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Inventive steps: the CRISPR patent dispute and scientific progress

The recent patent decisions about CRISPR tell us a lot about how advances in biology are actually made—and how they are not

Jacob S Sherkow

Recent decisions by patent offices in the USA and Europe concerning the revolutionary gene-editing technology, CRISPR/Cas9, have shed light on the importance—and puzzles—of one particular area of patent law: "nonobviousness", as it known in the USA, or, in Europe, the "inventive step". In February 2017, the US Patent Trial and Appeal Board (PTAB) found that the work of Feng Zhang, a researcher at the Broad Institute in Cambridge, MA, USA, constituted a "nonobvious" advance over the celebrated work of Jennifer Doudna of the University of California, Berkeley (USA) and Emmanuelle Charpentier, then at Umeå University, Sweden [1]. As a consequence, the Broad Institute will be able to keep its US patents covering the technology irrespective of how Doudna and Charpentier's patent application proceeds. By contrast, the European Patent Office (EPO) announced that it had granted Doudna and Charpentier's European patent application covering broad uses of CRISPR/Cas9 in essentially any cell type, despite the US Patent Office's decision to the contrary [2]. Other parties—including the Broad Institute—will be able to challenge Doudna and Charpentier's European patent. But for now, the EPO's decision is an implicit recognition that Doudna and Charpentier's work was, itself, a major "inventive step" over the work that came before it.

Patent law does not always neatly align itself with the realities of biological research. But these competing decisions have put those differences on parade. The US decision in particular—and even the nature of the controversy between the two US research institutions—has been widely criticized by scientists. One prominent researcher, Michael Eisen from the University of California, Berkeley, has taken particular issue with the PTAB's articulation of the typical manner in which molecular biologists adapt discoveries to different cell systems. "[O]ne can believe that it was obvious that CRISPR would work in eukaryotic cells, and still not expect that it would work the first time someone tried it or that the process would be free of frustration", he wrote on his blog several days after the US decision. "Because that's how science works!"

> *"... both patent offices' decisions are almost certainly correct as a matter of law if not the realities of scientific progress"*

But both patent offices' decisions are almost certainly correct as a matter of law if not the realities of scientific progress. The US opinion concerning nonobviousness—the *sine qua non* of patentability—is fairly accurate: Whether prior research "would have suggested to one of ordinary skill in the art that [the new] process should be carried out and would have a reasonable likelihood of success" [1]. In Europe, one is entitled to a broad patent on a new technique, if it demonstrates an "inventive step" over prior methods—even if there no guarantee that it will work for all of its claimed applications. As noted by a number of intellectual property scholars, this standard highlights a long-standing division between science and patent law concerning how biological research is actually conducted—a division that is likely to widen as research in molecular biology advances. This article briefly explains these differences in patent law, especially with respect to the law's critical "nonobviousness" or "inventive step" requirements, and explains their importance to CRISPR researchers and molecular biologists of all sorts.

The importance and history of obviousness

Since modern patents were first granted in the 17th century, governments were faced with the conundrum of "drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not" [3]. Patents were established as incentives for inventors to spend time and money developing new inventions. Without some rights to prevent others from copying their inventions once they were first sold—so the economic theory goes—developers would not undertake the ardor of research in the first instance. But this right to exclude others from practicing new and useful technologies was considered to be a powerful one, and determining which inventions merited the law's security poised no shortage of administrative, legal, and philosophical problems.

In the USA, the courts took up the mantle of assessing the worth of new technology under the patent laws. Like the technologies they were charged with

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investigating, their opinions consisted of various attempts—trials and errors—to make workable what was otherwise an imperfect machine. In the early part of the 19th century, courts required patented inventions to be "of more ingenuity and skill than that possessed by an ordinary mechanic" [4]. Litigating genius, suffice it to say, proved less than fruitful, so courts adopted a variety of standards, none of which proved any easier. By the mid-20th century, things had deteriorated to the point that US Supreme Court Justice Robert H. Jackson remarked that "the only patent that is valid is one which this Court has not been able to get its hands on" [5].

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In 1952, as part of a major overhaul of the patent laws, Congress tasked two prominent patent attorneys, Pasquale Joseph Federico and Giles Sutherland Rich, with giving form to this elusive "inventiveness" requirement. Their invention: what we call "nonobviousness" today, the prohibition on patents covering inventions for which the "differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious … to a person having ordinary skill in the art to which the claimed invention pertains" [6]. This description of the question prior governments had failed to answer had numerous advantages: It focused its inquiry on documents—the *prior art* in the field; it fixed itself to a point in time—the time of the *invention*; and it had an object—this hypothetical person having ordinary skill in the patent's art. It gave form to what before was a formless idea. In short order, the standard was adopted in similar form in Europe as requiring patents to demonstrate an "inventive step" over prior references [7].

These standards also seemed tethered to the way scientific research is actually conducted. They aspired to critically examine prior papers to assess whether the patented invention was truly a significant advance, much in the same spirit as Isaac Newton's reference to standing on the shoulders of giants. It required a concrete comparison between the elements of prior studies and the current one—the patent on examination. And it posed these questions to a hypothetical scientist—an ordinary one in the same field—to assess what he or she thought. In an age when good government was widely perceived as being one that ushered scientific research into the fore, Federico and Rich's invention of "nonobviousness" was a both a political and legal triumph.

Today, obviousness is by far the most crucial doctrine of the patenting process. It is the primary source of patent offices' rejection of patent applications. And it arises as a defense in virtually every patent case litigated in court. In addition, many other procedures at patent offices in the USA and throughout the world consider the potential obviousness of a patent even after it may have already been issued. For this reason, nonobviousness or an inventive step has become "the heart of the patent law" [7].

The obviousness inquiry in molecular biology

Despite the improvements of the obviousness doctrine in aligning patent law with scientific research, it has presented unique problems for molecular biology. Unlike other fields, such as mechanical engineering, molecular biology is considered substantially more "unpredictable". Given biology's complexity, the outcome of any given experiment is increasingly uncertain. Experimental trial and error—more than design in the "dry" engineering fields—is critical to research in biology. This complicates courts' and patent offices' obviousness analyses, because even standard combinations of elements in the field routinely yield unpredictable results. The discovery of nonsequence-specific siRNA silencing in gene regulation in the early 2000s serves as but one example [8].

In other cases, standard combinations of molecular cloning techniques may produce synergies not expected by their researchers, as with the production of monoclonal antibodies. The half-life of several antibodies, for example, can surprisingly be regulated by developing otherwise similar constructs for controlling fucosylation pathways. Furthermore, biology—unlike, say, physics—is not practiced in a sterile environment. Work conducted in molecular biology often takes place within the medium of living cells or complex genetic environments. As a result, translating a technique from one system to another frequently proves difficult. And even where researchers seem capable of attaining promising results, issues over experiments' reproducibility abound. This has complicated the task of asking whether an average molecular biologist—a "person of ordinary skill in the art" in patent law's parlance—would think the invention to be "obvious" or lack an "inventive step" over what came before it.

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This complication has only worsened recently. Prior to 2007, obviousness analyses almost exclusively used documentary evidence, such as patents and articles in scientific journals. In 2007, however, the US Supreme Court took up the case of *KSR International Co. v. Teleflex Inc.*, and determined whether such a narrow focus on patents and papers was appropriate. The Court concluded that, in addition to the documents traditionally considered by the Patent Office in determining obviousness, it should now also look to factors such as common sense, market pressures, and the number of possible permutations of individual elements of a given invention. In addition, the Court rejected patent law's long-held axiom that obviousness could not turn on whether an invention was simply "obvious to try".

Adopting these standards for laboratory molecular biology has proven enigmatic. Few advances in molecular biology are the result of simple "common sense", however defined. And while it is, in some sense, obvious to try different laboratory techniques across different systems, successfully getting such techniques to work under different conditions—even different laboratories—is rarely easy.

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As a consequence, legal scholars have long complained of obviousness's mismatch with biology [9]. Following the final completion of the Human Genome Project in 2003, Dan L. Burk and Mark A. Lemley wrote about "an increasing divergence between the [patent] rules actually applied to different industries", including courts having "repeatedly held that uncertainty in predicting the structural features of biotechnological inventions renders them nonobvious, even if the prior art demonstrates a clear plan for producing the invention" [9]. Today, scholars have expressed concern that recent groundbreaking advances in cloning, sequencing, and high-throughput screening may render even significant advances in synthetic biology obvious under the patent laws. The truth, of course, is that for many biotechnologies reasonable minds could—and often do—easily differ on whether a new technique contains a truly "inventive step". Trivial improvements to some are colossal advances to others.

The CRISPR patents

Despite these puzzles, obviousness and the inventive step requirement are at the heart of the CRISPR patent inquiries in both Europe and the USA. To start with, the patent dispute in the USA was structured as an "interference proceeding", a legal procedure unique to US patent law. Interferences attempt to ascertain whether two related patents "claim patentably indistinct subject matter", that is, whether they claim the same invention and, if so, which party was the first to invent. But if the inventions appear to be different—if, for example, the later invention was a nonobviousness improvement—there is no true interference, in fact, between the dueling inventions. In the CRISPR interference, the US Patent Trial and Appeal Board (PTAB) defined the invention in dispute between the University of California and the Broad Institute as a single-guide RNA (sgRNA) CRISPR/Cas9 editing system in a eukaryotic cell. To determine whether Zhang's eukaryotic-specific invention was a nonobviousness advance over Doudna and Charpentier's, the PTAB homed in on one "consistent criterion" in its jurisprudence: Whether the invention, as described by Doudna, "would have had a reasonable likelihood of success".

