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Regents of Univ. of California v. Broad Inst., Inc., 903 F.3d 1286 (Fed. Cir. 2018)

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I. INTRODUCTION

Appellants consisting of The University of California, the University of Vienna, and Emmanuelle Charpentier, (collectively "UC"), appealed a decision of the Patent Trial and Appeal Board who unanimously held there was no interference-in-fact between UC's application for CRISPR patents, and the CRISPR patents originally awarded to appellees Broad Institute, Inc., Massachusetts Institute of Technology, and the President and Fellows of Harvard College, (collectively "Broad").[1] The patents disputed involved CRISPR-Cas9 technology that enables swift cutting of DNA molecules.[2] The CRISPR-Cas9 system has two molecules that implement a mutation into the DNA, including an enzyme named Cas9 that cuts twos stands of DNA at a particular location within the genome, allowing DNA bits to be added or removed.[3] The other molecule is a piece of RNA known as guide RNA (gRNA), which helps guide the Cas9 enzyme in cutting the right point within the genome.[4] The patents that Broad was awarded were confined to the use of eukaryotic cells, which is vital in that CRISPR-Cas9 systems have not been found to naturally exist in eukaryotes[5], such as plant

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1 *Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286, 1289 (Fed. Cir. 2018).

2 *Id.*

3 *What is CRISPR-Cas9?*, YOUR GENOME (Dec. 19, 2016), https://www.yourgenome.org/facts/what-is-crispr-cas9.

4 *Id.*

5 *Eukaryotic Cell*, BIOLOGY DICTIONARY, https://biologydictionary.net/eukaryotic-cell/ (last visited Oct. 27, 2019). Eukaryotic cells have a nucleus and organelles, and are enclosed by a plasma membrane. Organisms that consist of eukaryotic cells include protozoa, fungi,

and animal cells.[6] In contrast, UC's original publication involved CRISPR-Cas9 systems within the prokaryotic cell setting (single cell organisms lacking distinct nuclei).[7] As genetic editing in the form of CRISPR-Cas9 technology enters the realm of eukaryotic alteration, the instant case demonstrates how patent jurisprudence can serve as an effective catalyst for the progression toward idealistic human health.

II. BACKGROUND

A. Factual Background

In August 2012, researchers from UC published an article in reference to usage of CRISPR-Cas9 and its ability to be used in vitro in a non-cellular experimental environment.[8] The UC publication did not report any results of experimentation utilizing CRISPR-Cas9 within a eukaryotic cell.[9] In February 2013, researchers from the Broad Institute published an article on their triumphant use of CRISPR-Cas9 in a human cell line.[10] UC and Broad then both pursued patent protection for their scientific findings.[11]

B. Procedural Posture

The Patent and Trial Appeal Board instituted an interference (an administrative proceeding to determine priority of invention and patentability of invention); however, Broad moved to terminate such interference, as they alleged that their successful findings of CRISPR-Cas9 usage in eukaryotic cells was patentably distinct from UC's patent claim of CRISPR-Cas9 usage in prokaryotic cells.[12] Broad's reasoning for such termination, was based on a

plants and animals. Eukaryotic cells are larger and more complex than prokaryotic cells, which are found in Archaea and Bacteria, the other two domains of life.

6 *Regents of Univ. of California*, 903 F.3d at 1289.

7 *Regents of Univ. of California*, 903 F.3d at 1286.

8 *Regents of Univ. of California*, 903 F.3d at 1289 (citing J.A. at 4799–804).

9 *Id.*

10 *Regents of Univ. of California*, 903 F.3d at 1289 (citing J.A. at 4682–86).

11 *Id.*

12 *Id.* at 1290.

person of ordinary skill in the art not having a reasonable expectation that the CRISPR-Cas9 system would work successfully within the confines of a eukaryotic cell.[13] In taking such reasoning into account, the Board held no such interference-in-fact, as the realm of eukaryotic and prokaryotic systems served as non-similar entities to one another.[14] Therefore, 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.[15]

As such, the Board determined that UC's claims regarding CRISPR-Cas9 usage did not render obvious Broad's claims to its successful use in eukaryotic cells.[16] Because the respective patents were filed in the era of the Pre-America Invents Act (Pre-AIA), the US Court of Appeals for the Federal Circuit had jurisdiction to resolve the interference issue between the respective parties under 28 U.S.C. § 1295 (a)(4)(a).[17]

