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PERSPECTIVE

The CRISPR Patent Landscape: Past, Present, and Future

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Abstract

The development of CRISPR depends, in part, on the patents—past, present, and future—covering it. As for the past, the origins of the CRISPR patent landscape predate its use as a gene editing technology. Fundamental patents covering CRISPR-Cas9 as a genomic editing system did not first arise until 2012; they sparked the now canonical dispute between the University of California and the Broad Institute. The present dispute has not stopped widespread licensing of critical patents, however, bringing with it an explosion of research from both academic and commercial sectors. Whether this broad availability will persist in the future remains uncertain. The ease and reliability of CRISPR threatens many future patents as being "obvious." Nor is it clear how academic scientists and technology transfer offices will respond to the patent dispute. Like the technology itself, the future of the CRISPR patent landscape depends on researchers and their institutions.

Introduction

Besides revolutionizing molecular biology, CRISPR* has intensified public discourse on science and science policy. For better or worse, this has also included a focus on the contentious and rapidly burgeoning patent estate covering CRISPR and its various applications. News stories describing CRISPR as a groundbreaking gene editing technology number in the thousands; hundreds of those, surprisingly, discuss the variety of patent issues involved.

The inaugural issue of *The CRISPR Journal* presents an excellent opportunity to take stock of the CRISPR patent landscape as a whole. As our new readers—namely, academic researchers and industry scientists—find themselves interacting with the patent system more and more, it becomes increasingly important for them to understand the major patent issues in this area. This shouldn't fail to include attorneys and social scientists who see the CRISPR patent estate as a case study of technological adoption and property rights. And this inaugural issue also provides the public—given its outsized interest in the technology—with a window for observing the history of the CRISPR patent estate. To that end, this Commentary provides not only a snapshot of the CRISPR patent dispute, but also an assessment of where the patents covering the technology have been, where they are now, and how they will be extended in the future: the past, present, and future landscape of CRISPR patents.

Past

The CRISPR patent estate—much like the invention of CRISPR itself—has been cloaked in its own mythology, an *ur*-combat myth between Jennifer Doudna (Howard Hughes Medical Institute (HHMI)/University of California, Berkeley [UC]) and Emmanuelle Charpentier (then of the University of Umëa, Sweden), on one side, and Feng Zhang (Broad Institute) on the other. The historical record of CRISPR's origins in the patent office, however, is much more prosaic.

The first U.S. patent to mention CRISPR in any form is likely U.S. Patent No. 7,919,277, naming W. Michael Russell, Rodolphe Barrangou,† and Philippe Horvath as inventors, and originally filed April 28, 2004—a full 8 years before patents claiming CRISPR as a gene editing technology. This '277 patent, assigned to Danisco A/S, the Danish food chemistry company, modestly claimed a method of sequencing certain CRISPR regions in a sample

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to detect variants of *Lactobacillus acidophilus*, the bacterial workhorse of industrial yogurt production. Barrangou and his collaborators filed several more CRISPR-related patent applications around this time, for similarly narrow applications encompassing strain typing, phage resistance, and various uses in bacteria.[1–3] Several more CRISPR patents followed soon after, including a patent claiming the use of CRISPR guide sequences to inactivate, through cleavage, microbial DNA—U.S. Patent No. 8,546,553, from the Terns' lab at University of Georgia, filed on July 25, 2008. Notably, Francisco Mojica—the Spanish microbiologist who was the first researcher to catalog CRISPR sequences across prokaryotic domains (see ''Crazy About CRISPR: An Interview with Francisco Mojica'' in this issue)—is not listed as an inventor on any patent applications, CRISPR or otherwise, filed around this time. The origins of the CRISPR patent estate, far from being forged in combat, were gently cultured in distant tuns.

