

Next Steps After Broad Institute's Big Gene-Editing Patent Win

Law360, New York (February 16, 2017, 11:29 AM EST) -- The U.S. Patent and Trademark Office's Patent Trial and Appeal Board has been thrust into a dispute pitting University of California, Berkeley ("UC") and the University of Vienna against the Broad Institute of MIT and Harvard ("Broad Institute"). The technology at the center of the dispute is a gene-editing tool called CRISPR-Cas9, and the PTAB's decision could leave the winner holding a patent portfolio worth billions of dollars. In the first round of this dispute, the PTAB handed the Broad Institute a resounding victory by declaring that the Broad Institute is entitled to claims for the use of CRISPR-Cas9 in eukaryotic cells because that is patentably distinct from UC's earlier disclosure.

The CRISPR-Cas9 gene-editing system finds its roots in the observations that prokaryotes utilized CRISPR as a way to identify and destroy viruses. Jennifer Doudna of UC along with Emmanuelle Charpentier of the University of Vienna showed that CRISPR-Cas9 system could use short strands of guide RNA that recognize and direct the Cas9 to a specific target DNA sequence and the Cas9 protein could slice the target section of the DNA. This initiates the natural cellular repair process to knock out, repair, or insert a gene. In a patent application and a related scientific paper, Doudna, along with her colleagues Martin Jinek and Charpentier, disclosed a successful test of a prokaryotic CRISPR-Cas9 gene-editing tool in vitro.

Around the same time, Feng Zhang, a scientist at the Broad Institute, was working on creating and using various bacterial Cas9 in mammalian cells, i.e., eukaryotic cells. A few months after Doudna and Charpentier's publication, Zhang and his colleagues filed a patent application and published a paper showing the use of CRISPR-Cas9 with human and mouse cells. Because Zhang and his colleagues requested and paid for expedited review of their patent applications, the USPTO has issued several patents to the Broad Institute for the use of CRISPR-Cas9 in gene-editing in eukaryotic cells. Upon seeing the issuance of these patents, UC requested that the USPTO declare an interference between UC and the Broad Institute to determine which group of inventors is entitled to claims that encompass the use of CRISPR-Cas9 in eukaryotic cells.

Threshold Motions Requested and Those Addressed

In early December 2016, the PTAB held oral arguments on several motions that would eventually determine the outcome of the interference. The PTAB granted the Broad Institute permission to file



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several threshold motions.[1] The most interesting of these motions was the motion to assert that no interference-in-fact exists, i.e., the Broad Institute claims are sufficiently different than the UC's pending patent claims.[2] UC also requested the opportunity to submit several other threshold motions, including a motion that asserted that the Broad Institute's patents were obvious in light of the disclosure of the UC patent application and existing prior art. The PTAB denied UC's request, finding that the patentability of the Broad Institute patents is not a threshold issue of standing that affects whether the interference may proceed. Although the PTAB denied UC's request to submit a threshold motion concerning the patentability of the Broad Institute's claims in light of the UC patent application's disclosure, the PTAB decision appears to put this issue to rest.

The Broad Institute asserted that UC's claims differ from its own because UC's claims encompass contacting or hybridizing components of the CRISPR-Cas9 system with target DNA without requiring a specific environment. This encompasses cell-free and test tube experiments.[3] By comparison, the Broad Institute claims require that the use of CRISPR-Cas9 occur in eukaryotic cells.[4] Based upon this distinction, the Broad Institute asserted that the PTAB should find that an interference does not exist because a "person of ordinary skill would not have had any reasonable expectation that the CRISPR-Cas9 system, which is found naturally only in prokaryotic cells as an immune system, would successfully work for a different purpose, such as genome editing, in a different environment such as a eukaryotic cell." [5]

To support its position, the Broad Institute peppered the record before the PTAB with various statements from the UC inventors and others concerning the additional work required to move from in vitro data that shows CRISPR-Cas9 worked to the ability to edit DNA in a eukaryotic cell. The Broad Institute noted that Doudna had described her work as "a big success, but there was a problem. [The UC inventors] weren't sure if CRISPR/Cas9 would work in eukaryotes — plant and animal cells." [6] When discussing the work of the Broad Institute scientists, Doudna explained that "the techniques for making [] modifications in animals and humans [had] been a huge bottleneck" and the publications showing success in a eukaryotic cell would remove that bottleneck.[7] Such statements, in the Broad Institute's view, show that one of ordinary skill in the art would not have a reasonable expectation that the in vitro data disclosed by the UC team would be predictive of CRISPR-Cas9 functioning in a eukaryotic cell.[8]

UC sought to counter these arguments by pointing to contemporaneously published statements about the UC inventors' work that describes that work as showing that highly specific customizable RNA-directed DNA nuclease could be useful in editing whole genomes, including introducing breaks at unique sites in any eukaryotic genome.[9] UC also argued that its inventors jumpstarted the work of other scientists who were able to adapt the concept to mammalian cells quite easily.[10] In its own threshold motions, UC sought to explain that the disclosure of its patent applications, including its earliest provisional application, enables the use of CRISPR-Cas9 in eukaryotic cells. UC noted that its first provisional application included an in vitro experiment that shows the necessary components of the CRISPR-Cas9 system along with an explanation that the method may be adapted for use in eukaryotic cells.[11] Based upon the PTAB's decision discussed in detail below, one may question whether UC can succeed on this point going forward.

