36 Biotechnology Law Report 167
Number 4, 2017

DOI: 10.1089/blr.2017.29024.jww

The Importance of CRISPR-9 Due Diligence

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ABSTRACT

On February 15, 2017, the United States Patent and Trademark Office's Patent Trial and Appeal Board announced its long-awaited decision finding no interference-in-fact between patents and patent applications directed to CRISPR-Cas9 owned by Broad Institute, Inc. *et al.* and patent applications owned by Regents of the University of California *et al*. The decision found that the CRISPR-Cas9 gene-editing system *in a eukaryotic environment* (as generally claimed by Broad Institute) was found to be patentably distinct from a CRISPR-Cas9 gene-editing system *in any environment*, including in prokaryotic cells or *in vitro* (as claimed by the University of California), "because one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment." Therefore, no interference of the claims was found and the proceedings were terminated. This decision has been appealed to the Federal Circuit Court of Appeals. The background, implications of this decision, and possible future issues related to the respective patent portfolios are explored herein.

I. INTRODUCTION

A NEW GENE-EDITING TOOL—CRISPR-Cas9—has garnered significant interest in biotechnology industries. CRISPR-Cas9 is a combination of protein and ribonucleic acid (RNA) that can alter the genetic sequence of an organism. Several parties have heavily invested in intellectual property rights attempting to cover the revolutionary technology and have embarked upon equally aggressive licensing programs. Thus, those intending to use this new technology need to be wary of investing without thorough due diligence.

Keywords: CRISPR, CRISPR-Cas9, patent interference, priority contest, Broad, Berkeley, Charpentier

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Researchers first identified the CRISPR sequence in 1987.[1] Yet, it was not until 2012 when the University of California Berkeley lab first published its results that researchers demonstrated practical uses of the sequence. Since then, many patent applications have been filed with the United States Patent and Trademark Office (USPTO) and around the world. In particular, two competing and pioneering research groups have been entangled in a patent dispute that is sure to impact the biotechnology and patent worlds for years to come. This battle has been closely followed by many, as its outcome will inform best practices for research groups' freedom-to-operate and ability to commercialize inventions and improvements based on or using the CRISPR-Cas9 gene-editing technique for decades to come.

The first group, including the University of California at Berkeley, University of Vienna, and Emmanuelle Charpentier (collectively, Berkeley or UC), published its results describing use of

[1]Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), https://www.quantamagazine.org/20150206-crispr-dna-editor-bacteria/

the CRISPR-Cas9 gene-editing tool in *Science* on June 28, 2012,[2] shortly after filing its first provisional application with the USPTO.[3] Seven months later the second group, including the Broad Institute, Massachusetts Institute of Technology, and Harvard University (collectively, Broad), filed a series of applications directed to the CRISPR-Cas9 gene-editing tool. The UC application was directed to the use of CRISPR-Cas9 in all cells, while Broad applications specifically disclosed and claimed use of the gene-editing technique in eukaryotic cells. Notably, the UC inventors publicly expressed difficulties adapting the gene-editing technique to more complex cells, like eukaryotic cells, in interviews given around the time they filed their application and published their *Science* article.

Although Broad filed months after UC, Broad's patents issued first because Broad took advantage of the USPTO's accelerated examination procedures.[4] Subsequently, and perhaps not all too surprisingly, UC attempted to invoke an interference before the USPTO of the gene-editing technology, claiming that they were the first to invent and should be the only party entitled to a patent for the invention.[5] The USPTO Patent Trial and Appeal Board (the Board or PTAB) declared an interference on January 11, 2016.[6,7] On February 15, 2017, the USPTO PTAB announced its long-awaited decision finding no interference-in-fact of the challenged claims between UC and Broad. On April 12, 2017, UC filed a Notice of Appeal with the Federal Circuit Court of Appeals to challenge the PTAB's interference decision.

II. SETTING THE SCENE

A. The technology

Clustered regularly interspaced short palindromic repeats—commonly known as CRISPR[8]—are "short, repeating, palindromic DNA sequences separated by short, non-repeating, 'spacer' sequences."[9] Thus, CRISPR has two characteristic features: nucleotide repeats and spacers interspaced therein.[10] The spacers or targeting sequences "match sequences from foreign, mobile genetic elements, such as bacteriophages and plasmid."[11] Otherwise stated, the spacers mirror "viruses that previously attacked the organism."[12] The CRISPR array can readily acquire and incorporate newly encountered spacer sequences (*i.e.*, viruses previously unseen).[13] Consequently, CRISPR functions as a "genetic memory" or "adaptive immune system" for organisms such as bacterium, which can detect and destroy returning invaders (*i.e.*, viruses).[14]

[2]Martin Jinek, Krzysztof Chylinski, Ines Fonfara, Michael Hauer, Jennifer A. Doudna, Emmanuelle Charpentier, *A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 Sci. 816 (2012).