Ultimately, the Federal Circuit Judge favored Broad in determining there was a lack of reasonable expectation of success regarding CRISPR-Cas9's application into the realm of eukaryotic cells.[18] Thus, finding no interference-in fact, the Court rendered Broad's usage of CRISPR-Cas9 in eukaryotic cells patentably distinct from UC's usage of CRISPR-Cas9 in prokaryotic cells.[19]

III. LEGAL ANALYSIS

Before analyzing the issues in the case, the Court mentioned that the Board utilized a two-way test to determine whether a claim is patentably distinct.[20] The Board specifically inquired whether "the subject matter of a claim of one party would, if prior art, ha[d] anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa."[21] The Court mentioned that if the threshold of the two-way test is not adhered to, then no such

13 *Regents of Univ. of California*, 903 F.3d at 1290.
14 *Id.*
15 *Id.*
16 *Regents of Univ. of California*, 903 F.3d at 1290 (citing J.A. at 49).
17 *Id.*
18 *Id.* at 1296.
19 *Id. at* 1286.
20 *Id.* at 1291.
21 *Regents of Univ. of California*, 903 F.3d at 1291.

interference-in-fact is present.[22] When the interference-in-fact centers on an obviousness inquiry, the standard of review involves a question of law.[23]

The Court's analysis included precedence from *Graham v. John Deere Co.*, where the Supreme Court laid factors to frame a proper analysis of obviousness including: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness.[24] As such, the obviousness determination mandates a finding that a person of ordinary skill within the art, would have been inspired to combine the teachings in prior art, along with having a reasonable expectation of success in combining such teachings.[25] An analysis of a reasonable expectation of success is a question of fact.[26] Thus, the Court analyzed the issue of obviousness de novo, and the factual findings, including the reasonable expectation of success, under a substantial evidence standard.[27]

Thus, with the standards of review in-place, the Court is to analyze the issues of whether the Board: (1) incorrectly included a rigid test of obviousness that mandated the prior art to include specific instructions, and (2) whether the Board erred in dismissing evidence of simultaneous invention as irrelevant.[28]

[22] *Id.*

[23] *Regents of Univ. of California*, 903 F.3d at 1291 (citing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1326 (Fed. Cir. 2016)).

[24] *Regents of Univ. of California*., 903 F.3d at 1291 (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S. Ct. 684, 15 L.Ed.2d 545 (1966); *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1358 (Fed. Cir. 2017)).

[25] *Regents of Univ. of California*, 903 F.3d at 1291 (citing *In re Stepan Co.*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017)).

[26] *Regents of Univ. of California*, 903 F.3d at 1291 (citing *In re Stepan Co.*, 868 F.3d at 1346).

[27] *Regents of Univ. of California*, 903 F.3d at 1291 (citing *In re Mouttet*, 686 F.3d 1322, 1330–31 (Fed. Cir. 2012)).

[28] *Regents of Univ. of California*, 903 F.3d at 1291.

A. Reasonable Expectation of Success

The Court referred to Broad's expert testimonial from Dr. Paul Simons.[29] Dr. Simons mentioned discrepancies between prokaryotic and eukaryotic cellular conditions that would make the functionality of CRISPR-Cas9 in eukaryotes unpredictable.[30] The unpredictability of such functionality comprised of intracellular temperature, the concentration of various ions, pH, and the presence of other molecules that may be present in one type of cell, but not the other.[31] Dr. Simons testimonial included additional matters that would render a skilled artisan to not have a reasonable expectation of success regarding CRISPR-Cas9's application in a eukaryotic cell.[32] The structural differences between the two cell-lines included, eukaryotic cells having ribonucleases that are absent in prokaryotic cells.[33] Notably, ribonucleases specialize in cutting up RNA molecules.[34] RNA molecules haves an abundance of functions, from "translating genetic information to regulating the activity of genes during development, cellular differentiation, and changing environments."[35]

To further the differences between the two-cell lines, Dr. Simons also mentioned that eukaryotic cells degrade double-stranded RNA, and prokaryotic cells do not.[36] What was concerning to Dr. Simon, was that the human genome is bigger than an average bacterial genome, like a eukaryote.[37] In addition, the frequency of similar DNA sequences that are present in the human genome is different than what is present within a bacterial genome.[38] Overall, Dr. Simons determined these differences formulated a conclusion that a skilled artisan would not have a reasonable expectation of