In practical terms, this meant that the PTAB's obviousness decision centered on whether Doudna and Charpentier's application of CRISPR/Cas9 *in vitro* and in bacterial systems would have had a "reasonable likelihood of success" in eukaryotic cells. And in doing so, they focused on testimony from a variety of experts on a laundry list of differences among cell systems that could have affected Cas9's binding and nuclease activity: "gene expression, protein folding, cellular compartmentalization, chromatin structure, cellular nucleases, intracellular temperature, intracellular ion concentrations, intracellular pH, and the types of molecules in prokaryotic versus eukaryotic cells". Each of these, ventured the PTAB, "would contribute to unpredictability" in getting Doudna and Charpentier's invention to work in eukaryotes. The PTAB also—and perhaps unfairly—relied on statements made by Doudna and her research team that getting CRISPR to work in eukaryotic cells was an "exciting possibility", although no sure thing, and that Doudna herself experienced "frustrations" in getting the system to work in other cell types. These differences among cell systems, combined with statements Doudna made to the media in describing the development of her invention, convinced the PTAB that Zhang's invention was a nonobvious improvement over Doudna and Charpentier. An ordinary molecular biologist could not have a "reasonable expectation" that CRISPR-Cas9 would work in eukaryotic cells. And as a consequence, Zhang's patents did not interfere with Doudna and Charpentier's patent application.

This decision illuminates the disjointedness between nonobviousness and how biological research is, in fact, practiced. As a matter of legal interpretation, the PTAB's description of nonobviousness is almost certainly correct. Inventions that raise, but do not resolve, questions about how far the new technology can be applied do not necessarily give others a "reasonable expectation" that the invention will work well, if at all, in foreign systems, under different experimental conditions, or using different parameters. The development of a biologic compound in one cell system using a particular construct is famously not a guarantee that it will work in a different cell system or using a different construct. Indeed, the failure to move the manufacture of biologics from one system to another is so frequent, that there is surely no "reasonable expectation of success" in merely transposing a biologic construct to a different cell system. Consequently, actual descriptions of such efforts are, in a real sense, nonobvious: They could not have been predicted, without experimentation, by an average researcher.

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And yet, this does not mean researchers are completely at sea; biological research, while finicky and error-prone, is not random. Researchers are armed with a broad arsenal of tools to combat numerous technical problems that arise in translating developments from one cell system to another. Even using the PTAB's own list of differences between pro- and eukaryota, common molecular biological practices exist to mitigate each of these difficulties. For example, differential gene expression can be controlled by selecting appropriate promoters; protein folding can, in some instances, be made uniform by certain optimization techniques; chromatin structure can be altered by histone modification; nucleases can be blocked; temperature can be regulated; pH can be buffered; and so on. This is not to say that researchers could have *expected* that any of these techniques would have worked in moving CRISPR-Cas9 from bacteria to eukaryotes, or to predict which of these techniques, in combination, would have been successful. But Doudna and Charpentier's work, at a minimum, provided a clear set of paths forward to do so. To that end, Doudna's statements of "frustration" concerning translating her system to eukaryotes can be read—*should* be read—as being simply reflective of the uncertainties of moving between cell systems, not doubts that her process would have failed entirely.

By contrast, the EPO has given great accord to how molecular biologists actually view uncertainty in their own field. Doudna and Charpentier formally applied for their European patent in August 2014. And shortly after their application, received *eight* separate challenges to their application in the form of "Observations by Third Parties"—scientific references and legal argument from members of the public on why the patent at issue should not be granted (there is no precisely analogous procedure in the USA). These observations, like the PTAB's decision, tended to focus on the differences between what Doudna and Charpentier disclosed in their application and the potential difficulties in moving their same system to living, eukaryotic cells. One such observation—notably, from the Broad Institute—highlighted that its own work demonstrated that simply moving Doudna and Charpentier's system, as described, into eukaryotic cells was "inoperable". Doudna and Charpentier's attorneys' responded to such criticisms by noting that the average level of skill in the molecular biology field was "high" and that strategies to solve the problems raised by the Broad Institute were part of the "mental furniture" of any laboratory biologist [10].

In March 2017, the European Patent Office discounted the full set of Observations as "not relevant" to its inquiry of whether Doudna and Charpentier were entitled to a patent. Rather, the EPO communicated its intent to grant Doudna and Charpentier's patent—even with their originally broad claims. While the EPO did not discuss in detail why it came to different conclusions from its US counterpart, it did note that it was ultimately persuaded by Doudna and Charpentier's attorneys' response to such criticisms—tethering its decision of patentability to scientific claims of disclosure perhaps more than legal ones.

The future of obviousness in CRISPR

Conflicting decisions or otherwise, the CRISPR patent disputes complicates how obviousness will be assessed for CRISPR technologies in the future. Perhaps the most salient example concerns the discovery of new nucleases that work with CRISPR Type II systems. At the time of Doudna and Charpentier's original publication in *Science*, only a single nuclease—Cas9 derived from *Streptococcus pyogenes*—was known. Since then, a host of orthologs and entirely new enzymes have been discovered, including Zhang's discovery of Cpf1; Doudna's discovery, along with her University of California colleague, Jillian F. Banfield, of CasX and CasY, derived from uncultivated bacteria obtained from an abandoned mine, and the recent announcement from Korea of CjCas9 from *Campylobacter jejuni*. Now that such orthologs are known—and especially because they appear to work in currently deployed CRISPR Type II systems as predicted—this raises the question of whether the application of CRISPR using new nucleases is, in some senses, "obvious". The answer is far from clear.

More broadly, CRISPR truly challenges what constitutes an "inventive step" because the ambit of the technology seems to be limited almost only by human imagination. Since Doudna and Charpentier's canonical description of CRISPR as a precise tool for double-stranded DNA cleavage, researchers have modified the system to induce single-stranded DNA breaks; to purposefully introduce levels of imprecision to DNA cleavage; to merely block DNA sequences through competitive binding; and to use the system as a single nucleotide editing tool. Indeed, the value of CRISPR is not merely that it can precisely edit DNA, but that its specificity to DNA sequence can be used to create, report, and analyze the genome. As a result, some applications of CRISPR are surely major intuitive leaps—inventive steps by any other name—such as the recent development of "gene drives": CRISPR mediated extinguishing of heterozygosity such that a single allele is "driven" through the population. And yet, these advances are, by and large, combinations of known tools in the CRISPR-space that have predictable outcomes when deployed. Obviousness's insistence that we would treat such advances under patent law differently from how they are perceived in the field is puzzling.

By the same token, the yet-to-be-demonstrated clinical success of CRISPR therapies in humans is incredibly uncertain. Taking the PTAB's metric for assessing Doudna and Charpentier's US patent application, no clinician has a "reasonable expectation of success" that any given therapy will work. Most clinical trials, in fact, fail. This strongly suggests that the developments of human CRISPR therapies, writ large, will have to overcome obviousness hurdles. And yet, their success will likely turn on predictable applications of known CRISPR techniques to human patients. Here, too, CRISPR challenges our notions of both obviousness and expectations of success.

As is true with any groundbreaking technology, it is impossible to predict how CRISPR will develop in the future. But as it develops, molecular biologists' techniques to work with the system—and their understanding of what is likely to be successful and what is not—will undoubtedly mature. Dynamically aligning these future advances with patent law's obviousness requirement will remain an incredible challenge.

Lessons about science and society

This story about research and the obviousness requirement demonstrates a broader disconnect between science and the law—even law concerned with assessing science. And there are broader lessons about what the CRISPR dispute can—and cannot—tell us about science in general. Doudna and Charpentier clearly invented *something*. Zhang did too. Nonetheless, the patent system struggles to give appropriate credit to researchers depending on their relative contribution to the field. To use an analogy from physics, scientific advance is chromatic—but it is not quantized. Small scientific contributions are still, of course, contributions. Patent doctrines, on the other hand, are like elections for parliamentary ridings: Prizes are awarded only to the first past the posts the law erects, whether they are grounded in contemporary science or otherwise.

We should not let the outcomes of patent disputes teach us lessons about whether, or to what degree, scientific contributions are significant to their respective fields. We all stand on the shoulders of giants. And while in the course of research, some will undoubtedly stand taller, the goal is to always see farther than our horizons, even if only by inches.

Conflict of interest

The author declares that he has no conflict of interest.

