



Archetype IPSM

Federal Circuit Friday

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In *Regents of the University of California et al. v. Broad Institute, et al.* (September 10), the Federal Circuit affirmed a Patent Trial & Appeal Board ("PTAB") decision that there was no "interference-in-fact" between UC and Broad patents and applications relating to the CRISPR-Cas9 gene editing system. The absence of an interference-in-fact means that the UC and Broad inventions, as claimed in their respective patents and applications, were sufficiently different that there was no need to determine who invented first – *i.e.*, the UC and Broad inventions were "patentably distinct."

UC's invention was the use of the prokaryote-derived CRISPR-Cas9 system to cleave a DNA strand at a particular sequence, while Broad's invention was the use of the CRISPR-Cas9 system in eukaryotic cells. The basic issue was whether Broad's use of the CRISPR-Cas9 system in eukaryotes was obvious over the prokaryotic CRISPR-Cas9 system invented by UC, and the PTAB found (and the Federal Circuit affirmed) that use in eukaryotes was not obvious because there was no reasonable expectation that the CRISPR-Cas9 system would work in eukaryotes.

Setting aside the legal standards and issues regarding interferences (which are of lesser relevance in the post-AIA, first-to-file world), there are several interesting issues in this case that have broader applicability.

1. Substantial Evidence and the Price of Losing on the Facts at the Trial Court or PTAB.

The Federal Circuit stated that this "case turns in its entirety on the substantial evidence standard."¹ That technically overstates the situation because there were legal issues on appeal as well, but it accurately depicts the long shadow the core fact issues cast over the rest of the case.

Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion."² In general, the substantial evidence standard applies to facts found by a jury or an agency and is more deferential to the determination made below than are the *de novo*³ and "clearly erroneous"⁴ standards but less deferential than the "abuse of discretion"⁵ standard. If a factual determination made in a trial court or the PTAB is supported by such relevant evidence as a reasonable mind might accept as adequate, that determination will not be overturned on appeal. The essential point is that when you lose on

¹ Slip. op. at 7.

² See, e.g., *Consolidated Edison Co. of New York v. N.L.R.B.*, 305 U.S. 197, 229 (1938). Factual determinations by the PTO are subject to the substantial evidence standard per the Administrative Procedure Act (APA), 5 U.S.C. § 706, *Dickinson v. Zurko*, 527 U.S. 150 (1999), and *On-Line Careline, Inc. v. Am. Online, Inc.*, 229 F.3d 1080, 1085 (Fed. Cir. 2000).

³ *De novo* review involves little or no deference to the trial court or PTAB (the appeals court reviews the determination anew, as if no determination had been made below), and typically is applied to questions of law such as statutory interpretation, standing, claim construction, indefiniteness, and the ultimate conclusion of enablement (as opposed to the underlying facts).

⁴ The "clearly erroneous" standard is more deferential to the lower tribunal, acknowledging that there may some evidence to support the determination but calling for reversal if the appeals court is nevertheless left with definite and firm conviction that mistake has been made. The clearly erroneous standard typically is applied to all fact determinations other than those made by a jury or the PTO.

⁵ Reversal under the "abuse of discretion" standard occurs when the appeals court finds clear error of judgment in weighing the relevant factors or an exercise of discretion based on error of law or clearly erroneous fact finding. Abuse of discretion applies to trial supervision issues like evidentiary rulings and denials of new trial motions.

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the facts at the trial court or PTAB, you will have a significant uphill battle to change those fact findings on appeal.