[3]U.S. provisional patent application Serial No. 61/652,086, filed May 25, 2012.

[4]Accelerated examination before the U.S. Patent and Trademark Office (USPTO) requires submitting a petition making certain certifications and submitting an accompanying fee to the USPTO. M.P.E.P § 708.02(a) sets forth the specific requirements for accelerated examination. *See generally Accelerated Examination*, United States Patent and Trademark Office, https://www.uspto.gov/patent/initiatives/accelerated-examination (last visited May 4, 2017).

[5]Sara Reardon, *CRISPR Heavyweights Battle in US Patent Court*, Nature (Dec. 6, 2016), http://www.nature.com/news/crispr-heavyweights-battle-in-us-patent-court-1.21101

[6]U.S. Patent Interference No. 106,048 involved Broad U.S. Patents Nos. 8,697,359 (claims 1–20); 8,771,945 (claims 1–29); 8,795,965 (claims 1–30), 8,865,406 (claims 1–30), 8,871,445 (claims 1–30), 8,889,356 (claims 1–30), 8,895,308 (claims 1–30); 8,906,616 (claims 1–30); 8,932,814 (claims 1–30); 8,945,839 (claims 1–28); 8,993,233 (claims 1–43); 8,999,641 (claims 1–28); Broad's U.S. Application Serial No. 14/704,551 (U.S. Pub. No. 2015/0247150 (Claims 2 and 4–18)) and UC's U.S. Application Serial No. 13/842,859 (U.S. Pub. No. 2014/0068797 (claims 165–200, 202–218, 220–222, and 224–247)).

[7]*See infra* Part II.C.

[8]The acronym first appears in the 43rd volume of Molecular Microbiology article, *Identification of Genes That Are Associated with DNA Repeats in Prokaryotes*, authored by Rudd Jansen, Jan D.A. van Embden, Wim Gaastra, and Leo M. Schouls in 2002. *See* Bob Grant, *Credit for CRISPR: A Conversation with George Church*, The Scientist (Dec. 29, 2015), http://www.the-scientist.com/?articles.view/articleNo/44919/title/Credit-for-CRISPR–A-Conversation-with-George-Church/

[9]Benjamin C. Tuttle, *The Failure to Preserve CRISPR-Cas9's Patentability Post Myriad and* Alice, 98 J. Pat. & Trademark Off. Soc'y 391, 393 (2016) (citing T. Ishino *et al.*, *Nucleotide Sequence of the iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia coli, and Identification of the Gene Product*, 169 J. Bacteriology 5429, 5429–5433 (1987)).

[10]Aparna Vidyadager, *What Is CRISPR?*, Livescience (Apr. 21, 2017), http://www.livescience.com/58790-crispr-explained.html

[11]Luciano A. Marraffini and Erik J. Sontheimer, *CRISPR Interference: RNA-Directed Adaptive Immunity in Bacteria & Archaea*, 11 Nat. Rev. Genet. 181 (2011), available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928866/

[12]Vidyadager, *supra* note 10.

[13]Marraffini, *supra* note 11.

[14]*Questions and Answers About CRISPR*, Broad Institute, https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr (last visited Apr. 24, 2017).

Accompanying the described CRISPR regions (*i.e.*, repeats plus spacers) are enzyme encoding genes known as CRISPR-associated genes, commonly referred to as "*Cas*-genes," which generate Cas9 proteins.[15] The Cas9 proteins are restriction-type enzymes responsible for cleaving target DNA.[16] Short ribonucleic acid (RNA) sequences, CRISPR RNAs or crRNA sequences, transcribed by the spacer sequences guide the system to matching DNA sequences (*i.e.*, attacking virus) to which the Cas9 will bind.[17] Cas9 will cleave the target DNA, shutting-off the targeted gene and protecting the bacterium from the viral attack.[18] Unlike traditional cleaving methods (*e.g.*, Cpf1), Cas9 cuts both DNA strands at the same place leaving even blunt ends.[19]

