanced Studies in Biomedical Innovation Law, University of Copenhagen Faculty of Law, Copenhagen, Denmark.

*Address correspondence to: Jacob S. Sherkow, 185 West Broadway, New York, NY 10013, E-mail: jacob.sherkow@nyls.edu

but its factual conclusions deserve deference. That's entirely a correct reading of the law. The Federal Circuit does not retry cases; it only looks for legal errors. This is an important but perhaps subtly missed point by most scientists. Just as in criminal prosecutions, it is exceedingly rare to get two jury trials.

UC could also appeal to the Supreme Court in a "petition for certiorari." There too the possibility of the Supreme Court hearing the case is unlikely. "Cert petitions" are typically granted where there is a novel legal issue in dispute or widespread disagreement among courts as to the interpretation of a particular law. In other cases, the Supreme Court hears cases because the effect of the Court's decision is likely to alter millions of lives. There are, to put it bluntly, not any of these cases. There are no novel legal issues in dispute; there is no contest as to how to interpret "no interference in fact" decisions from the PTAB; and the case, despite its *technical* importance, is unlikely to change millions of lives.

2. What Is the Status of UC's Patent Application?

The Federal Circuit's decision now means UC must go back to the Patent Office to salvage from it what it can. This is important: the Patent Office's decision on UC's patent application is unlikely to be the rubber stamp that some commentators have made it out to be.⁴ Using the analogy forwarded by the UC during the pendency of the interference, simply because the PTAB decided there wasn't an interference, *does not* mean UC will get a patent covering "all tennis balls," while the Broad Institute's eukaryotic patents will cover only green ones. Patent examiners can, and in some cases must, "reopen prosecution" of patent applications following a no interference-in-fact decision.⁵ And in high-profile cases such as this, with an expansive PTAB decision that goes well beyond the merits of simply whether an interference occurred, it would be surprising if the examiner did otherwise.

This is significant because of two documents that issued from the Patent Office during UC's case. The first is the PTAB's own no interference-in-fact decision that said in no uncertain terms that UC did not sufficiently describe or enable eukaryotic work in its patent application. Again, there are many reasons to doubt this from a scientific perspective, as I wrote earlier,⁶ but it is likely true as a matter of patent law. The second document is Virginijus Šikšnys's patent, disclosing ribonucleic CRISPR-Cas9 gene-editing complexes that also issued during that time (see Table 1).⁷ Šikšnys's patent was filed 6 weeks before UC's, and while patent applications are secret for the first 18 months after they are filed, if they are issued, they can be used against future patent applications according to the date they were *filed* not merely pub-

Table 1. Important Dates in the CRISPR-Cas9 Interference

Šikšnys files patent	March 20, 2012
UC files patent application	May 25, 2012
Broad files first patent	December 12, 2012
UC requests PTO declare an interference	April 13, 2015
PTO declares an interference	January 11, 2016
Interference oral argument	December 6, 2016
PTAB interference decision	February 15, 2017
Interference appeal	April 12, 2017
Appeal oral argument	April 30, 2018
Appeal decision	September 10, 2018

UC, University of California; PTO, Patent and Trademark Office; PTAB, Patent Trial and Appeal Board.

lished. Though this may seem like a rare circumstance, there is a provision of the patent statute that deals specifically with this exact situation, §102(e).

Given that, what path forward is there for UC's patent application? The PTAB's decision and Šikšnys's patent sit as the Scylla and Charybdis for UC's continued prosecution of its application. The navigable routes are likely claims covering gene editing using CRISPR-Cas9 but only through endogenous expression of Cas9 in prokaryotic cells. That of course is incredible narrow—it excludes RNP-mediated editing (as in Šikšnys) and all eukaryotic applications. But the method is still important for some applications, such as agriculture, which use expressed CRISPR-Cas9 to transform bacteria. Important single-guide, expressed CRISPR-Cas9 work is being conducted in *Agrobacterium tumefaciens*, for example.⁸

3. Is There Anything for UC and the Broad to Negotiate?

If those do end up as UC's claims, is there anything for the two sides to negotiate? Does UC have any leverage whatsoever? UC does have some; there is still some uncertainty regarding the dispute—what lawyers refer to as a "nuisance cost"—that is worth the parties at least sitting down to try to hammer things out. And beyond that, both sides likely want to save face from what has by and large been a source of embarrassment for two otherwise upstanding institutions. Such a settlement could be a cross-royalty agreement, where both sides receive royalties from licensing each other's patents (although the Broad would presumably take the lion's share). The parties could also pool their patents, with royalties flowing to a new institution that would fund research efforts between UC and the Broad.⁹ But these are hypotheticals; how the two sides will resolve their differences remains unclear, especially given the geographic differences in how the dispute continues to unfold. It is fair to say the Broad has "won" the CRISPR-Cas9 dispute here in the United States. However, the Broad has lost the majority of its patents on the same technology in Europe—a

dispute that is still ongoing and unlikely to be resolved any time soon. It is not as if UC has no leverage to negotiate; it's simply that its leverage is weak.

