Science & Society

EMBO reports

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

Innovation Center for Law and Technology, New York Law School, New York, NY, USA. E-mail: jacob.sherkow@nyls.edu
DOI 10.15252/embr.201744418 | Published online 23 May 2017

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].

"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."

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.

"Unlike other fields, such as mechanical engineering, molecular biology is considered substantially more "unpredictable"…"

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.

> *"Few advances in molecular biology are the result of simple "common sense", however defined."*

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.

> *"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."*

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