In sum, CRISPR adaptive immune system has three steps: (1) adaptation of the spaces (*i.e.*, viral DNA) into the CRISPR sequence; (2) production of the CRISPR RNAs; and (3) targeting and destroying—the CRISPR RNAs guide the CRISPR array to the target DNA and Cas9 cleaves and destroys the viral invader.[20]

Molecular biologists are using modified CRISPR arrays as genome-editing tools to slice genomes of their choosing at sites of their choosing.[21] By selecting the *ideal* guide RNA, "virtually any genomic location of choice" can be targeted by the CRISPR nuclease Cas9, allowing scientists to improve their understanding of various genomes in various fashions and to edit DNA.[22,23] CRISPR-Cas9 use has exploded because of its "relative simplicity and versatility compared to other gene-editing methods."[24] CRISPR-Cas9 "is expected [by all involved] to be a multibillion annual market."[25]

B. Licensing by the patent owners

As briefly mentioned above, the patents and patent applications embroiled in the interference dispute are owned by two institutions and one inventor (Emmanuelle Charpentier), all of whom have licensed their patents or patent applications. Notably, there are many other patents and applications that claim aspects of CRISPR-Cas9 technology beyond those discussed here and which may implicate and further impact widespread use of CRISPR-Cas9 gene-editing techniques in the future.

i. The Broad Institute, Massachusetts Institute of Technology, Harvard University. Broad is reported to have licensed its CRISPR-Cas9 patents and applications to different parties for different fields of use.[26] For example, for human therapeutic applications, Broad's exclusive licensee is Editas Medicine, Inc. (Editas). Via this license, Editas has the exclusive right to use Broad's CRISPR IP on targets of its choosing for the development of genomic medicines. However, after an initial period, certain rights may revert back to Broad for genes that are not being actively pursued by Editas.[27] Thus, when certain conditions are met in the future, other companies may be able to license Broad's CRISPR intellectual property (IP) for human therapeutics for select genes of interest not being pursued by Editas.

In all other non-human fields of research, Broad indicates that its CRISPR IP is available for non-exclusive licensing to companies for commercial research or companies wishing to sell tools and reagents for genome editing.[28] For non-human therapeutics, Broad has licensed various companies in different fields of use, such as agricultural use to

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[15]Tuttle, *supra* note 9.

[16]*CRISPR/ Cas9 and Targeted Genome Editing: A New Era in Molecular Biology*, New England BioLabs, Inc., https://www.neb.com/tools-and-resources/feature-articles/crispr-cas9-and-targeted-genome-editing-a-new-era-in-molecular-biology (last visited Apr. 24, 2017).

[17]*Questions and Answers About CRISPR*, *supra* note 14.

[18]*Id.*

[19]*Id.*

[20]*CRISPR: A Game-Changing Genetic Engineering Technique*, Science in the News (Harvard University Graduate School of Arts and Sciences), http://sitn.hms.harvard.edu/flash/2014/crispr-a-game-changing-genetic-engineering-technique/ (last visited Apr. 25, 2017).

[21]Heidi Ledford, *CRISPR: Gene Editing Is Just the Beginning*, 531 Nature 156, 156–57 (2016).

[22]Xin Luo, Min Li, and Bing Su, *Application of the Genome Editing Tool CRISPR/CAS 9 in Non-Human Primates*, 37 Dongwuxue Yanjiu 241 (2016), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980068/

[23]Ledford, *supra* note 21.

[24]Heidi Ledford, *Bitter Fight over CRISPR Patent Heats Up*, 529 Nature 265, 265 (2016).

[25]Sharon Begley, *Broad Institute Prevails in Heated Dispute over CRISPR Patents*, Stat (Feb. 15, 2017), https://www.statnews.com/2017/02/15/crispr-patent-ruling/

[26]While licensing information is often confidential and not publicly available, various information about licensing for these CRISPR-Cas9 patents and patent applications has been publicly available as set forth in Jorge L. Contreras, Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 Sci. 6326, 698–700 (Feb. 17, 2017); Jon Cohen, *How the Battle Lines over CRISPR Were Drawn* Sci. (Feb. 15, 2017), http://www.sciencemag.org/news/2017/02/how-battle-lines-over-crispr-were-drawn

[27]*Information About Licensing CRISPR Genome Editing System,* Broad Institute, https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-genome-edi (last visited May 6, 2017).