References

1. The Broad Institute, Inc. v. The Regents of the University of California, Interference No. 106,048, Decision on Motions (U.S. Patent Trial & Appeal Board, Feb. 15, 2017). https://perma.cc/Z4P3-ALTU

2. The Regents of the University of California, Appl. No. 13/793 997.1 – 1401, Intent to Grant, (Eur. Patent Office, Mar. 24, 2017), https://perma.cc/W4J8-FW3B
3. Jefferson T (1854) Letter to Mr. Isaac M'Pherson. In *Writings of Thomas Jefferson (vol. VI)*, Washington HA (ed.), p 181. Washington, DC: Taylor & Maury
4. Graham v. John Deere Co., 383 U.S. 1 (1966).
5. Jungerson v. Otsby & Barton Co., 335 U.S. 560 (1949).
6. 35 U.S.C. § 103 (1958).
7. Duffy JF (2007) Inventing invention: a case study of legal innovation. *Tex Law Rev* 86: 1 – 72
8. Jackson AL, Bartz SR, Schelter J, Kobayashi SV, Burchard J, Mao M, Li B, Cavet G, Linsley PS (2003) Expression profiling reveals off-target gene regulation by RNAi. *Nat Biotechnol* 21: 635 – 637
9. Burk DL, Lemley MA (2003) Biotechnology's uncertainty principle. In *Advances in genetics (vol. 50)*, Kieff FS (ed.), pp 305 – 353. Cambridge, MA: Academic Press
10. The Regents of the University of California, Appl. No. 13/793 997.1 – 1401, Applicant's Response to Observations, (Eur. Patent Office, Sept. 22, 2016). https://perma.cc/3U54-RXYE

Law, history and lessons in the CRISPR patent conflict

Jacob S Sherkow

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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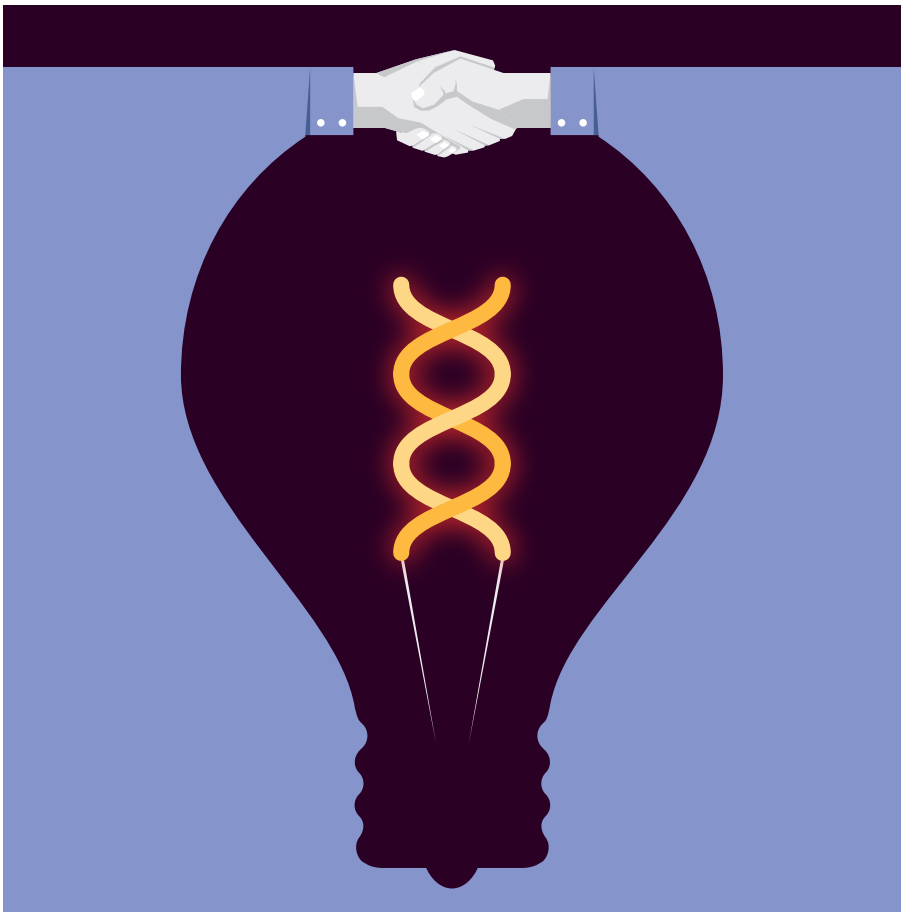
1. Jinek, M. *et al. Science* **337**, 816–821 (2012).
2. Jinek, M. *et al.* US Patent Application No. PCT/US2013/032589 (2013).
3. Cong, L. *et al. Science* **339**, 819–823 (2013).
4. Zhang, F. US Patent No. 8,697,359 (2014).
5. Miller, J.C., Rebar, E.J. & Zhang, S.H. US Patent Application No. 2014/0336133 (2014).
6. 35 USC § 135 (2010).
7. *Madey v. Duke University*, 357 F.3d 1351 (Fed. Cir. 2002).
8. 35 USC § 271(e) (2012).
9. 35 USC § 103 (2010).
10. Feldman, M.P. *et al. Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. Krattiger, A. *et al.*) 1797–1807 (MIHR, Oxford, 2007).
11. Rojahn, S.Y. Broad Institute gets patent on revolutionary gene-editing method. *MIT Technology Review* http://www.technologyreview.com/view/526726/broad-institute-gets-patent-on-revolutionary-gene-editing-method/ (2014).
12. Fore, J. Jr., Wiechers, I.R. & Cook-Deegan, R. *J. Biomed. Discov. Collab.* **1**, 7 (2006).



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Pursuit of profit poisons collaboration

The CRISPR–Cas9 patent battle demonstrates how overzealous efforts to commercialize technology can damage science, writes **Jacob S. Sherkow**.

Last month, in an extraordinary dispute before the US Patent and Trademark Office (USPTO), university lawyers laid out their clients' legal strategies for claiming patents that cover the celebrated gene-editing technology CRISPR–Cas9. Over the next year, the USPTO will receive volumes of evidence centred on who first invented the technology.

Battles over scientific priority are as old as science itself. But the CRISPR–Cas9 patent dispute is unusual because it pits two leading research institutions against one another for the control and industrial development of a foundational technology: the University of California, Berkeley (UC Berkeley), and the Broad Institute of MIT and Harvard in Cambridge, Massachusetts.

As scientific institutions increase their involvement in the commercialization of research[1], it is worth considering the potential consequences for science if more institutions follow the path of UC Berkeley and the Broad Institute.

HIGH STAKES

In May 2012, researchers at UC Berkeley, led by Jennifer Doudna and her collaborator, Emmanuelle Charpentier (then located at the University of Vienna in Austria) filed a patent application in the United States for CRISPR–Cas9. Seven months later, Feng Zhang, a researcher at the Broad Institute, filed a competing application that covered similar uses of the technology. After Zhang's lawyers requested that his application be fast-tracked, the USPTO awarded one patent to Zhang in April 2014, followed by a dozen more in the subsequent 12 months. Meanwhile, the application made by Doudna and her colleagues languished.

Last April, Doudna's lawyers requested that the USPTO conduct a specialized legal trial, known as a patent interference, to determine the ownership of the US patents that cover the CRISPR–Cas9 system. This January, the USPTO formally agreed to carry out the proceeding.

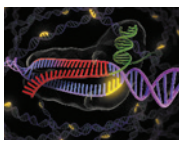
One conspicuous aspect of this case, in my opinion, is the degree to which UC Berkeley and the Broad Institute have weighed in on what is essentially a dispute over scientific priority.

The Broad Institute has produced press releases, videos and a slick feature on its website that stress the importance of Zhang's contributions to the development of the CRISPR–Cas9 technology. And earlier this year, the central positioning of Zhang's work in a historical perspective of CRISPR published in *Cell*[2] by the president and director of the Broad Institute, Eric Lander, prompted a storm of angry responses from scientists, including Doudna and Charpentier. Meanwhile, at UC Berkeley, a press release that discussed the potential of CRISPR described Doudna as "the inventor of the CRISPR–Cas9 technology" (see go.nature.com/cm2gvx).

The financial stakes are high. The CRISPR–Cas9 patents are widely viewed to be worth hundreds of millions, if not billions, of dollars. Both organizations have invested directly in spin-off companies that were co-founded by their researchers — the Broad Institute in Editas Medicine, co-founded by Zhang, and UC Berkeley in Caribou Biosciences, co-founded by Doudna. A report submitted by Editas in January to the US Securities and Exchange Commission lists the Broad Institute and other Harvard-affiliated institutions as owning a major equity stake in the company: about 4.2% of its common shares (see go.nature.com/45c1ey).

DIFFERENT TIMES

Efforts to commercialize the research output from universities played out differently in the past. Since 1980, US universities have been able to patent the inventions of their researchers, thanks to the Bayh–Dole Act — legislation that determines the ownership of intellectual property arising from federally funded research. But for the most part, institutions have kept their distance from disputes over scientific priority. In fact, after factoring in the costs of filing patents and staffing, university technology-transfer offices have generally been money losers for their institutions[3].



NATURE.COM
For more of *Nature*'s coverage on CRISPR, see:
nature.com/crispr

L: RICK FRIEDMAN/CORBIS; R: JOHN ELK III/LONELY PLANET/GETTY

Even in the case of lucrative patents, commercial development has frequently been left to venture capitalists and the researchers themselves. Take the Cohen–Boyer patents, which covered early gene-splicing technology and netted Stanford University and the University of California, San Francisco (UCSF), both in California, hundreds of millions of dollars in licensing fees during the 1980s and 1990s. In this instance, Genentech, the company in South San Francisco, California, that was formed to commercialize the underlying technology, sprung from the efforts of Herbert Boyer, one of the founding researchers, and the financier Robert Swanson. The company was neither owned by, nor an exclusive licensee of, Stanford or UCSF.

Research institutions in general are starting to play a bigger part in shepherding their researchers' projects through the commercialization process. A 2014 report from the Association of University Technology Managers in Oakbrook Terrace, Illinois — an organization that supports managers of intellectual property at academic research institutions, non-profit organizations and government agencies worldwide — documented that universities are increasing equity investments in their researchers' start-up companies. Of the patent licences granted by universities in 2014, 10% were tied to such investments[1], compared with 6.7% in 1999 (ref. 4).

I am concerned that such involvement in commercialization has the potential to clash with the broader, educational mission of research institutions.

Universities worldwide have long strived to foster a culture of scientific collaboration. Even when universities have obtained broad patents, as the Carnegie Institute of Washington in Washington DC did in the early 2000s for a gene-expression control technology known as RNA interference, licences have been cheap and easy for researchers to obtain[5]. In other cases, scientists have simply ignored patents that cover fundamental technologies[6].