In *UC v. Broad*, Broad successfully convinced the PTAB that 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. Broad accomplished this using:

- Testimony of its own expert witness regarding "differences between prokaryotic systems and eukaryotic systems that rendered the application of the Cas9 system in eukaryotic cells unpredictable," the presence of ribonuclease activity in eukaryotic cells that could degrade components of the CRISPR-Cas9 system, and the potential for "excessive number of double stranded DNA breaks given factors such as the greater size of the human genome compared to typical bacterial genome and the frequency with which similar DNA sequences appear in the human genome";
- An article **written by UC's expert witness** regarding "the possibility that CRISPR-Cas9 might be degraded by nucleases in eukaryotic cells," explaining that there was "no guarantee that Cas9 will work effectively on a [eukaryotic] chromatin target or that the required DNA-RNA hybrid can be stabilized in that context," and concluding that "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'"; and
- Statements **by UC's inventors** that there was a "huge bottleneck" in making genetic modifications in eukaryotes, that "[w]e weren't sure if CRISPR/Cas9 would work in eukaryotes," and that there were "many frustrations" in getting CRISPR-Cas9 to work in human cells and that success in doing so would be "a profound discovery."
- Other evidence of difficulties and failures in translating other prokaryote-derived systems to eukaryotic cells and evidence that Broad's application of CRISPR-Cas9 to eukaryotes was recognized as significant by persons skilled in the art.

UC argued that substantial evidence supported their side of the story, that a person of ordinary skill would have had a reasonable expectation of success in implementing the CRISPR-Cas9 system in eukaryotes. But the Federal Circuit rejected that argument, highlighting the function of an appeals court and the pitfalls of losing on the facts at the trial court or PTAB:

We 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. Here, we conclude that it does.⁶

2. Reasonable Likelihood of Success in Obviousness Determinations.

UC also argued that the PTAB made a legal error in the standard it applied for determining reasonable likelihood of success. Unlike fact determinations, legal standards applied by trial court and the PTAB are subject to *de novo* review (*i.e.*, no deference to the trial court or PTAB).

Although better positioned for success on this argument in terms of the standard of appellate review, the Federal Circuit found no error in the standard applied by the PTAB. UC argued that the PTAB required that

⁶ Slip Op. at 12.

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there be "specific instructions" in the prior art to establish a reasonable likelihood of success, a standard that was too rigid and that set the bar too high. The Federal Circuit explained that the PTAB "did *not* hold specific instructions were needed"⁷ and instead had merely stated the correct propositions that:

- "specific instructions that are relevant to the claimed subject matter or success in similar methods or products" can lead to or compel "findings of a reasonable expectation of success"; and
- "the combination of only generalized instructions *and* evidence of failures with similar subject matter indicated there was not a reasonable likelihood of success."⁸

Thus, the PTAB correctly applied the law that specific instructions can help establish a reasonable likelihood of success, but the absence of specific instructions does not itself preclude a reasonable likelihood of success.

3. Simultaneous Invention as Evidence of Obviousness.

UC argued that the PTAB ignored evidence of simultaneous invention that indicated a reasonable expectation of success. UC pointed to six research groups in addition to Broad that independently applied CRISPR-Cas9 in eukaryotic cells within months of UC disclosing the CRISPR-Cas9 system in a research publication, and argued that those activities demonstrated that application of the CRISPR-Cas9 system in eukaryotes "was the product only of ordinary mechanical skill or engineering skill," rather than genuine invention.

The Federal Circuit explained that "simultaneous invention may serve as evidence of obviousness when considered in light of all of the circumstances" and made three useful points about the utility of evidence of simultaneous invention:

- "First, it is evidence of the level of skill in the art";
- "Second, it constitutes objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem"; and
- Third, while it can be strong evidence that there was a motivation to combine the prior art in a manner to create the claimed invention, it does "not necessarily indicate an expectation of success prior to the completion of the experiments."⁹

The Federal Circuit found that rather than ignoring the evidence of simultaneous invention, the PTAB treated UC's evidence of simultaneous invention as relevant to the obviousness determination, but properly circumscribed its meaning and evidentiary value in light of "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" and correctly decided that the evidence did not compel the conclusion that there was a reasonable expectation of success in applying CRISPR-Cas9 in eukaryotes.

⁷ *Id.* at 13 (emphasis in original).

⁸ *Id.* at 13 (emphasis in original).

⁹ *Id.* at 14-15 (internal quotations omitted).