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Federal Circuit Affirms PTAB in Appeal of CRISPR Interference

By Kevin E. Noonan / September 10, 2018

Barring the unlikely event that the Federal Circuit rehears *en banc* today's decision in *Regents of the University of California v. Broad Institute, Inc.* (or, even more unlikely, that the Supreme Court grants *certiorari*), the interference between the Broad Institute and the University of California/Berkeley is now concluded. The Court affirmed the Patent Trial and Appeal Board's decision (*see* "PTAB Decides CRISPR Interference -- No interference-in-fact"; "PTAB Decides CRISPR Interference in Favor of Broad Institute -- Their Reasoning") that there is no interference-in-fact between the Broad's twelve patents (the Federal Circuit citing U.S. Patent No. 8,697,359 as being representative) and one application-in-interference and the University of California/Berkeley's pending application (Application No. 13/842,859).

To recap, the Board found that there was no interference-in-fact based on these requirements:

> *In this proceeding, to prevail on its argument that there is no interference, Broad must 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 claims, 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.*
>
> *Broad will prevail and a determination of no interference-in-fact will be made if a preponderance of the evidence indicates one of these conditions is not met.*

In considering the evidence before it, the PTAB gave great weight to contemporaneous, cautious statements in the art in view of Professor Doudna's disclosure of *in vitro* CRISPR activity regarding whether the system would work in

eukaryotic cells. Specifically, these statements convinced the Board that while the results "suggested the 'exciting possibility'" that CRISPR-Cas9 could be operative in eukaryotic cells, "it was not known whether such a bacterial system would function in eukaryotic cells." And "[i]n another report, Doudna was quoted as stating that she had experienced 'many frustrations' getting CRISPR to work in human cells and that she knew that if she succeeded, CRISPR would be 'a profound discovery.'" UC's assertion of other statements by their inventors that could be interpreted more positively did not convince the Board that there was a reasonable expectation of success in the art for getting the CRISPR-Cas9 system to work in eukaryotic cells, the Board stating that:

> *Although the statements express an eagerness to learn the results of experiments in eukaryotic cells and the importance of such results, none of them express an expectation that such results would be successful.*

The Board swept aside Berkeley's arguments that this reasoning was flawed because the standard is not the inventor's expectations but those of the worker of ordinary skill by stating that "if the inventors themselves were uncertain, it seems that ordinarily skilled artisans would have been even more uncertain." The Board also quoted Berkeley's expert as having said (contemporaneously with Professor Doudna's report of *in vitro* CRISPR activity):

> *There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA-RNA hybrid can be stabilized in that context.*

The Board concluded that "[w]e fail to see how 'no guarantee' indicates an expectation of success."

Nor was the Board convinced based on the history of the development of CRISPR technology, which showed that many laboratories independent of the Doudna group quickly applied the new technology to manipulate eukaryotic cell genomic DNA:

> *Regardless of how many groups achieved success in eukaryotic cells, we are not persuaded that such success indicates there was an expectation of success before the results from these experiments were known. The unpublished results*

> *of research groups are not necessarily an indication of whether ordinarily skilled artisans would have expected the results achieved. Instead of viewing such work as evidence of an expectation of success, we consider the number of groups who attempted to use CRISPR-Cas9 in eukaryotic cells to be evidence of the motivation to do so, an issue that is not in dispute. We agree with Broad's argument that a large reward might motivate persons to try an experiment even if the likelihood of success is very low.*

On balance, the Board found that this evidence further supported their decision that there was insufficient evidence of a reasonable expectation of success to support Berkeley's allegation that their earlier work and publications would have rendered Broad's invention obvious. This evidence was that "differences in 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, would contribute to this unpredictability [regarding whether the CRISPR-Cas9 system would be operative in eukaryotic cells]." In response to Berkeley's allegations that these considerations turned out not to be an impediment to CRISPR's activity in eukaryotic cells, the Board said "[t]he relevant question before us is whether those of skill in the art would have *expected* there to be problems *before* the experiments were done," not whether it turned out that the experiments were successful once they were tried.

Finally, the Board rejected Berkeley's citation of other prokaryotic genetic modification systems found to work in eukaryotes, generally on the grounds that there was no "commonality" in these methods that would have refuted Broad's evidence that the skilled worker would not have had any reasonable expectation of success.