Academic research institutions now seem less shy about taking each other to court for patent infringement. In 2011, the University of Utah in Salt Lake City sued the Max Planck Society for the Advancement of Science in Germany over claims to a patent that covered a technology called short interfering RNA, which inhibits gene expression (see go.nature.com/vyujnp). And over the past four years, Stanford University and the Chinese University of Hong Kong in Sha Tin have engaged in a heated patent litigation over prenatal genetic diagnostic blood tests, a market that was worth US$530 million in 2013.

In the current era of budget tightening, universities of all stripes might be tempted to use licensing fees as another funding mechanism. The University of South Florida in Tampa, for example — a public institution that had its state funding cut by $48 million in 2012 — holds a substantial number of patents that have not yet been licensed and has a famously low ratio of patent-licence revenue to research expenditure[7]. If its financial situation were to deteriorate further, the university might be compelled to extract licence fees from other research institutions for those patents.

The Broad Institute of MIT and Harvard (left) and the University of California, Berkeley (right).

PATH TO PROFIT

It would be wrong to suggest that patents, writ large, are failing educational research institutions. In the cases of gene splicing, RNA interference and human embryonic stem cells, patents have been major earners for institutions and researchers without damaging the scientific enterprise[5].

"Efforts to commercialize the research output from universities played out differently in the past."

But an obvious danger of increasing the focus on commercialization is that educational institutions will view scientific research as a path to profit, above all else. It is not hard to imagine that patent disputes might lead to university administrators pushing certain views on their scientists, denigrating collaboration with researchers from competing institutions and tasking tenure committees with valuing patents over publications.

Where scientific advances have the potential to be profitable, universities should support researchers to bring that work to fruition. This might include helping them to secure patents. But it is my view that serious commercialization efforts — such as granting exclusive licences or receiving equity ownership in researchers' start-ups — should be left to industry.

The CRISPR–Cas9 dispute could have played out very differently. Zhang and Doudna were both co-founders of Editas. And UC Berkeley and the Broad Institute could have filed patent applications that listed the research teams from both institutions as co-inventors. Any resulting patents could then have been freely or cheaply licensed to other research institutions, or used to fund a joint academic organization dedicated to studying the technology. The patents could also have been widely, but not exclusively, licensed to a variety of industry competitors — promoting a robust, competitive market for commercial CRISPR–Cas9 applications and creating a funding stream for further academic research.

Biomedical research in educational institutions has long prided itself on a culture of openness and sharing — one that both Zhang and Doudna have exercised by donating various components of the CRISPR–Cas9 system to the open-science consortium Addgene in Cambridge, Massachusetts. The incentives that patents create for educational institutions should not be allowed to erode scientific collaboration. ■

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1. Association of University Technology Managers. *AUTM US Licensing Activity Survey: FY2014* (AUTM, 2014).
2. Lander, E. S. *Cell* **164,** 18–28 (2016).
3. Abrams, I., Leung, G. & Stevens, A. J. *Res. Mgmt. Rev.* **17,** 18–50 (2009).
4. Association of University Technology Managers. *AUTM US Licensing Survey: FY1999* (AUTM, 1999).
5. Sherkow, J. S. *Nature Biotechnol.* **33,** 256–257 (2015).
6. Eisenberg, R. S. *Houston Law Rev.* **45,** 1059–1099 (2008).
7. Feldman, R. & Price, N. W. II *Stanford Tech. Law Rev.* **17,** 773–808 (2014).

Who owns gene editing?

Patents in the time of CRISPR

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New gene-editing technologies, like CRISPR, promise revolutionary advances in biology and medicine. However, several patent disputes in the USA and UK may have complicated who can use CRISPR. What does this mean for the future of gene editing?

Precisely editing the genetic code of living organisms has long been a supreme ambition of biologists. Editing the genome has the potential to cure genetic diseases, revive extinct species and combat public health crises, among other advances. The potential for the technology seems limited only by the human imagination. Previous efforts in the area, however, have proven less than satisfactory .

A recent advance in one gene-editing technology, Clustered Regularly Interspaced Short Palindromic Repeats—better known as CRISPR—may bring biologists' ambitions to fruition. This precision-editing system has so far lived up to its hype: CRISPR has been demonstrated to work in virtually every cell type attempted and appears almost infinitely flexible in modification .

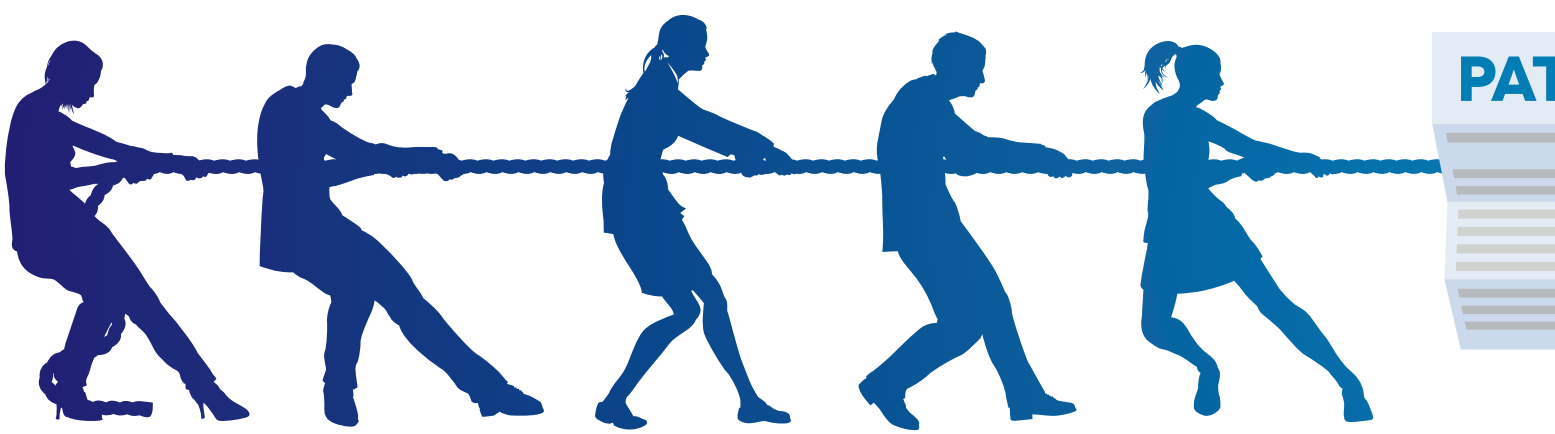
But the promise of the technology has generated a patent dispute among the technologies' creators: Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, now at the Max Planck Institute for Infection Biology in Berlin, on one side, and Feng Zhang of the Broad Institute, on the other. Resolving the patent dispute may ultimately decide who owns the rights to this crucial piece of biotechnology. This article outlines the law surrounding patents on biotechnology and explains the contours and effects of the current CRISPR patent disputes.

Patents

Broadly speaking, inventions present an informational paradox: often, costly and burdensome research is required to bring them to fruition, but once developed the invention becomes known to the public. Without some law restricting the copying of these inventions, many researchers may not have the incentive to engage in foundational research in the first instance.

Since at least the fifteenth century, the solution to this problem has been some form of patents: government issued rights to inventors—rights that allow inventors, for a limited period of time, to prevent others from copying their inventions. To be clear, patents are not inventors' rights to use and develop their own inventions; they are rights only to exclude others from copying them. Patents, consequently, are viewed as "limited rights, for a limited time". Nonetheless, this limited right can be tremendously valuable. Many pharmaceutical patents, for example, are worth billions of dollars.

Not all inventions deserve patent protection. Precisely because patents can be so valuable—and because patentees can essentially exclude others from developing certain areas of technology—patent laws throughout the world have established certain standards in an effort to ensure that only significant advances in science and technology receive patent protection. Today,



in the USA and UK, patents may be granted only for inventions that are new, useful and "inventive" or "non obvious." In addition, patentees must sufficiently disclose their inventions to the public—enough to enable others to make and use the invention. To meet these twin aims, patents, as documents, contain two parts: a written description of the invention, known as the specification, and the claims, short statements identifying the "metes and bounds" of the invention. The claims, in essence, define the patented invention.

In this way, the current system of patents ideally does double-duty in breaking the informational paradox of inventions. It encourages researchers to invest in expensive research by holding up the reward of a patent if they are successful. And it also requires inventors to disclose the fruits of that research to the public. Today, for better or worse, patents form an integral part of the research and development lifecycle for a host of industries.

The CRISPR patent dispute

Patent law has long faced the problem of contemporaneous invention: what to do when two inventors contemporaneously invent the same or a similar invention and each file competing patent applications? In much of the world, administrative efficiency dictates that the patent should be awarded to the first person to file. But, up until 2013 in the USA, the USA Patent and Trademark Office (PTO) awarded the patent to the first inventor . This presented several problems for the PTO—especially where, because of quirks of timing at the Patent Office, a later inventor but earlier filer was awarded the first patent. Through a restrictive reading of the patent statute, this circumstance potentially blocked the first inventor's patent application from being awarded.

The current CRISPR dispute involves similar difficulties. Doudna and Charpentier filed an early patent application covering a limited form of the CRISPR technology in May 2012. Zhang filed a similar application seven months later, in December 2012. But Zhang's attorneys requested that the PTO "fast-track" his application: a procedure allowed—for a fee—on shorter, less contentious applications. Zhang's attorneys' strategy worked and, as a result, Zhang was awarded his first patent in April 2014 and over a dozen more by the following year. During this time, however, Doudna and Charpentier's application suffered numerous technical difficulties at the PTO. And through much of 2014, it appeared that Zhang's issued patents would block their applications, even though the duo had good claims as both the first inventors and first filers.