4. What Does this Mean for Scientists and Commercial Developers?

Academic scientists need not worry about the Federal Circuit's decision. CRISPR research should proceed as usual. Many CRISPR researchers' institutions already have licenses from both institutions, typically through constructs deposited with Addgene, a nonprofit repository of CRISPR plasmids.¹⁰ Beyond that, it is wholly unlikely that either institution—UC or the Broad—would sue other institutions for patent infringement, even if those institutions' researchers practiced the patented technology without a license. While there is no U.S. “research exemption” from patent infringement, the vast majority of CRISPR research seems covered by licenses, materials transfer agreements, or beneficence.

For for-profit companies, however, the decision is a bigger deal. Using CRISPR-Cas9 technology for therapeutic applications without a license from the Broad would be seriously problematic. This includes CRISPR Therapeutics and Intellia, who have stood shoulder-to-shoulder with UC during the dispute's trying times.¹¹ Those companies, if they continue to use Cas9, are ultimately going to need to visit the Broad, hat in hand, and somehow bargain for a license. And after the heat of the patent dispute between UC and the Broad, the Broad may well be obdurate. To some degree, you can't blame them. The UC's supposed refusal to negotiate and petition for an interference imposed tens of millions of dollars' worth of attorneys costs on the Broad and Editas.¹² Any license from the Broad to CRISPR Therapeutics or Intellia may seek to recoup those costs or at least some fraction of them. It's wholly unclear whether the companies would be willing to do so.

Conclusion

All of this—the patents, the dispute, the angst, and the bad blood—may be obviated by the rapid development of CRISPR technology. It is worth underscoring that the dispute *only* covers CRISPR Type II systems using

Cas9. However, there is now a menagerie of enzymes—some natural, others recombinant—that work as well, or better, or in other contexts.¹³ This development of the CRISPR technology—new enzymes, new systems, new applications, and new researchers—is what *The CRISPR Journal* is all about. New enzymes may very well make the patent dispute between UC and the Broad rather quaint. The dispute, and the Federal Circuit's decision, may have been important in their time, but like science generally, CRISPR too marches on.

Author Disclosure Statement

The author declares no competing interests.

References

1. Regents of the Univ. of Cal. v. Broad Institute, Inc., Case No. 2017-1907 (Fed. Cir. Sept. 10, 2018). Available online at <https://perma.cc/8ZFU-2NJA> (accessed October 9, 2018).
2. Sherkow JS. The CRISPR patent decision didn't get the science right. That doesn't mean it was wrong. STAT News, Sept. 11, 2018. Available online at <https://www.statnews.com/2018/09/11/crispr-patent-decision-science/> (archived at <https://perma.cc/34BB-CEP7>; accessed October 9, 2018).
3. Sherkow JS. The CRISPR patent landscape: past, present, and future. *CRISPR J* 2018;1:5–7. DOI: 10.1089/crispr.2017.0013.
4. Noonan KE. Federal Circuit affirms PTAB in appeal of CRISPR interference. Patent Docs (Blog), Sept. 10, 2018. Available online at www.patentdocs.org/2018/09/regents-of-the-university-of-california-v-broad-institute-inc-fed-cir-2018.html (archived at <https://perma.cc/KMB2-7GDQ>; accessed October 9, 2018).
5. Manual of Patent Examining Procedure § 2308. Available online at <https://www.uspto.gov/web/offices/pac/mpep/s2308.html> (archived at <https://perma.cc/K6BE-RERX>; accessed October 9, 2018).
6. Sherkow JS. Inventive steps: the CRISPR patent dispute and scientific progress. *EMBO Rep* 2017;18:1047–1050. DOI: 10.15252/embr.201744418.
7. Šikšnys V, Gasiunas G, Karvelis T, inventors; Vilnius University, assignee. RNA-directed DNA-cleavage by the Cas9-crRNA complex. U.S. Patent 9,637,739. March 15, 2013.
8. Kabin X, Minkenberg B, Yang Y. Boosting CRISPR/Cas9 multiplex editing capability with the endogenous tRNA-processing system. *Proc Natl Acad Sci U S A* 2015;112:3570–3575. DOI: 10.1073/pnas.1420294112.
9. Sherkow JS. Pursuit of profit poisons collaboration. *Nature* 2016;532:172–172. DOI: 10.1038/532172a.
10. LaManna CM, Barrangou R. Enabling the rise of a CRISPR world. *CRISPR J* 2018;1:205–208. DOI: doi.org/10.1089/crispr.2018.0022.
11. Ledford H. Court rules on CRISPR. *Nature* 2017;542:401.
12. Begley S. CRISPR patent fight: the legal bills are soaring. STAT News, Aug. 16, 2016. Available online at <https://www.statnews.com/2016/08/16/crispr-patent-fight-legal-bills-soaring/> (archived at <https://perma.cc/Z4FE-CT44>; accessed October 9, 2018).
13. Murovec J, Pirc Ž, Yang B. New variants of CRISPR RNA-guided genome editing enzymes. *Plant Biotech J* 2015;15:917–926. DOI: 10.1111/pbi.12736.