The PTAB's Decision and UC's Options

The PTAB found that the Broad Institute showed that its claims that require use of CRISPR-Cas9 in a eukaryotic cell are "patentably distinct" from UC's claims that are silent as to the environment in which a CRISPR-Cas9 system is employed.[12] The PTAB specifically held that the evidence shows that the use of CRISPR-Cas9 systems in "eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro, because one of ordinary skill

in the art would not have a reasonably expected CRISPR-Cas9 system to successful in a eukaryotic environment.”[13] To support its conclusion, the PTAB paid particular attention to statements made contemporaneously to the UC inventors’ disclosure of a prokaryotic CRISPR-Cas9 system in a non-cellular in vitro experimental environment.[14] These statements included numerous statements by the U.K. inventors Jinek and Doudna that appeared to question whether the in vitro testing would predict success in eukaryotes.[15] The PTAB found UC’s attempts to refute these statements unavailing.[16]

The PTAB also rejected UC’s argument that the rapid success by other labs in adapting CRISPR-Cas9 system to eukaryotes shows that a person of ordinary skill in the art would have had a reasonable expectation of success. The PTAB noted that a scientist’s “belief” in the success of her own experiment does not equate to a reasonable expectation of success under U.S. patent law.[17] In addition, the PTAB rejected UC’s assertion that because other gene-editing techniques had shown success in both prokaryotes and eukaryotes, a person would expect the same for a CRISPR-Cas9 system.[18] In the end the PTAB concluded that the Broad Institute’s claims were not drawn to the same invention as the UC claims and that it is well-settled law that a narrow species claim can be nonobvious and patent-eligible in view of a claim to a genus.[19]

In the past, UC would have been able to bring an action in a district court under 35 USC § 146 to challenge the final judgment in an interference. This would have afforded UC the opportunity to supplement the evidentiary record at a district court with the submission of further testimony or other evidence. But after enactment of the America Invents Act, the Federal Circuit has held that the only path for a losing party to an interference to challenge a final judgment for post-AIA interference is through an appeal to the Federal Circuit.[20] Thus, UC will be required to proceed on the record established at the PTAB — which the PTAB found insufficient to support UC’s arguments.

Although the final judgment by the PTAB “neither cancels nor finally refuses [UC’s] claim,” one may question whether UC will be able to assert that any claim it receives from the USPTO will be able to cover use of a CRISPR-Cas9 system in a eukaryotic cell in light of the PTAB’s decision. UC may be able to obtain claims that cover the use of CRISPR-Cas9 for in vitro testing. These claims may have value because UC may be able to assert that use of in vitro testing of a CRISPR-Cas9 system in the development of a drug may entitle UC to royalties based upon a reach-through theory. But those claims will not be as valuable as claims that cover the use of a CRISPR-Cas9 system in eukaryotes.

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[1] Interference No. 106,048, Order Authorizing Motion and Setting Times [Paper 33]

[2] The PTAB had granted the Broad Institute permission to file a motion to assert that the UC application fails to provide a written description for the interference count. Order Authorizing Motion and Setting Times [Paper 33]. Interestingly, The Broad Institute decided not to file the motion. See Broad Notice Re Substantive Motion 4 [Paper 565].

[3] Broad Motion 2 [Paper 77] at 2

[4] Id. at 1.

[5] Id. at 2.

[6] Id. at 4 citing Catalyst Magazine, The CRISPR Revolution July 9, 2014 [Ex. 2207]

[7] Id. at 9 citing Berkeley News, Cheap and easy technique to snip DNA could revolutionize gene therapy [Ex. 2259]

[8] Id. at 7.

[9] UC Opposition to Broad Motion 2 [paper 652] at 1 and 9 citing Brouns, A Swiss Army Knife of Immunity [Exhibit 1471] at 809.

[10] Id. at 6 and 10.

[11] UC Substantive Motion 4 [Paper 57] at 5-6.

[12] Decision on Motions [Paper 893] at 2.

[13] Decision on Motions [Paper 893] at 2.

[14] Decision on Motions [Paper 893] at 13-14.

[15] Decision on Motions [Paper 893] at 14-15.

[16] Decision on Motions [Paper 893] at 15-16.

[17] Decision on Motions [Paper 893] at 23-24.

[18] Decision on Motions [Paper 893] at 41.

[19] Decision on Motions [Paper 893] at 49.

[20] Biogen MA, Inc. v. Japanese Foundation For Cancer Research, 785 F.3d 648, 654 (Fed. Cir. 2015).