In April 2015, with the CRISPR patent race slipping away from them, Doudna's attorneys requested that the PTO declare an interference proceeding: a trial, within the PTO, to determine the first inventor of a disputed technology. After receiving a recommendation from the patent examiner responsible for Doudna and Charpentier's application, the PTO formally instituted an interference proceeding in January 2016 .

At its core, the interference proceeding is designed to answer who invented what, first. To do that, a three-judge panel at the PTO will receive evidence concerning what Doudna, Charpentier and Zhang did in their laboratories, what they disclosed in their original patent applications and how an average molecular biologist would have viewed this information as the technology progressed through 2012. In addition, the panel must determine exactly which parts of Doudna and Charpentier's application overlap with Zhang's patents. To aid them in that determination, the panel drafts a "count," a hypothetical patent claim that covers both sets of technologies. Moving forward, the scientists' attorneys will file several sets of motions arguing that the count does or does not cover the technology in dispute, or that the count needs to be rewritten or broken up into several pieces to cover the contested inventions. In

addition, the attorneys will also file motions arguing that their respective clients were, in fact, the first to invent the CRISPR technology. The panel's ruling on these motions should come in January 2017 if not earlier.

Outside of the USA, however, no analogue to interference proceedings exists. European patent offices faced with the contemporaneous invention problem simply award the patent to the first filer. But there are other procedures to contest already issued patents at their respective patent offices. At the European Patent Office, for example, anyone may file an opposition to a patent issued within nine months, arguing that the granted patent fails the novelty, inventive step or disclosure requirements. This has, in fact, happened with the CRISPR technology, where, to date, nine entities—including one company, CRISPR Therapeutics, founded by Charpentier—have filed oppositions to one of Zhang's European patents. Decisions in those cases are not expected until the end of 2017, at the earliest. These disputes—both in the USA and elsewhere—concerning control of the CRISPR technology suggest that ownership over the CRISPR patents will take years to unravel, and will result in a complicated system of patent rights throughout the world.

The future of CRISPR research

The patent disputes over CRISPR will likely have significant impact over the future of research in the area. First and foremost, the disputes may very well affect the funding of companies currently engaged in CRISPR research. A recent Bloomberg report by Caroline Chen and Doni Bloomfield noted that several drug manufacturers have entered into funding arrangements with various CRISPR start-ups, some worth hundreds of millions of dollars. The companies currently developing CRISPR either have a direct stake in the outcome of the current patent dispute or could be affected if the ultimate victor decides to enforce its patents against them. As a consequence, the patent dispute may shape which companies are allowed to commercially develop the CRISPR technology.

Second, the patent dispute may also alter which research institutions continue to study CRISPR as a gene-editing technology. Well-heeled research

institutions that cannot come to a license agreement with the eventual owner of the CRISPR patents may find themselves on the outside, looking in. This is important to mention—especially in the USA—because, contrary to popular belief, there is no "research exemption" for patent infringement. In Europe, however, such research exemptions do exist under the national laws of each country, but may be limited where academic institutions partner with commercial developers.

Third, the CRISPR patent dispute, no matter which way it turns, may signal a fundamental shift in the litigation and enforcement of foundational biotechnology. Most revolutions in molecular biology—like recombinant DNA, PCR and RNAi—have been patented. And almost without exception, those technologies have been subject to free and easy licenses. But the CRISPR patent dispute appears to be shaping up to something different. It may very well signal a culture shift in academic research institutions from pure and translational research into profit-maximizing commercialization. While this is not altogether bad, it's likely to conflict with universities' broader educational missions to the public. As a result, which aspects of CRISPR will become subject to research, and by whom, may turn on those universities' financial interests in developing certain CRISPR technologies rather than their scientific or therapeutic importance.

Taken together, these shifts may complicate the future of gene editing. It may be difficult, for example, simply to determine whether one is infringing one of the variety of patents covering gene-editing technology. And even if the CRISPR patent disputes produce a clear winner, it is unclear how the victor will deploy licenses, to whom and at what price. Furthermore, gene editing, and CRISPR in particular, is progressing so rapidly that is unclear whether new developments will be covered by the current landscape. As one example, the count at issue in the USA interference proceeding requires the "hybridization" of a guide RNA and a tracrRNA . But it's unclear whether this allows the RNAs to exist in two separate pieces or if they need to be linked, covalently or by sequence, somehow.

To both of their credits, Doudna and Zhang have supported some "open science" protocols by making CRISPR constructs available through an online repository called AddGene. In that way, the scientists are engaging in that most noble of scientific practices: the sharing of results. But it remains unclear how their benevolence jibes with their patents and the current patent dispute. It is likely that the litigation will need to be resolved first.

Gene editing, and CRISPR in particular, heralds a foundational advance in molecular biology. Like previous advances in biotechnology, CRISPR is subject to several patents and is at the centre of a current wide-ranging patent dispute. But the current patent dispute surrounding CRISPR seems quite different from past cases. Even with a clear winner, the CRISPR patent dispute may ultimately complicate who can practise the technology going forward. It seems, then, that the development of CRISPR as a technology is a study as much of law as science. ■

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References

1. The National Academies of Sciences, Engineering, and Medicine, Committee on Science, Technology and Law. (2015) International summit on human gene editing: a global discussion
2. Harrison, M.M., Jenkins, B.V., O'Connor-Giles, K.M. and Wildonger, J. (2014) Genes & Dev. 28, 1859–1872
3. Sherkow, J.S. and Greely, H.T. (2015) The history of patenting genetic material. Ann. Rev. Genet. 49, 161–182
4. Hemphill, C.S. and Sampat, B. (2013) Drug patents at the Supreme Court. Science 339, 1386–1387
5. Merges, R.P. (2012) Priority and novelty under the AIA. Berkeley Tech. Law J. 27, 1023–1046
6. Sherkow, J.S. The CRISPR patent interference showdown is on: how did we get here and what comes next? Stanford Ctr. Law Biosci. Blog (29 December 2015), law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/
7. European Patent Register, Ep2771468 - Engineering of systems, methods and optimized guide compositions for sequence manipulation (11 February 2015), register.epo.org/application?number=EP13818570&lng=en&tab=doclist
8. Chen, C. and Bloomfield, D. The gene-editing tool on every drugmaker's wish list this year, Bloomberg (24 December 2015), http://www.bloomberg.com/news/articles/2015-12-24/the-gene-editing-tool-on-every-drugmaker-s-wish-list-this-year.
9. Kupecz, A., et al. (2015) Safe harbors in Europe: an update on the research and Bolar exemptions to patent infringement. Nat. Biotech. 33, 710–715
10. Sherkow, J.S. (2015) Law, history and lessons in the CRISPR patent conflict. Nat. Biotech. 33, 256–257
11. Sherkow, J.S. (2016) Nature (forthcoming)
12. Noonan, K.E. CRISPR interference declared. PatentDocs (28 January 2016), www.patentdocs.org/2016/01/crispr-interference-declared.html
13. www.addgene.org

rity is compromised in government. They can fiercely protect university independence. And they can defend peers who become political targets for speaking up (*17*).

We maintain hope that these concerns will not be realized. But the scientific community is well positioned for what may lie ahead. Already, scientific societies have asked the Trump Administration to appoint a science adviser and more than 5500 scientists have signed a letter asking the Administration to uphold scientific integrity (*18*). Alarms must sound when science is silenced, manipulated, or otherwise compromised. When science is sidelined from policy decisions, we all lose. ■

REFERENCES AND NOTES

1. L. M. Krauss, *New Yorker*, 13 December 2016); www.newyorker.com/tech/elements/donald-trumps-war-on-science.
2. S. Otto, *The War on Science: Who's Waging It, Why It Matters, What We Can Do About It* (Milkweed Editions, Minneapolis, MN, 2016).
3. UCS, "Preserving scientific integrity in federal policy-making: Lessons from the past two Administrations and what's at stake under the Trump Administration" (UCS, Cambridge, MA, 2017); www.ucsusa.org/preservingscientificintegrity.
4. C. Mooney, *The Republican War on Science* (Basic Books, New York, 2005).
5. Office of Inspector General, Department of the Interior, *Investigative report: On allegations against Julie MacDonald, Deputy Assistant Secretary, Fish, Wildlife, and Parks* (Department of Interior, Washington, DC, 2006); https://www.doioig.gov/sites/doioig.gov/files/Macdonald.pdf.
6. A. C. Revkin, "Bush vs. the laureates: How science became a partisan issue," *New York Times*, 19 October 2004, p. F1; www.nytimes.com/2004/10/19/science/19poli.html.
7. UCS, Scientist statement on restoring scientific integrity to federal policy making (UCS, Cambridge, MA, 2004); www.ucsusa.org/our-work/center-science-and-democracy/promoting-scientific-integrity/scientists-sign-on-statement.html#.WErynFUrKUk.
8. UCS, "Voices of federal scientists" (UCS, Cambridge, MA, 2007); www.ucsusa.org/sites/default/files/legacy/assets/documents/scientific_integrity/Voices_of_Federal_Scientists.pdf.
9. E. Williamson, *Washington Post*, 1 May 2007; www.washingtonpost.com/wp-dyn/content/article/2007/05/01/AR2007050101920.html.
10. F. Grifo *et al.*, *Federal Science and the Public Good* (UCS, Cambridge, MA, 2008); www.ucsusa.org/sites/default/files/legacy/assets/documents/scientific_integrity/Federal-Science-and-the-Public-Good-12-08-Update.pdf.
11. G. Goldman *et al.*, "Progress and problems: Government scientists report on scientific integrity at four agencies" (UCS, Cambridge, MA, 2015); www.ucsusa.org/scientistsurvey.
12. U.S. Environmental Protection Agency, *FY 2015 Allegations* (EPA, 2015); https://www.epa.gov/osa/fy-2015-allegations.
13. W. Wagner, E. McGarrity, *Bending Science: How Special Interests Corrupt Public Health Research* (Harvard Univ. Press, Cambridge, MA, 2012).
14. P. Ryan, A Better Way (2016); http://paulryan.house.gov/top5issues/a-better-way-our-vision-for-a-confident-america.htm.
15. Office of Management and Budget, "Draft report to Congress on the benefits and costs of federal regulations and agency compliance with the Unfunded Mandates Reform Act" (OMB, 2015); https://obamawhitehouse.archives.gov/omb/inforeg_regpol_reports_congress/.
16. A. A. Rosenberg *et al.*, *Science* **348**, 964 (2015).
17. M. Halpern, M. Mann, Science **348**, 479 (2015).
18. UCS, An open letter to President-elect Trump and the 115th Congress (UCS, Cambridge, MA, 2016); ucsusa.org/trumpscientistletter.