[28]*Id.*

Monsanto, research applications to GE Healthcare and Sigma-Aldrich, research tools to Clontech, and research and drug discovery to Evotec, among others. Broad also works with Addgene, a non-profit plasmid repository, that freely permits use of CRISPR tools, knowledge, methods, and other IP for genome editing.[29] However, this use is only available for non-commercial entities, such as academic institutions or not-for-profit organizations.

ii. The University of California, University of Vienna. UC is similarly reported to have licensed its patent application directed to CRISPR technology based on different fields of use. For human therapeutics, UC's exclusive licensee is Intellia Therapeutics, Inc. It is reported that Intellia has sublicensed in distinct fields of use. For example, therapeutic products for the liver reportedly have been licensed to Regeneron and chimeric antigen receptor T-cells to Novartis.

For non-human therapeutics, UC's exclusive licensee is Caribou Biosciences, Inc. The non-human therapeutics have likewise been sublicensed in various distinct fields of use. For example, use of the CRISPR-Cas9 IP in agriculture and main-row crops has been licensed to DuPont.

iii. Emmanuelle Charpentier. Lastly, Emmanuelle Charpentier is also an owner of CRISPR-Cas9 patent applications and patents (she retained rights in the UC patent application[s]). Dr. Charpentier has exclusively licensed her rights in the field of human therapeutics to CRISPR Therapeutics, Ltd.[30] CRISPR Therapeutics has in turn sublicensed different fields of use to different companies. For example, use of CRISPR-Cas9 for blood, eye, and heart disease has been licensed to Casebia, while use for cystic fibrosis and sickle cell diseases has been licensed to Vertex.

For non-human therapeutics, the exclusive licensee is ERS Genomics Ltd. (ERS). ERS has also sublicensed in different fields of use. For example, ERS has licensed non-human cross-divisional applications to Bayer and industrial applications to Evolva.

C. The U.S. patent interference dispute

In the U.S., an interference proceeding is a procedure to determine who is entitled to claim an invention when a first person's invention was potentially made before a second person's invention and the invention was not abandoned, suppressed, or concealed by the first person.[31] During an interference proceeding, the PTAB may initially compare one or more claims of a first patent or application with one or more claims of a second patent or application to determine if each is directed to the same invention. If the patents or applications are determined to claim the same invention, the party determined to be the earlier or senior party which has fulfilled certain conditions will be entitled to claim the disputed invention and to be granted a patent.

An interference[32] involving twelve of Broad's issued patents,[33] one pending Broad patent application,[34] and one pending UC patent application[35] directed to CRISPR-Cas9 claims was terminated on February 15, 2017, because the PTAB found no interference-in-fact between patents and patent application owned by Broad, the junior parties, and the patent application owned by UC, the senior parties.[36] The crux of the issue revolved around whether UC's broad claims directed to CRISPR-Cas9[37] in any environment for any cell would bar

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[29] *Id.*

[30] *Id.*

[31] Pre-America Invents Act (pre-AIA) 35 U.S.C. § 102(g): "A person shall be entitled to a patent unless - … (1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other." Notably, the AIA eliminated § 102(g). *See generally, Patent Interference Information*, USPTO, https://www.uspto.gov/patents-application-process/a00000ppealing-patent-decisions/patent-interference-information (last visited May 8, 2016).

[32] *The Broad Institute, Inc., et al. v. The Regents of the University of California et al.*, Interference No. 106,048 Decision on Motions 37 C.F.R. §41.125(a) (PTAB Feb. 15, 2017).

[33] U.S. Patent Nos. 8,697,359 (the '359 Patent); 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; and 8,999,641.

[34] U.S. Patent Application Serial No. 14/704,551 (U.S. Pub. No. 2015/0247150).

[35] U.S. Patent Application Serial No. 13/842,859 (the '859 Application) (U.S. Pub. No. 2014/0068797).

[36] The references to senior and junior parties relates to the filing dates of the respective parties. As noted above, although Broad was the junior party and filed months after UC, Broad's patents issued first because Broad took advantage of the USPTO's accelerated examination procedures. *See supra* Part I.