29 *Id.* at 1292.
30 *Regents of Univ. of California*, 903 F.3d at 1292 (citing J.A. 5527 at ¶ 6.13).
31 *Id.*
32 *Id.*
33 *Id.*
34 *Id.*
35 *Role of RNA in Biology*, RNA THERAPEUTICS INSTITUTE, https://www.umassmed.edu/rti/biology/role-of-rna-in-biology/ (last visited Oct. 27, 2019).
36 *Regents of Univ. of California*, 903 F.3d at 1292.
37 *Id.*
38 *Id.*

success in implementing CRISPR-Cas9 within the confines of a eukaryotic cell.[39] The Court mentioned that UC's expert witness Dr. Dana Carroll was aware of the same issues that persist when attempting to implement the CRISPR-Cas9 system within the eukaryotic biological regime.[40] Because of the uncertain nature in implementation, the Court stated such substantial evidence represented the issues that could arise in CRISPR-Cas9's application within a eukaryotic cell.[41]

The Court referred to UC inventors' acknowledgment of doubts within CRISPR-Cas9's successful implementation in eukaryotic cells.[42] There was evidence that UC acknowledged the significance of Broad's success in implementing CRISPR-Cas9 in eukaryotic cells.[43] The Court also noted that the Board considered evidence in reference to other gene editing systems, which were not helpful in analyzing whether there was a reasonable expectation of success of applying CRISPR-Cas9 in eukaryotic cells.[44] Thus, the Court supported the Board's finding of the unpredictable nature of CRISPR-Cas9's application within eukaryotic cells and thus, a lack of reasonable expectation of success.[45]

B. Specific Instructions

In determining whether the Board erred in adopting a test mandating specific instructions in the prior art to establish obviousness, the court found no such error.[46] The Court focused on specific instructions and its correlation to a reasonable expectation of success.[47] The Board stated that it "look[ed] to whether or not there were instructions in the prior art that would be specifically relevant to CRISPR-Cas9," along with "whether there [were] examples in the prior art of the success or failure of similar

[39] *Id.*
[40] *Id.*
[41] *Regents of Univ. of California*, 903 F.3d at 1293.
[42] *Id.*
[43] *Id.*
[44] *Id.*
[45] *Regents of Univ. of California*, 903 F.3d at 1294.
[46] *Id.*
[47] *Id.* at 1295.

systems."[48] The Court discussed the Board's acknowledgement that "[s]pecific instructions that are relevant to the claimed subject matter or success in similar methods or products have directed findings of a reasonable expectation of success."[49] The Court concurred with the Board's recognition that the combination of only generalized instructions along with evidence of failures with similar subject matter was indicative of a lack of reasonable expectation of success.[50] The Court mentioned the Board's finding that there were no specific instructions in the art regarding CRISPR-Cas9, that would enable one of ordinary skill in the art a reasonable expectation of success.[51] The Court agreed with the Board's finding that "the failure demonstrated with other systems would have indicated the lack of a reasonable expectation of success."[52] Thus, the Court saw no error in the Board's analysis of the lack of specific instructions, to go along with prior failures of adopting prokaryotic systems to eukaryotic cells based on general instructions.[53] Indicating, that there was indeed a lack of reasonable expectation of success.[54]

C. Relevance of Simultaneous Invention Evidence

The Court referred to the Board's expressive recognition that simultaneous inventions are evidence of obviousness when "considered in light of all the circumstances."[55] The Court recognized that simultaneous inventions can impact an obviousness analysis in a few ways.[56] First, simultaneous inventions serve as evidence of the level of skill within the art.[57] Second, simultaneous

[48] *Regents of Univ. of California*, 903 F.3d at 1295 (citing J.A. 28–29).
[49] *Id.*
[50] *Id.*
[51] *Id.*
[52] *Id.*
[53] *Regents of Univ. of California*, 903 F.3d at 1295.
[54] *Id.*
[55] *Regents of Univ. of California*, 903 F.3d at 1295 (citing *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1460 (Fed. Cir. 1984)).
[56] *Regents of Univ. of California*, 903 F.3d at 1295 (citing *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998)).
[57] *Regents of Univ. of California*, 903 F.3d at 1295.

inventions are objective evidence that persons of ordinary skill in the art understand the issue, along with a solution to that issue.[58] UC's evidence of simultaneous invention, where six independent research groups succeeded in implementing CRISPR-Cas9 in eukaryotic cells within a short period of time after UC's article publication, demonstrated compelling evidence that there was a motivation to combine the prior art in this manner.[59] However, this was not necessarily indicative of an expectation of success prior to the completion of the experiments.[60] The Court ultimately agreed with the Board, in that simultaneous invention did not establish a reasonable expectation of success, due to the context of the art at the time.[61] The context of the art included "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."[62] Thus, the Court supported the Board's finding of evidence of simultaneous invention; regarding (1) the state of the art, (2) the statements of the inventors, (3) failures involving similar technologies, and (4) the remainder of the record evidence as relevant to an obviousness determination, but not indicative of a reasonable expectation of success.[63]