10.1126/science.aam5733

BIOTECHNOLOGY AND LAW

CRISPR, surrogate licensing, and scientific discovery

Have research universities abandoned their public focus?

By **Jorge L. Contreras**[1] *and* **Jacob S. Sherkow**[2]

Several institutions are embroiled in a legal dispute over the foundational patent rights to CRISPR-Cas9 gene-editing technology, and it may take years for their competing claims to be resolved (*1*–*4*). But even before ownership of the patents is finalized, the institutions behind CRISPR have wasted no time capitalizing on the huge market for this groundbreaking technology by entering into a series of license agreements with commercial enterprises (see the figure). With respect to the potentially lucrative market for human therapeutics and treatments, each of the key CRISPR patent holders has granted exclusive rights to a spinoff or "surrogate" company formed by the institution and one of its principal researchers (*5*, *6*). Although this model, in which a university effectively outsources the licensing and commercialization of a valuable patent portfolio to a private company, is not uncommon in the world of university technology transfer, we suggest it could rapidly bottleneck the use of CRISPR technology to discover and develop useful human therapeutics.

> ***"The institutions controlling CRISPR patent rights have delegated [them]... to surrogate companies, which determine...[who] will be able to exploit [them]."***

Several patterns emerge from the web of transactions shown in the figure (we make the documents used in our analysis available at https://dataverse.harvard.edu/dataverse/crisprlicenses). The right to use CRISPR techniques has been divided into three broad "fields of use": (i) basic, noncommercial research; (ii) development and sale of tools (kits, reagents, and equipment) that aid CRISPR-based gene editing; and (iii) development, sale, and use of therapeutics and treatments using CRISPR techniques. This last field broadly covers the most commercially significant applications and includes gene editing to develop agricultural products, veterinary medicine, and human diagnostics and therapeutics.

Precisely demarcating these fields of use—especially for a flexible, broadly applicable technology like CRISPR—and awarding appropriate license grants can be challenging. Nonetheless, the institutions have largely granted nonexclusive licenses with respect to noncommercial research and tools development. This means that licensees, including academic researchers, are permitted to engage in these activities, but do not have the right to market and sell products derived from their research. It also means that the CRISPR patent holders are free to grant licenses for their respective technologies to other research institutions. However, in the case of therapeutics and treatments, with few exceptions, exclusive licenses to surrogate companies (Editas, Caribou, or CRISPR Therapeutics) prevent the institution from granting similar licenses to other companies without the surrogate's permission. Caribou's exclusive license covers all fields of use, and it has in turn granted an exclusive license in the field of human therapeutics to Intellia Therapeutics.

SURROGATE LICENSING AND CRISPR

The companies to which the patent-holding institutions grant exclusive licenses effectively stand in as surrogates for the institutions themselves. These surrogates control a large and lucrative field for the exploitation of the licensed technology, and have significant freedom both to exploit it themselves and to seek partners and sublicensees. The surrogates take on the role of the patent owner and retain a lion's share of the resulting profits. Many

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universities prefer this model because it gives them a substantial share of profits with minimal risk through, for example, equity stakes in their researchers' surrogate companies (*7*, *8*).

The surrogate licensing model, in theory, permits the university to focus on a broader range of commercialization projects with a limited staff, and delegates the job of licensing to experts focused on the relevant technology. Although a university could license its rights individually to the range of commercial enterprises illustrated in the figure, it is often more efficient to grant rights in bulk to a single company and let that company scour the market for viable licensing candidates. The university profits from its equity interest in the surrogate and from any royalties that are generated by the technology.

In addition, the individual investigators, who often have a substantial equity interest in the surrogate company, stand to profit far more than they otherwise would. For all of these reasons, the surrogate licensing model has become popular with universities, investigators, and companies across a wide range of technologies (*7*, *8*).

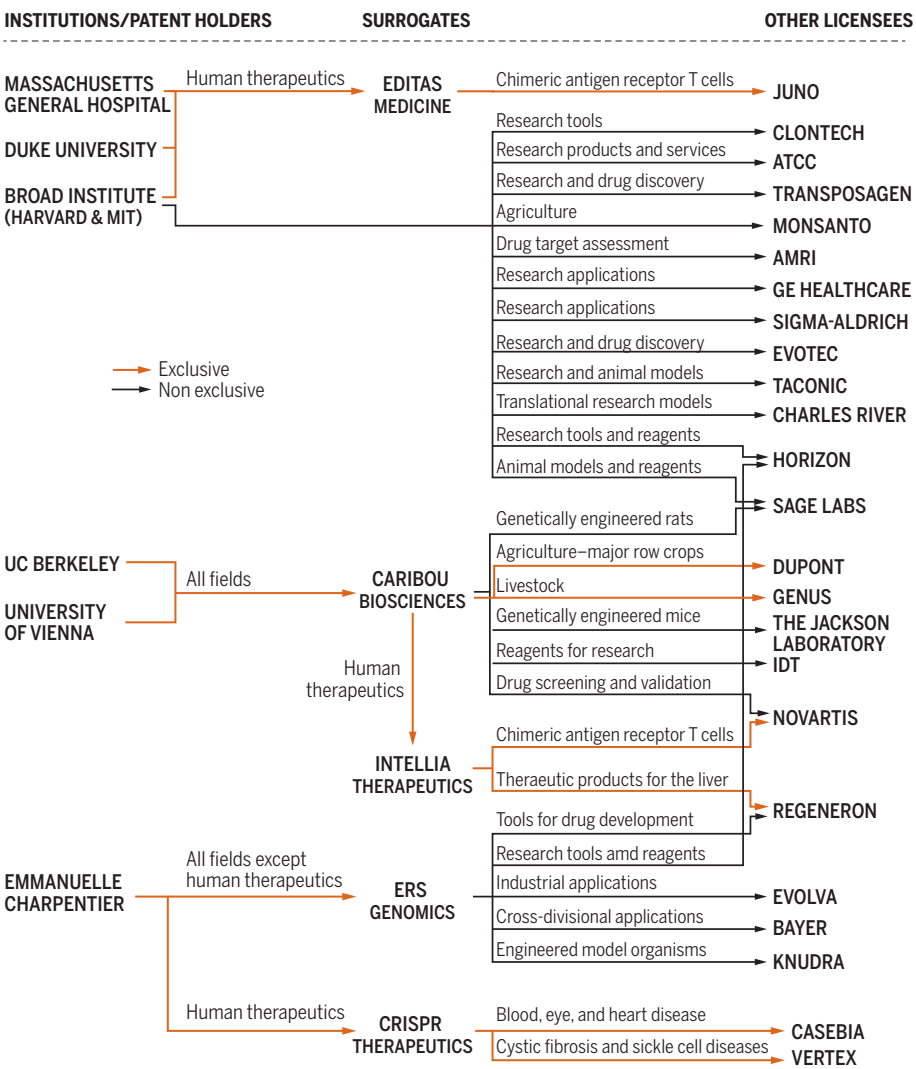
We reviewed all of the CRISPR surrogate license agreements made publicly available through filings with the U.S. Securities and Exchange Commission, requests under state and federal "freedom-of-information" acts, and through press releases and public announcements. In each of the principal surrogate licenses that we reviewed, the patent-holding institution has granted its surrogate the exclusive right to use CRISPR to develop human therapeutics targeting any of the 20,000+ genes that comprise the human genome. Because no single company could develop, test, and market therapeutics on the basis of even a fraction of the entire human genome, the surrogates are authorized and expected to sublicense their rights to others.

Despite this, it is still unlikely that any of the surrogate companies could explore a significant fraction of the potential human health applications that CRISPR could enable, even with a range of experienced commercial partners and collaborators. If an unlicensed company has the expertise and wherewithal to develop a novel human therapy using CRISPR—even if that therapy concerns a previously unexplored gene—that company might not be able to obtain the sublicense necessary to undertake this work. In some instances, such as the license to Editas from the Broad Institute of MIT and Harvard, the institution retains some right to entertain proposals from other companies if the surrogate is not pursuing work on a specific gene and does not plan to do so in the future. The scope of this limitation, however, is narrow and still leaves all "unclaimed" portions of the genome in the surrogate's hands.