[37] While UC broadly claimed any cell, its initial patent application and examples only described successful CRISPR-Cas9 use in prokaryotic cells (cells that lack nuclei, mitochondria, organelles, such as bacterial cells).

patentability to Broad's later claims directed to CRISPR-Case 9 for a eukaryotic cell.[38] Broad persuaded the PTAB that it claimed a patentably distinct invention, where CRISPR-Cas9 systems are used in a eukaryotic environment, and that its claims were not drawn to the same invention as UC's claims, all directed to CRISPR-Cas9 systems not restricted to any environment. Broad submitted evidence that the invention of such systems in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 in any environment, because one of ordinary skill in the art would not have reasonably expected the CRISPR-Cas 9 system to be successful in a eukaryotic environment. Thus, the PTAB decided that the claims in Broad's patents and UC's patent application were not directed to the same invention and, thus, both the senior and junior parties can have coexisting patents.

Although both parties filed a number of motions, the PTAB elected to consider Broad's second motion arguing no interference-in-fact "because it will determine if the interference should have been declared and if it should continue."[39,40,41] In accordance with 35 U.S.C. § 102(g), the PTAB held that to prevail on its argument that there is no interference, Broad had to show that the parties' claims do *not* meet at least *one* of the following two conditions:

> 1) that, if considered to be prior art to UC's claim, Broad's involved claims would not anticipate or render obvious UC's involved claims, or
> 2) that, if considered to be prior art to Broad's claims, UC's involved claims would not anticipate or render obvious Broad's claims.[42]

Broad argued that the latter of these two conditions was not met.[43] UC had conceded that if treated as prior art, none of its claims anticipate Broad's claims "because none of UC's claims recite a limitation to a eukaryotic environment and each of Broad's claims contains this limitation."[44] With respect to obviousness, Broad argued that a person of ordinary skill in the art would not have reasonably expected the CRISPR-Cas9 system claimed by UC to be successful in a eukaryotic cell, as evidenced by contemporaneous statements of the UC inventors and others skilled in the art when UC first published its results.[45] UC argued instead that the contemporaneous statements evidenced an expectation of success and merely indicated that positive experimental results had not been reported.[46]

The PTAB, finding that Broad met its burden, concluded that "[a]lthough the statements express[ed] an eagerness to learn the results of experiments in eukaryotic cells and the importance of such results,

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[38]Eukaryotic cells are those that have nuclei or organelles and include those found in animals and plants.

[39]*See* Interference No. 106,048 *supra* note 32, at 7–8.

[40]The Patent Trial and Appeal Board (PTAB) compared representative Claim 165 of UC's '859 Application and representative Claim 1 of Broad's '359 Patent. Interference No. 106,048 *supra* note 32, at 10–11.Claim 165 of UC's '859 Application:

> *165.* A method of cleaving a nucleic acid comprising contacting a target DNA molecule having a target sequence 11 with an engineered and/or non-naturally-occurring Type II Clustered 12 Regularly Interspaced Short Palindromic Repeats (CRISPR)—13 CRISPR associated (Cas) (CRISPR-Cas) system comprising
> a) a Cas9 protein; and
> b) a single molecule DNA-targeting RNA comprising
> i) a targeter-RNA that hybridizes with the target 17 sequence, and
> ii) an activator-RNA that hybridizes with the targeter-19 RNA to form a double-stranded RNA duplex of a 20 protein-binding segment,
> wherein the activator-RNA and the targeter-RNA are covalently 22 linked to one another with intervening nucleotides,
> wherein the single molecule DNA-targeting RNA forms a 24 complex with the Cas9 protein,
> whereby the single molecule DNA-targeting RNA targets the 26 target sequence, and the Cas9 protein cleaves the target DNA 27 molecule.

Claim 1 of Broad's '359 Patent:

> *1.* A method of altering expression of at least one gene product 4 comprising introducing into a eukaryotic cell containing and 5 expressing a DNA molecule having a target sequence and encoding 6 the gene product an engineered, non-naturally occurring Clustered 7 Regularly Interspaced Short Palindromic Repeats (CRISPR)–CRISPR 8 associated (Cas) (CRISPR-Cas) system comprising one or more 9 vectors comprising:
> a) a first regulatory element operable in a eukaryotic cell 11 operably linked to at least one nucleotide sequence encoding a 12 CRISPR-Cas system guide RNA that hybridizes with the target 13 sequence, and
> b) a second regulatory element operable in a eukaryotic cell 15 operably linked to a nucleotide sequence encoding a Type-II Cas9 16 protein,
> wherein components (a) and (b) are located on same or different 18 vectors of the system, whereby the guide RNA targets the target 19 sequence and the Cas9 protein cleaves the DNA molecule, whereby 20 expression of the at least one gene product is altered; and, wherein the 21 Cas9 protein and the guide RNA do not naturally occur together.