It was not until 2012, rather, that U.S. patent applications claiming the use of CRISPR as a gene editing system began to appear—immediately prior to the seminal papers from the Virginijus Šikšnys lab (Vilnius University, Lithuania)[4] and the Doudna and Charpentier collaboration.[5] These patent applications from Šikšnys (filed March 20, 2012),[6] Doudna and Charpentier (filed May 25, 2012),[7] and Zhang (filed December 12, 2012)[8] all claimed some variation of the engineerable, single-guide RNA (sgRNA), Type II CRISPR system well-known today, focusing on the promising Cas9 endonuclease. Despite this sequence of patent filings, Zhang's patent application was the first to be granted by the U.S. Patent and Trademark Office (PTO), owing to the Broad's attorneys use of a strategically risky ''fast tracking'' procedure (formally known as a ''Petition to Make Special,'') and, arguably, the limiting of the application's claims to eukaryotic uses.[9] This established the now famous conflict between UC and the Broad Institute: Zhang's patent was granted first, even though, on the papers filed with the PTO, Doudna and Charpentier appeared to be both prior inventors and prior applicants.[3]

Beginning in January 2016, the PTO attempted to resolve this conflict through a particular type of procedure, an interference proceeding, at the suggestion of UC's attorneys.[10] Interference proceedings operate, essentially, as trials within the PTO to determine the scope and priority of two sets of conflicting patent applications. UC's attorneys argued that the Doudna patent application was the first to disclose the use of a sgRNA CRISPR-Cas9 gene-editing system in any cell type—prokarya, archaea, or eukarya.[11] The Broad's attorneys, by contrast, argued that Zhang's application was the first to demonstrate how the system worked specifically in eukaryotes, a separately patentable invention by their count.[11] After a year's worth of filings by each side's attorneys, a panel of Administrative Patent Judges heard oral arguments in a 40-minute hearing—held on a rainy Tuesday, December 6, 2016, in Hearing Room A at the PTO's headquarters in Alexandria, Virginia. Neither Doudna, Charpentier, Zhang, nor Šikšnys were present (Fig. 1).

On February 15, 2017, the PTO sided with the Broad's attorneys that Zhang's patent application covering eukaryotic applications of the technology was a separately patentable invention.[11] As a result, the two sets of applications—Doudna and Charpentier's and Zhang's—did not ''interfere in fact'' with one another. But as with many legal judgments, there is always the possibility of appeal—an avenue UC employed shortly after the PTO's decision.[12] We currently await the outcome of the appeal—likely to arrive in mid-2018—and the close of one chapter of the CRISPR patent estate's past.

Present

If the past of the CRISPR patent estate was one of narrow conflict, the present is one of widespread cooperation. CRISPR patents from both UC and the Broad Institute have been widely licensed to academic and industrial developers alike. UC, the Broad Institute, and more than 700 other institutions have all agreed to make their CRISPR constructs—and intellectual property—widely available through AddGene, a nonprofit repository and patent licensor of CRISPR technologies for academic organizations.[13] Despite the potential for conflict among the many institutions involved, academic CRISPR research has accelerated.

Academic institutions have also engaged in broad cross-licensing agreements. With respect to UC's foundational CRISPR patent application, for example, Doudna, Charpentier, and their spinoffs—Caribou Biosciences and CRISPR Therapeutics, respectively—originally had their own separate interests to the patent, a point of some contention during the interference trial. But shortly after the interference argument in 2016, all parties concerned announced a global cross-licensing agreement, putting to rest any potential conflict among them.[14]

The Broad Institute, too, recently announced a significant cross-licensing effort for its CRISPR patents for agricultural applications. The agreement brings together the Broad, Monsanto, DuPont Pioneer, Caribou Biosciences, ERS Genomics, and Vilnius University, apparently pooling the patent interests held by Doudna, Charpentier, Zhang, and Šikšnys.[15] Some of the agreement is perhaps a clever effort in gamesmanship to resolve the dispute partially between the Broad and UC. But all current

FIG. 1. "May it please the court": a courtroom artist captures legal arguments during a hearing at the PTO headquarters in Alexandria, Virginia, in December 2016. Courtesy: Dana Verkouteren.

agricultural users of CRISPR-Cas9 can reap its social benefits.