Further, traditional contractual safeguards against overbroad exclusive licenses will likely work poorly under this model. Diligence milestones, for example, require an exclusive licensee to demonstrate progress toward commercialization of a licensed technology (often through the achievement of various regulatory hurdles, testing, and trials). But a surrogate can easily show some progress in some subset of a broader field to meet this requirement, even if it does not intend to, or cannot, pursue all aspects of the licensed field. Giving one company an exclusive right to use CRISPR to develop human therapies targeting every segment of the human genome could thus limit the creation of potentially beneficial therapies.

CRISPR-CAS9 licensing agreements

Exclusive licenses to surrogates for human therapeutics limit access to CRISPR as a platform technology.



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NONEXCLUSIVITY AND RESEARCH TOOLS

CRISPR is a broadly applicable, enabling technology platform, similar in many respects to "research tools": equipment, reagents, and methods that enable a broad range of downstream research (*9*). Exclusive rights in research tools are generally unnecessary for commercialization of downstream products developed using them. Rather, exclusive licenses are only needed with respect to specific therapeutic uses discovered using those tools. For example, a molecular drug target may be discovered using research tools like the polymerase chain reaction (PCR) but then require considerable and costly product development, clinical trials, and regulatory

approval before it can be marketed (*9*).

For this reason, in 1999 the U.S. National Institutes of Health (NIH) recommended that patents on research tools developed using federal funding be licensed nonexclusively to promote their greatest utilization, commercialization, and public availability (*9*). In 2007, eleven major U.S. research universities—including the University of California, Berkeley (UCB), Harvard, and Massachusetts Institute of Technology (MIT), all of which have made CRISPR patent claims—committed to a set of core licensing values, known as the "Nine Points," one of which states that universities should make patented research tools as broadly available as possible (*10*).

Although CRISPR is not necessarily a "research tool" in that its function is generally not to enable downstream research, it is a broadly applicable "platform" technology—like stem cells or the Internet—that could enable innumerable specific applications. To that end, foundational CRISPR patents, like patents covering research tools, should be licensed and disseminated as widely as possible especially when developed with public funding by universities operating in the public interest (*11*–*14*).

"Platform technologies such as CRISPR should be recognized as offering the same potential for industry-wide innovation and discovery as traditional research tools."

To their credit, the UCB and the Broad Institute have not sought to limit academic research through their exclusive CRISPR licenses (*1*). Both have made many of their CRISPR research tools available freely or cheaply through AddGene, a nonprofit organization in service of academic and nonprofit institutions (*1*, *14*). Likewise, as noted above, the institutions have granted nonexclusive licenses in the area of tool development.

But the exclusive licenses granted to the institutions' surrogates for human therapeutics limit access to CRISPR as a platform technology, potentially hindering competition and creating innovation bottlenecks. For example, the Broad's surrogate, Editas, has granted Juno Therapeutics an exclusive license to develop a host of CRISPR therapies—across multiple genes—using chimeric antigen receptor T cell (CAR-T) technology (*15*). This broad license threatens to complicate both research and development for CRISPR-based CAR-T technologies for gene targets chosen by Juno, but that neither Editas nor Juno have the bandwidth to pursue. In other instances, overly broad exclusive licenses may hinder research into socially valuable—but unprofitable—therapeutics, such as those indicated for rare diseases or treating illnesses prevalent in disadvantaged populations or regions, a separate yet equally important principle advanced in the Nine Points document.

Situations like these—in which exclusive licenses have the potential to extend beyond that which can be developed—are precisely what the NIH guidelines and the Nine Points sought to avoid. Yet the surrogate licensing model adopted by the CRISPR patent-holding institutions seemingly allows them to circumvent this proscription by ceding licensing authority to private companies not bound by the guidelines and Nine Points.

RECONCEPTUALIZING CRISPR LICENSING

Given the potential bottlenecks created by the current surrogate licensing model, UCB, Harvard, and MIT should broaden access to CRISPR technology for human therapeutics. Given that the technology is developing rapidly and, in some instances, now being disputed among the parties, there is still time to do so. This dynamism in CRISPR's patent landscape should provide the impetus for these institutions—and their surrogate companies—both to amend their existing agreements and to cross-license their respective patent rights to one another. And these cross-licenses need not be exclusive.

As an example, Broad and UCB could reserve their rights to license CRISPR to other commercial firms engaged in therapeutic research on areas of the genome that their surrogates do not have a reasonable plan to develop. The institutions could thus open up larger swaths of the genome to beneficial commercial research. Both UCB and Broad have recently shown some attraction to this approach by announcing limited cross-licensing agreements with other institutions, albeit not with one another (*16*, *17*). A more flexible licensing approach would result in greater competition and innovation in the marketplace—in the spirit of the Nine Points agreement.

The emergence of CRISPR as an important new platform technology should also prompt NIH to update its guidelines regarding the licensing of federally funded inventions. Platform technologies such as CRISPR should be recognized as offering the same potential for industry-wide innovation and discovery as traditional research tools. A similar updating of, and recommitment to, the Nine Points may also be in order.

As the National Academies of Science have noted, "the first goal of university technology transfer involving (intellectual property) is the expeditious and wide dissemination of university-generated technology for the public good" (*12*). The institutions controlling patent rights in CRISPR have delegated that responsibility to surrogate companies, which determine how many or few commercial firms will be able to exploit it. We urge these institutions to rethink their use of exclusive, surrogate licenses across the entire genome. Those institutions should ensure that any exclusive licenses are narrowly drawn to specific genes, to maximize competition in the development of the revolutionary technology they have created. ■

REFERENCES AND NOTES

1. J. S. Sherkow, *Nature* **532**, 172 (2016).
2. J. S. Sherkow, *Nat. Biotechnol.* **33**, 256 (2015).
3. H. Ledford, *Nature* **537**, 460 (2016).
4. K. J. Egelie, G. D. Graff, S. P. Strand, B. Johansen, *Nat. Biotechnol.* **34**, 1025 (2016).
5. License agreement between the President and Fellows of Harvard College, the Broad Institute, Inc., and Editas Medicine, Inc. (29 October 2014).
6. Exclusive License between Caribou Biosciences, Inc., and the University of Vienna and The Regents of the University of California for methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription (16 April 2013).
7. L. Pressman *et al.*, *Nat. Biotechnol.* **24**, 31 (2006).
8. J. Carter-Johnson, J. S. Carter-Johnson, J. L. Contreras, in *Bioinformatics Law: Legal Issues for Computational Biology in the Post-Genome Era*, J. L. Contreras, A. J. Cuticchia, Eds. (American Bar Association, 2013), pp. 97–112.
9. NIH, *Fed. Regist.* **64** (246), 72090 (1999).
10. Association of University Technology Managers, in *the Public Interest: Nine Points to Consider in Licensing University Technology* (AUTM, Washington, DC, 2007).
11. I. Ayres, L. L. Ouellette, *Cornell Law Rev.* **102**, 271 (2017).
12. National Research Council, *Managing University Intellectual Property in the Public Interest*, S. A. Merrill and A.-M. Mazza, Eds. (National Academy Press, 2010).
13. A. K. Rai, R. S. Eisenberg, *Law Contemp. Probl.* **66**, 289 (2003).
14. L. McGuire, *Nature* **534**, 37 (2016).
15. Collaboration and license agreement between Editas Medicine, Inc., and Juno Therapeutics, Inc. (25 May 2015).
16. Caribou Biosciences, CRISPR Therapeutics, Intellia Therapeutics, Caribou Biosciences, and ERS Genomics announce global agreement on the foundational intellectual property for CRISPR/Cas9 gene editing technology [press release] (2016); http://bit.ly/2jWnkON.
17. Editas Medicine, Editas Medicine extends CRISPR genome editing leadership through licensing of new CRISPR technologies [news] (Editas Medicine, 2016); http://bit.ly/2k8C8MN.

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The rise of the ethical license

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The Broad Institute's recent licensing of its gene editing patent portfolio demonstrates how licenses can be used to restrict controversial applications of emerging technologies while society deliberates their implications.

In September 2016, the Broad Institute announced that it had licensed its patents for the groundbreaking CRISPR technology on terms intended to benefit a party not at the negotiating table: the public. As broader policy positions on gene editing technologies emerge, this agreement illustrates how licensing can serve as a tool to limit potentially controversial uses of patented technologies as they enter the marketplace. Here, we discuss some of the advantages and barriers to using this approach.

CRISPR (bacterial clustered, regularly interspaced, short palindromic repeats) is a gene editing tool that can disable, replace, or insert specific nucleotides in a genome, and the Broad owns what are considered to be the foundational patents on this technology[1]. Although the University of California has launched a vigorous challenge to the Broad's patent rights[2], since 2014 the Broad has been offering licenses to its CRISPR patent portfolio for research and commercial purposes. A number of licensees are moving forward with applications of the technology while other researchers are developing their own intellectual property in unclaimed uses of CRISPR[1]. In 2015, over 100 patent applications on CRISPR technology were pending[3]. Meanwhile, companies using first-generation gene editing technologies like zinc finger nucleases and TALENs (transcription activator–like effector nucleases) are on the verge of bringing new products to market[4].

As intellectual property rights in this technological space have multiplied, so, too, have ethical and social concerns about CRISPR's potential applications. Those applications include altering human somatic cells, which make up organs, blood, and skin, and human germ cells, which include sperm and egg cells. While few would object to editing genes to cure devastating diseases, CRISPR technology has the potential to alter the health, behavior, and appearance of every life form. Some fear that in unscrupulous hands, CRISPR might one day be used to create humans genetically enhanced for intelligence, beauty, and strength. These fears are multiplied in cases of germline editing, where changes are passed on to future generations[5]. Worries about germline applications are heightened by CRISPR's ability to power so-called 'gene drives' that alter normal patterns of inheritance such that engineered genes are always passed on to future generations[6]. This technology can be used, for example, to engineer the extinction of an organism.