[41]*See generally* 37 C.F.R. § 41.125(a).

[42]Interference No. 106,048 *supra* note 32, at 9.

[43]*Id.* at 10.

[44]*Id.* at 11–12.

[45]*Id.* at 14–15.

[46]*Id.* at 16.

none of them express[ed] an expectation that such results would be successful."[47] As such, the PTAB concluded that if UC claims were considered prior art, the claims would not have rendered Broad's claims obvious.[48] Because UC's involved claims would not anticipate or render obvious Broad's claims, the claims are not drawn to the same patentable subject matter and there can be no interference-in-fact between the claims and Broad's patents and application stand.[49] The PTAB finding of no interference-in-fact deprived UC of standing to raise additional challenges.[50] Accordingly, the PTAB "terminated the proceeding [in its entirety] without entering judgment against either party's claims."[51]

III. MOVING FORWARD—HOW DOES THE PTAB'S DECISION AFFECT RESEARCHERS?

A. The appeal to the Federal Circuit

The interference decision by the USPTO PTAB is not final. On April 12, 2017, UC filed a Notice of Appeal with the Federal Circuit Court of Appeals challenging the PTAB's interference decision.[52] As explained by Associate Dean of Biology and Special Advisor on CRISPR, Edward Penhoet, UC seeks to "establish definitively that the team led by Jennifer Doudna and Emmanuelle Charpentier was the first engineer CRISPR-CAS9 for use in *all* types of environments, including in non-cellular settings and within plant, animal and even human cells."[53] Ultimately, as summarized by UC's attorney Lynn Pasahow, Berkeley argues that the inventions, UC's and Broad's, "are not separate inventions."[54] Rather, Broad's "inventions" are "encompassed by what [the UC] inventors already invented."[55]

In response, Broad renewed its stance and reportedly remains "confident [that] the Federal Circuit will affirm the PTAB decision and recognize the contribution of Broad, MIT and Harvard in developing th[e] transformative technology."[56] As noted in Broad's press release, the Federal Circuit reviews "the Board's factual determinations for substantial evidence and its legal determinations *de novo*."[57] As such, the Federal Circuit will "not independently weigh the facts determined by the PTAB[, and t]o overturn the PTAB decision, the Court w[ill] need to decide that the PTAB committed an error of law or lacked substantial evidence to reach its decision." Unmistakably, however, the likelihood of continued (and prolonged) litigation begs the question: what will happen to present licensees if, following subsequent litigation, Broad's patents are determined to be partially or wholly invalid? Likewise, for current licensees of the UC applications, based on the factual record of the USPTO, a looming question remains about the possible scope of U.S. claims that might be patentable.

B. Vulnerability of UC Berkeley's U.S. applications

First, the USPTO's interference decision may be problematic for UC with respect to the pending patent application at issue and its various progeny applications. While not directly at issue in the interference, the USPTO PTAB essentially found that the UC inventors had not invented the CRISPR-Cas9 technology for all cells, but rather only for prokaryotic cells at the time when they filed their first patent application. The interference decision appears to indicate that the UC inventors had not yet enabled one of ordinary skill in the art as to how to make and use their technology in all cells (*e.g.*, eukaryotic cells). U.S. law requires claimed inventions of a patent to be enabled, meaning the specification of the patent must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude

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[47] *Id.* at 17.
[48] *Id.* at 49.
[49] *Id.*
[50] *Id.*
[51] *Id.* at 50.
[52] USPTO Patent Application Retrieval Information for U.S. App. No. 13/842,859 Appeal to CAFC (Apr. 12, 2017); *see also* Robert Sanders, *UC Appeals U.S. Patent Board Decision on CRISPR-Cas9*, BERKELEY NEWS (Apr. 13, 2017), http://news.berkeley.edu/2017/04/13/uc-appeals-u-s-patent-board-decision-on-crispr-cas9/ *See also* Kevin E. Noonan, *University of California/Berkeley Appeals Adverse CRISPR Decision by PTAB*, PATENTDOCS (Apr. 13, 2007), http://www.patentdocs.org/2017/04/university-of-californiaberkeley-appeals-adverse-crispr-decision-by-ptab.html
[53] *Id.*
[54] Christine Lee, *UC Appeals Decision That Both Parties in CRISPR-Cas9 Lawsuit Can Maintain Patents*, DAILY CALIFORNIAN (Apr. 18, 2017), http://www.dailycal.org/2017/04/18/uc-appeals-decision-parties-crispr-cas9-lawsuit-can-maintain-patents/
[55] *Id.*
[56] Lee McGuire, *For Journalists: Statement and Background on the CRISPR Patent Process* (Apr. 18, 2017), https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process
[57] *Intellectual Ventures II LLC v. Ericsson Inc.*, No. 2016-1803, 2017 U.S. App. LEXIS 6566, at *9 (Fed. Cir. Apr. 18, 2017) (citing *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015)).