The University appealed, and today the Federal Circuit affirmed, in an opinion by Judge Moore joined by Chief Judge Prost and Judge Schall. After a recitation of a description of CRISPR (*see "*CRISPR Interference Declared" for a description of this technology) and the substantive and procedural posture before the PTAB, the Court addressed the legal arguments proffered by California in support of its argument against the PTAB's decision of no interference-in-fact. As stated in the opinion,

> *The case turns in its entirety on the substantial evidence standard. The Board found a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the CRISPR-Cas9 system in eukaryotic cells. . . . Given the mixture of evidence in the record, we hold that substantial evidence supports the Board's finding that there was not a reasonable expectation of success, and we affirm.*

The opinion then addressed California's two arguments contrary to the PTAB's decision: "that the Board: (1) improperly adopted a rigid test for obviousness that required the prior art contain specific instructions, and (2) erred in dismissing evidence of simultaneous invention as irrelevant." The Court based its opinion on the evidence presented by one of the Broad's experts with regard to the difference between prokaryotic and eukaryotic cells (which it recited extensively) "that rendered the application of the CRISPR-Cas9 system in eukaryotic cells unpredictable." The issues these differences raised relevant to whether the skilled worker would have had a reasonable expectation of success in applying CRISPR to eukaryotic cells were also, according to the opinion, recognized by California's expert, including *inter alia* statements like "[t]here is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA-RNA hybrid can be stabilized in that context" and "whether the CRISPR-Cas9 system will work in eukaryotes 'remains to be seen' and '[o]nly attempts to apply the system in eukaryotes will address these concerns.'" This evidence was supported, in the panels' opinion, from California's own inventors (including Jennifer Doudna) "acknowledging doubts and frustrations about engineering CRISPR-Cas9 systems to function in eukaryotic cells and noting the significance of Broad's success." In addition, the Court noted evidence that other prokaryotic systems adapted to eukaryotic cells ("riboswitches, ribozyme systems, and group II introns") "either [had] limited efficacy or the technology required a specific strategy to adapt it for use in eukaryotic cells." This evidence amounted to substantial evidence that the skilled worker would not have had a reasonable expectation of success in achieving CRISPR in eukaryotic cells.

(The opinion recognizes that California had presented evidence in support of its position, but noted "[w]e are, however, an appellate body. We do not reweigh the evidence. It is not our role to ask whether substantial evidence supports fact-findings not made by the Board, but instead whether such evidence supports the findings that were in fact made.")

The opinion also rejected California's arguments that the Board had used a rigid test that required specific instructions in the prior art and ignored the "inferences and creative steps" recognized as being relevant to an obviousness determination under the Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 420 (2007). And with regard to "simultaneous invention" evidence (which California argues the Board ignored), the opinion states that while "[s]imultaneous invention may serve as evidence of obviousness when considered in light of all of the circumstances," citing *Lindemann Maschinenfabrik GmbH v. Am. Hoist & Derrick Co*., 730 F.2d 1452, 1460 (Fed. Cir. 1984), the existence of interferences means that simultaneous invention cannot, by itself, be evidence of obviousness. The Federal Circuit rejected California's argument that evidence that six independent research groups applied CRISPR to eukaryotic cells "within a short period of time" after publication of Its discovery on prokaryotes rendered the Broad's claims obvious, and approved the legal rationale used by the PTAB:

> *The Board explained that "[e]ach case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." . . . (quoting Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008)). We do not see any error in this analysis.*

The consequence of this decision (assuming it is the final word) is that the *status quo* will remain: the Broad will maintain its extensive CRISPR patent portfolio and the University's patent application (reciting claims broader than the Broad's and encompassing CRISPR without regard to the cells in which it is practiced) should grant as a patent in due course. Under these circumstances, a third party wishing to

practice the technology in eukaryotic cells (encompassing everything from yeast to man) would need a license from *both* the University and the Broad (absent the parties coming to an agreement on how their overlapping technologies will be licensed). This circumstance cannot fail to retard commercial adoption of the techniques, providing further impetus for some sort of co-licensing agreement between the parties to be forged.

Regents of the University of California v. Broad Institute, Inc. (Fed. Cir. 2018)
Panel: Chief Judge Prost and Circuit Judges Schall and Moore
Opinion by Circuit Judge Moore