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The potential applications of CRISPR to alter future generations in unpredictable and unacceptable ways led a group of scientists and ethicists—including some inventors of the technology—to strongly discourage clinical applications of human germline editing until the risks and benefits have been thoroughly examined[7,8]. Nonetheless, Chinese researchers have moved ahead with experiments having clear therapeutic goals. Using CRISPR in nonviable human embryos, one research team knocked out the human gene *HBB*, while another introduced *CCR5*, an HIV-resistance allele[9,10].

As the United States, China, and the United Kingdom coordinate policy responses to these issues[11], an international consensus on the use of CRISPR technologies is slowly emerging: controlled and transparent basic research should continue, but clinical applications

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should be banned until relevant safety, efficacy, and ethical issues have been resolved. Meanwhile, a National Academy of Sciences committee is gathering information for the purpose of guiding US policy (http://nationalacademies.org/gene-editing/index.htm).

Given the enormous challenges of developing practice and legal standards that appropriately balance the interests of individuals, society, and future generations, it is no surprise that researchers and policy makers are approaching these issues cautiously and with great care. The slow pace of social and ethical reckoning, however, means that until stakeholders fully process CRISPR's potential, it is free to be used—and abused—with few legal constraints.

Notably, the use of patent licensing to limit applications has not yet entered the national or international policy conversation. Yet, the Broad's recent license of its CRISPR patent portfolio to Monsanto exemplifies a potentially powerful new solution to this temporal problem: using patent licenses to restrict socially controversial applications of a technology. During a patent's term, one may not practice an invention claimed in the patent without a license from the patent holder. By prohibiting uses the patent holder deems unethical, a patent license can function as a tool of private governance. And because the patent right is limited in duration, this approach has a built-in expiration date far enough in the future to provide policy makers and broader society more time to move deliberatively toward policy solutions.

According to the license agreed upon by the Broad and Monsanto, Monsanto may use the Broad's CRISPR patents for agricultural purposes, such as the production of seeds that resist drought or present improved nutritional profiles. In conducting this research, however, Monsanto may not engage in three activities that the Broad identified as raising ethical and safety concerns.

The prohibited activities are: (i) performing gene drives that spread altered genes quickly through populations, which can alter ecosystems; (ii) creating sterile 'terminator' seeds, which would impose a serious financial burden on farmers who would be forced to buy them each year; and (iii) conducting research directed to the commercialization of tobacco products, which might increase the public health burden of smoking[12].

Two years earlier, and with much less fanfare, the Broad exclusively licensed its CRISPR patents to Editas Medicine for human disease prevention and therapeutic purposes, and that license also includes socially beneficial restrictions. Specifically, Editas agreed not to use the technology to modify human germ cells or embryos for any purpose or to modify animal cells for the creation or commercialization of organs suitable for transplantation into humans[13].

Using patent licenses to pause worrisome applications of emerging biotechnologies has several advantages over formal policy making and standard setting. First, this private solution is more efficient than formal policy making because it does not require consensus among many stakeholders but only the commitment of a single entity: the patent owner. And because the patent owner is frequently the original developer of the technology, it can be in the best position to anticipate controversial applications. Second, unlike most professional guidelines, licensing restrictions are enforceable in court, and a licensor may include penalties in the license for violating those restrictions. Third, unlike laws and government regulations, which are typically blunt policy instruments, patent licenses can be tailored to the specific circumstances of their parties, who are motivated to ensure that any use restrictions are appropriately narrow. Fourth, licensing restrictions are the products of negotiation among affected parties and therefore should be associated with greater buy-in than federal statutes and institutional standards dictated, sometimes, by lay politics.

Despite these advantages, we recognize that there are substantial barriers to using patent licensing as a mechanism for curbing controversial technological applications. For one, adding ethically motivated use restrictions to licenses decreases the value of those licenses, since those who agree to such restrictions generally receive a discount to bear the additional burden. An institution with significant financial interests at stake in its patents may be unwilling to weaken the market for those patents by playing ethicist.

More broadly, however, patent owners may be torn about policing socially beneficial limits on their technologies since doing so requires making—and assuming responsibility for—difficult assessments of the implications for local, national, and global communities. For example, how should a licensor consider the ethics of technologies likely to affect the sequencing of native peoples who might oppose such research?

Although evaluations like these are imprecise, with respect to applications like germline editing, it is easier to conclude that concerns associated with those applications currently trump their potential benefits. In such instances, the social benefits associated with voluntarily engaging in ethical licensing will spill over beyond those who merely comply with such licenses. These spillover effects may include, for example, increased faith in scientific self-regulation and participation in research. Voluntarily restricting applications can also generate goodwill among the licensing parties and promote institutional leadership that might translate to new, collaborative partnerships. Presumably, at least some of these public and private benefits have prompted others to place patent-facilitated limits on controversial innovations. These include Massachusetts Institute of Technology scientist Kevin Esvelt's plan to enforce gene drive patents against academics who use the technology but do not disclose their research plans and attendant safety and ethical issues[14]. Similarly, these benefits likely dovetail with humanitarian instincts to license technologies in less-than-profit-maximizing ways, such as requiring the development and distribution of technologies to underserved populations[15].

For other technologies, however, there may be substantial uncertainty regarding which patent licensing restrictions will maximize social welfare—or at least prevent social harm. Technologies like CRISPR that implicate large numbers of disparate social interests may sound an alarm that drowns clear calls to action. As a result, some licensors may forego pursuing socially beneficial licensing. Alternatively, they may adopt license terms that are inconsistent or even mutually defeating. Taking the concern to its extreme, patent owners may even reject coordination and elect instead to separately pursue lucrative applications that are widely opposed as unethical, such as licensing CRISPR technologies for germline engineering.

These problems are not intractable, however. CRISPR stakeholders agree on the need for a coordinated response to the scientific, ethical, legal, social, and governance issues associated with human gene editing, and several major efforts are underway to develop relevant practices and policies. We believe that these efforts should include explicit consideration of patent licensing as a tool of privately driven governance, which thus far has been absent from the conversation. Further, as to any restrictions on CRISPR specifically, we urge the consideration of whether such restrictions should be incorporated in patent licenses.

In the meantime, and looking beyond CRISPR to other controversial biotechnologies such as non-invasive prenatal testing, we urge innovators to follow the Broad's lead and adopt the practice of using patent licenses to restrict socially harmful applications of their technologies. Innovators should be encouraged to identify and address such instances in their patent licenses.

For the sake of transparency and to facilitate further socially beneficial licensing, innovators should also be encouraged to follow the Broad's example of publicly disclosing the terms of and reasoning behind any license restriction policies they have adopted[16]. Where licensing includes confidential business information, the public does not need to know the financial details of a licensing deal. But if socially beneficial licensing is truly for the public, the patent holder should inform the public of any terms of use that are adopted on its behalf.

As a mechanism for addressing controversial applications of biotechnologies like CRISPR, we do not suggest that private agreements are preferable to, or should be used to the exclusion of, policy making or professional standards setting. We view these two systems—public regulation and private governance—as complements to each other. We hope simply to highlight the advantages of private agreements that have not yet been fully exploited. Most likely, some combination of public and private efforts will be necessary to ensure that CRISPR's promise of public welfare is fully realized.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Rood, J. *The Scientist* http://www.thescientist.com/?articles.view/articleNo/42595/title/Who-Owns-CRISPR-/ (3 April 2015).
2. *The Broad Institute, Inc. v. The Regents of the Univ. of California*. Declaration of Interference No. 106,048 (2016).
3. Sherkow, J.S. *Nat. Biotechnol.* **33**, 256–257 (2015).
4. Han, A.P. *GenomeWeb* https://www.genomeweb.com/gene-silencinggene-editing/non-crispr-genome-editing-technologies-find-niche-biotech-applications (8 August 2016).
5. Pollack, R. *Science* **348**, 871 (2015).
6. Abbasi, J. *JAMA* **316**, 482–483 (2016)
7. Baltimore, D. *et al. Science* **348**, 36–38 (2015).
8. Lanphier, E., Urnov, F., Haecker, S.E., Werner, M. & Smolenski, J. *Nature* **519**, 410–411 (2015).
9. Liang, P. *et al. Protein Cell* **6**, 363–372 (2015).
10. Kang, X. *et al. J. Assist. Reprod. Genet.* **33**, 581–588 (2016).
11. Olson, S. (ed.) *International Summit on Human Gene Editing: a Global Discussion* (National Academies Press, Washington, DC, 2016).
12. Begley, S. *STAT News* https://www.statnews.com/2016/09/22/monsanto-licenses-crispr/ (22 September 2016).
13. Editas Medicine, Inc. Securities and Exchange Commission Form S-1, amend. 1 (2016).
14. Regalado, A. https://www.technologyreview.com/s/602633/stop-gene-spills-before-they-happen/ *MIT Technol. Rev.* (20 October 2016).
15. Mimura, C. in *Working within the Boundaries of Intellectual Property: Innovation Policy for the Knowledge Society* (eds. Dreyfuss, R.C., First, H. & Zimmerman, D.L.) 269–295 (Oxford University Press, New York, 2010).
16. Rosen, I. https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations Broad Institute *News* (29 September 2016).