that the inventor had possession of the claimed invention.[58] Consequently, another open question in the aftermath of the PTAB's interference fact finding is whether UC will be able to obtain the broad patent claims it seeks in the U.S. Notably, the European Patent Office and the United Kingdom Intellectual Property Office have thus far found that the claims directed to all cells, including eukaryotic cells, are patentable under their respective patent laws.[59]

C. Potential liability for infringement damages of published applications

Provisional patent rights may be available for a patentee under U.S. law, giving the patentee the right to reasonable royalties for infringement that occurred while the patent application was pending and before it issued (from the time of the publication of a patent application to its issuance).[60] However, the patentee must provide actual notice to the putative infringer and the claims in the published application must be "substantially similar" to those in the granted patent. Thus, if UC is able to obtain issued claims substantially similar to those in its published application, various parties that had actual notice of the UC patent application(s) may be liable for reasonable royalties for infringement. In view of the litigation and other proceedings, this period of time may be extensive and possible royalties for the patentee (*e.g.*, UC) would be accruing.

D. Liability for CRISPR-Cas9 research and licenses

At least for now, the USPTO PTAB decision means that the CRISPR patents granted to Broad cover different inventions than those claimed in UC's pending applications. Thus, there will now be at least two parties independently pursuing patents to the CRISPR-Cas9 technology with potentially overlapping, but not identical, claims. To the extent that all these patents are granted, licenses may be necessary from multiple parties to avoid liability for infringement. Thus, for commercial enterprises wishing to use the CRISPR-Cas9-based technology, it may become necessary to obtain licenses from multiple patent owners. It bears noting that there are numerous other patents directed to the CRISPR-Cas9 technology, so freedom-to-operate and potential licensing will be an important consideration in the realm of research and for businesses using CRISPR-Cas9 gene-editing techniques. To the extent that licensing terms are uncertain or unfavorable among the various patentees, it may drive the industry to seek alternative gene-editing tools.

For limited non-commercial use, while one of the patent owners (*i.e.*, Broad) indicates that it will permit non-commercial activities to use the patented CRISPR-Cas9 gene-editing techniques, there may be several other patent owners that could eventually have potential claims of patent infringement for non-commercial use. Thus, even for non-commercial use of the CRISPR-Cas9 gene-editing, a freedom-to-operate assessment is recommended in this now-crowded field.

E. Avoiding the uncertainty: Alternatives to CRISPR-Cas9

Despite the revolutionary capabilities of CRISPR-Cas9, the uncertainty surrounding CRISPR's patent coverage (the only certainty, in fact, being continued litigation) may drive potential licensees and research groups to instead develop or license other "safer" genome-editing tools.[61] For example, some research groups (including teams at Broad) are using mini-Cas9, a system which is 1,000 DNA nucleotide

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[58]Pre-AIA 35 U.S.C. §112, first paragraph provides: "The specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the *best mode* contemplated by the inventor of carrying out his invention."

[59]*See, e.g.*, EP 2800811 granted on May 10, 2017, and GB 2518764 granted February 2, 2016. EP patents can be opposed after grant for a period of nine months.

[60]35 U.S.C. § 154(d). PROVISIONAL RIGHTS.

1) IN GENERAL—In addition to other rights provided by this section, a patent shall include the right to obtain a reasonable royalty from any person who, during the period beginning on the date of publication of the application for such patent under section 122(b) … and ending on the date the patent is issued—

A)(i) makes, uses, offers for sale, or sells in the United States the invention as claimed in the published patent application or imports such an invention into the United States; or

(ii) if the invention as claimed in the published patent application is a process, uses, offers for sale, or sells in the United States or imports into the United States products made by that process as claimed in the published patent application; and

B) had actual notice of the published patent application and, in a case in which the right arising under this paragraph is based upon an international application designating the United States that is published in a language other than English; and

C) had a translation of the international application into the English language.