D. Conclusion

Thus, with the amalgamation of factors brought forth, the Court affirmed the Board's judgement of no interference-in-fact.[64] The Court found that the Board performed an exhaustive analysis consisting of: (1) a variety of statements by experts for both parties and the inventors themselves, to go along with previous triumphs and disappointments in the field; (2), evidence of simultaneous invention; and (3), the degree to which the art provided instructions for applying the CRISPR-Cas9 technology in eukaryotic

58 *Id.*
59 *Regents of Univ. of California*, 903 F.3d at 1296.
60 *Id.*
61 *Regents of Univ. of California*, 903 F.3d at 1296 (citing J.A. 23–25).
62 *Id.*
63 *Id.*
64 *Id.*

cells.[65] The substantial evidence was indicative that there was not a reasonable expectation of success, thus, the Board did not err in its finding that there was no interference-in-fact.[66]

IV. CRISPR INTO THE FUTURE

Regents serves as an emblem of hope as we embark on a new decade. The Court's holding is symbolic of just how patent jurisprudence can catalyze innovation, while invoking limitless potential. *Regents* is a blueprint that scientists can favorably adhere to as they analytically frame their next genetic editing breakthroughs. Since the Court held Broad's patent to be distinct,[67] Broad's revolutionary finding of a particularized genetic editing technique within eukaryotic cells, combined with the Court's respect for such a finding, is indicative of the Circuit's admiration of risk taking amid scientific enlightenment. A third party who wishes to apply CRISPR-Cas9 in eukaryotic cells will need a license from Broad to utilize the ground-breaking technology in human cells and eukaryotic cells alike, however, CRISPR-Cas9 is just one systematic technology. Importantly, other scientists and third parties are now free to explore other genetic editing techniques within the eukaryotic regime that could spring human medical advancement further, as there is now a foundation that such techniques in eukaryotic cells will be recognized in the legal world.

As a result of *Regents*, there is now an incentive to increase genetic editing technique funds for research and development in the eukaryotic realm, which could begin an age of expansive medical advancement that borders the line of science fiction. As technology inevitably improves in the coming-years, our nation could be a foundational pillar of genetic advances that can cure and alleviate the most persistent diseases. Medical conditions that are inherently genetic, including cancer and hepatitis B, could be at the mercy of not only CRISPR-Cas9, but future genetic editing techniques yet to be discovered. Had *Regents* chosen not to recognize genetic techniques as patentable within eukaryotic cells, there could have been dire ramifications in human health development. For one,

65 *Id.*
66 *Id.*
67 *Regents of Univ. of California*, 903 F.3d at 1296-97.

scientists' motivation to battle the nuances that relay in the complex genetic make-up of humans, would be considerably stifled.[68] There would be no inclination to delve into research to combat human genetic deficiencies, as the Federal Circuit wouldn't recognize such techniques as patentably distinct.[69] With the Court's recognition that such techniques are patentable, the floodgates of human health preservation and augmentation is now a reality, as issues of free riding would be neutralized in the face of patent doctrine.

Regents will undoubtedly be remembered as a case that united the world of science and law, in which patent jurisprudence mediated a collective understanding of human genius in the realm of genetic modification. As 2020 commences, an age of discovery and wonderment is on the horizon for medical advancement, thanks to the wise decision to honor assertive and daring brilliance in *Regents*.

[68] *Invention: United States and Comparative Global Trends*, NATIONAL SCIENCE BOARD, https://www.nsf.gov/statistics/2018/nsb20181/report/sections/invention-knowledge-transfer-and-innovation/invention-united-states-and-comparative-global-trends (last visited Nov. 18, 2019) "Patents serve a different purpose. Inventors often have economic motivations to keep the details of their inventions secret. The patenting system provides the legal right for a limited time to exclude others from making, using, offering for sale, or selling the invention, in exchange for public disclosure of the technical information in the granted patent."

[69] David S. Olson, *Patent Protection for Genetic Innovation: Monsanto and Myriad*, 12 CATO SUPREME COURT REVIEW 283, 299 (2013) https://www.cato.org/sites/cato.org/files/serials/files/supreme-court-review/2013/9/olson.pdf.
"By allowing cDNA to be patented, the Court ensured that some incentives flow to genetic researchers for their discoveries of important gene-disease correlations."