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Law, History and Lessons in the CRISPR Patent Conflict

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Predicting the outcome of the ongoing patent disputes surrounding genome-editing technology is equal parts patent analysis and history.

Genome-editing technology based on clustered, regularly interspaced, short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) has generated great excitement in both academia and industry. But a potential patent dispute between two sets of inventors has left the biotech community pondering its fate. Understanding several facets of patent law and history may provide some lessons about the probable—and best—outcome for the dispute.

CRISPR and the patent landscape

The CRISPR-Cas9 genome-editing system is based on an endogenous, prokaryotic immune response to foreign nucleic acids, such as viral genomes or plasmids. When presented with viruses or plasmids, some prokaryotes integrate short fragments of the foreign sequence into one or more CRISPR loci, and then transcribe the loci and process the output to form short CRISPR RNAs (crRNAs). The newly created crRNAs then direct Cas9, a DNA nuclease, to cleave future foreign nucleic acids on the basis of sequence complementarity. The system's ability to precisely introduce foreign DNA sequences makes CRISPR-Cas9 an incredibly versatile, effective system for genomic editing.

That versatility, and the potential to use CRISPR-Cas9 for practical (and profitable) *in vivo* applications, has led to two competing patent claims on the CRISPR-Cas9 system. The first stems from work led by Jennifer Doudna, at the University of California, Berkeley (UC Berkeley), and Emmanuelle Charpentier, at the Helmholtz Centre for Infection Research in Germany, for a method of exploiting the system for genome editing *in vitro*[1]. Their patent application, which claims a priority date of May 25, 2012, includes 155 claims, encompassing numerous applications of the system for a variety of cell types[2]. The second comes from Feng Zhang of MIT on a method for using CRISPR-Cas9 for genome editing in eukaryotic cells[3]. Zhang's patent, which claims a priority date of December 12, 2012, has already been issued[4].

Since these filings, there has been a flurry of patent applications related to CRISPR-Cas9. More than a dozen new patents and 100 patent applications have claimed or described applications for the CRISPR-Cas9 system. Zhang alone has received eight CRISPR-Cas9 patents, all from 'fast-tracked' applications and drafted to very broad applications of the technology. Some of these patents are directed to more specific applications, such as the patent claiming the use of the technology to treat Huntington's disease[5].

Challenges to the patents

The breadth and competing claims of these patents and patent applications pose several challenges to their inventors—and to the biotech community at large. The first concerns the priority of the fomenting patent dispute between Doudna and Charpentier, on one side, and Zhang on the other. Currently, the patent application from Doudna and Charpentier appears to have priority over Zhang's earliest issued patent—theirs claims a priority date of May 25, 2012, whereas Zhang's claims a priority date of December 12, 2012. Assuming Zhang's claims overlap with those of Doudna and Charpentier, this may allow the Doudna-Charpentier team to petition the US Patent and Trademark Office (USPTO) to challenge Zhang's initial patent through an "interference proceeding" if their application is ultimately rejected[6]. The stakes for an interference proceeding would be high: if Doudna and Charpentier were to win, Zhang's earliest patent would be invalidated, although there would be no guarantee that the Doudna-Charpentier patent application would be granted. If Zhang were to win, he would keep his initial patent, and Doudna and Charpentier would likely walk away empty handed.

The second challenge concerns the patents' scope. All of the CRISPR patent applications filed thus far are drafted quite broadly. As a consequence, if the USPTO allows these patent applications to move forward—and if the patents are ultimately enforced—the patents are likely to prevent even the most basic use of the CRISPR-Cas9 system without a license. General academic research would almost certainly be liable for patent infringement[7]. At the same time, the patent statute immunizes research performed in connection with submitting new drug or biologic information to the US Food and Drug Administration[8]. Thus, depending on the enforcement scheme and the technology's development, academic research may be subject to claims of patent infringement while some commercial development may proceed unchecked.

Last, the patents themselves pose several questions concerning their validity. Specifically, patent claims that are "obvious" may be declared "invalid" and may be freely used by others[9]. In the biotechnology context, there has been a long-running and unresolved issue about whether certain applications of a technology are obvious once the fundamentals of a technology (such as PCR) are known. Now that the mechanics of CRISPR-Cas9 are known, have genome-editing applications become obvious? Answering that question in legal terms is immensely difficult, but the answer is likely to control the future of all CRISPR-Cas9 patent disputes.

Historical precedents

Whether and how these difficulties are resolved will be largely up to the assignees of

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the dueling patent applications: UC Berkeley, the University of Vienna, the Massachusetts Institute of Technology (MIT) and the Broad Institute. The history of licensing patents on earlier foundational technologies—recombinant DNA, small interfering RNA (siRNA) and PCR—provide several avenues for deploying CRISPR-Cas9 without lengthy patent fights. Stanford University's management of the Cohen-Boyer patents on recombinant DNA, for example, has become the gold standard for university technology licensing[10]. First, the patents' assignee, Stanford, licensed the technology nonexclusively and allowed nonprofit research institutions to use the technology without a license. Second, the university developed a graduated royalty system to ensure that smaller companies were not disadvantaged. And finally, Stanford preemptively consulted a wide variety of stakeholders and experimented with different licensing agreements, to much community fanfare.

Another helpful example to consider is MIT's 'Tuschl patents' on siRNA technology. As with CRISPR-Cas9, overly restrictive licensing could have significantly slowed scientific progress. MIT, however, was able to avert this problem through licensing. The university currently allows academic scientists with laboratory-made versions of the molecular components to use the technology for free and grants companies selling these molecular components nonexclusive licenses[11]. The startup Alnylam, however, has received an exclusive license to the technology for therapeutic applications.

The PCR patents provide another option for licensing and deployment. Because the technology was discovered in the context of industry, strong enforcement of PCR patents could have significantly hindered scientific progress. This problem was largely mitigated, however, through the twin policies of 'rational forbearance' from suing researchers for patent infringement and the adoption of widespread corporate licensing, business partnerships and adaptive licensing strategies[12]. In this way, PCR was widely—and quickly—disseminated.

Although these examples are quite different from one another, in all cases, the assignees chose an appropriate and user-specific combination of enforcement and licensing. Choosing the right strategy or strategies may help the CRISPR-Cas9 patent assignees to avert legal challenges, realize significant revenue streams and promote scientific progress simultaneously.

Conclusion

CRISPR-Cas9 is a very promising tool in the quest for genome editing. Whether the technology is allowed to develop with patent protection will be up to law and history, rather than science.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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