[61]*See* Joe Stanganelli, *Beyond CRISPR Cuts: Five Complements to Cas9*, BIO IT WORLD (Feb. 22, 2017), http://www.bio-itworld.com/2017/2/22/beyond-crispr-cuts-five-complements-to-cas9.aspx

letters smaller than conventional Cas9 and small enough to be put into a virus.[62] Other groups are looking to enzymes from microbes having different sequence requirements, including Cpf1 and C2c2.[63] Notably, Broad is pursuing patents directed to the Cpf1 enzyme-based technology. Cpf1 is a "CRISPR-associated two-component RNA-programmable DNA nuclease . . . , [which] mediates robust DNA interference with features distinct from Cas9."[64] C2c2 is "from the bacterium *Leptotrichia shahii* [and] provides interference against RNA phage."[65] Other groups are using target-AID complexes, which reduce toxicity associated with the nuclease-based CRISPR/Cas9 system.[66] Still other groups, research goals allowing, are avoiding the saga in its entirety by relying on pre-CRISPR-Cas9 methods, including zinc-finger nucleases (ZFNs) and transcription-activator like effector nuclease (TALENs).[67,68,69]

IV. CONCLUSION

CRISPR-Cas9 gene-editing techniques provide a revolutionary alternative to conventional gene-editing tools that may become a multibillion annual market.[70] Consequently, the ownership and licensing disputes are likely to continue for years to come. In view of expected continued litigation, an uncertain future for both the UC's and Broad's patents and applications remains. Research groups should take particular care in selecting a gene-editing tool to consider potential liability and licensing arrangements. Freedom-to-operate assessments will likely have increased importance in years to come for those active in this area.

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[62] *The Next New Thing*, GENOMEWEB (Aug. 09, 2016), https://www.genomeweb.com/scan/the-next-new-thing. Heidi Ledford, *Mini Enzyme Moves Gene Editing Closer to the Clinic*, NATURE (Apr. 1, 2015), http://www.nature.com/news/mini-enzyme-moves-gene-editing-closer-to-the-clinic-1.17234

[63] GENOMEWEB, *supra* note 62.

[64] Bernd Zetsche, Jonathan S. Gootenberg, Omar O. Abudayyeh, Ian M. Slaymaker, Kira S. Makarova, Patrick Essletzbichler, Sara E. Volz, Julia Joung, John van der Oost, Aviv Regev, Eugene V. Koonin, Feng Zhang, *Cpr1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, CELL (Sept. 25, 2015), available at http://www.cell.com/abstract/S0092-8674(15)01200-3

[65] Omar O. Abudayyeh, Jonathan S. Gootenbberg, Silvana Konermann, Julia Joung, Ian M. Slaymaker, David B.T. Cox, Sergey Shmakov, Kira S. Makarova, Ekaterina Semenova, Leonid Minakhin, Konstantin Severinov, Aviv Regev, Eric S. Lander, Eugene V. Koonin, Feng Zhang, *C2c2 Is a Single-Component Programmable RNA-Guided RNA-Targeting CRISPR Effector*, SCI. (Jun. 02, 2016), available at http://science.sciencemag.org/content/early/2016/06/01/science.aaf5573

[66] Keiji Nishida, Takayuki Arazoe, Nozomu Yachie, Satomi Banno, Mika Kakimoto, Mayura Tabata, Masao Mochizuki, Aya Miyabe, Michihiro Araki, Kiyotaka Y. Hara, Zenpei Shimatani, Akihiko Kondo, *Targeted Nucleotide Editing Using Hybrid Prokaryotic and Vertebrate Adaptive Immune Systems*, SCI. (Sept. 16, 2016), available at http://science.sciencemag.org/content/353/6305/aaf8729

[67] GENOMEWEB, *supra* note 62.

[68] NgAgo is not included herein, as a recognized alternative, because of its own troublesome beginnings. *See* David Cyranoski, *Replications, Ridicule and a Recluse: The Controversy over NgAgo Gene-Editing Intensifies*, NATURE (Aug. 8, 2016), http://www.nature.com/news/replications-ridicule-and-a-recluse-the-controversy-over-ngago-gene-editing-intensifies-1.20387

[69] It should be recognized that in certain instances improvements may themselves require licenses from the pioneering inventors, in this case UC and/or Broad.

[70] Begley, *supra* note 25.