Commercial human therapeutic research proceeds apace, too, although with more constraints. Both UC and the Broad Institute have granted surrogate companies—companies with dual responsibilities to develop and license out CRISPR technologies—broad exclusive licenses to their patent interests, Caribou Biosciences, in UC's case, and Editas Medicine, in Broad's.[16] These exclusive licenses are not specific to any gene in the genome or even a human disease indication. As such, they extend far often beyond what the surrogate can develop itself. To that end, these surrogate licenses threaten to bottleneck commercial research if smaller developers cannot obtain the rights they need from the surrogates.[16] Yet, these uncertainties surrounding licensing have not stopped commercial companies from announcing ambitious human pilot studies and future clinical trials.[17]

Beyond the license arrangements for these foundational patents, many newer patent CRISPR applications are being filed. To date, the PTO has granted more than 450 patents pertaining to CRISPR in some form, many to institutions that have no relationship with either UC or the Broad Institute.[18] And this is likely just the tip of the iceberg: the PTO keeps patent applications secret until 18 months after they are filed, providing a current snapshot of patent applications only before mid-2016. In contrast to the past, the CRISPR landscape of the present is enormously varied, with more specific claims scattered among the hands of many.

Future

The CRISPR patent landscape of the future is uncertain—uncertain due to the power of the technology, the sentiment of researchers and their institutions, and the quirks of patent law. In particular, the power of CRISPR raises difficult legal questions about what constitutes a significant invention. All patents must be new, useful, and ''nonobvious''—that is, more than a mere trivial application of prior research. Now that the power of CRISPR as a genome-editing technology has been elucidated, is any future application of it nonobvious? The interference decision between UC and the Broad Institute rested, in part, on the finding that, in 2012, there was no ''reasonable expectation of success'' in developing a Type II CRISPR-Cas9 system in eukaryotes.[11] Whether that was indeed

true in 2012 remains open for debate, but it is certainly no longer the case. Today, it seems that there is a reasonable expectation of success in using CRISPR as a genome-editing tool for any system or cell type, and that, at a minimum, is at least obvious to try using CRISPR to accomplish these goals—two standards in patent law that strongly counsel against the patenting of follow-on inventions. CRISPR-based genome editing, in other words, is becoming a more predictable technology. Future patents applications covering CRISPR should consequently be more difficult to obtain.

This assumes, of course, that CRISPR scientists will attempt to patent their inventions widely—a social event that may not come to pass. The patent dispute between UC and the Broad Institute has been met with disgust by some scientists. Michael Eisen, an HHMI/UC Berkeley colleague of Doudna's and ever the firebrand, condemned patents writ large as ''destroying the soul of academic science.''[19] Eisen's views surely cannot be unique. On a larger scale, hundreds of researchers have freely deposited their CRISPR constructs—subject to broad, academic-friendly license agreements—with AddGene.[13] And some institutions, notably the Montreal Neurological Institute, have sworn off patents altogether.[20] CRISPR still has the glint of lucre, and many scientists are likely to rush off to the gold mine, pickaxe in hand. But for others, the future of the CRISPR patent landscape may very well be less populated than its recent past.

The future of the CRISPR landscape will also depend, in part, on extending the recent shift toward cross-licensing. Eventually, the interference proceeding between UC and the Broad Institute will be resolved—either by agreement or by the heavy hand of a court judgment. So will ongoing proceedings regarding seminal patent applications in Europe, China, and elsewhere.[21] Researchers and industry can hope that the resolution of these past conflicts will further drive cooperative patent licensing among the major players, rather than a retrenchment of exclusive rights and patent thickets.

And yet, the future of the CRISPR patent landscape—like the *terra nova* of a new planet—may be altogether unseen. New applications for CRISPR—some wholly outside the context of genome editing—continue to arise at a rapid pace. RNA editing, astronomically powerful nucleic acid detection, and gene drives have all been developed since the invention of the single guide RNA in 2012, and all are expected to be patented.[22–24] This includes the continual discovery of new nucleases, such as CasX, CasY, and Cas13a, that belong to new types and subtypes of CRISPR-Cas systems.[25] The future of CRISPR, and its patents, lies in researchers' discoveries and imaginations, subject to their institutions' graces.

Conclusion

Although barely 5 years old, CRISPR as a genome editing system has transformed both laboratory practice and clinical aspiration. Whether it will fulfill these lofty promises lies in the hands of its practitioners and their interaction with the U.S. and other patent regimes—choices, ultimately, between conflict and cooperation. Patents can indeed serve as useful tools to develop a technology commercially. But like all tools, they wield no power apart from their users. The future of CRISPR patent landscape—like the future of CRISPR itself—depends on the stewardship of its researchers and their institutions.

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Author Disclosure Statement

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