United States Court of Appeals for the Federal Circuit

REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, EMMANUELLE CHARPENTIER,
Appellants

v.

BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, PRESIDENT AND FELLOWS OF HARVARD COLLEGE,
Appellees

2017-1907

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. 106,048.

Decided: September 10, 2018

DONALD B. VERRILLI, JR., Munger, Tolles & Olson LLP, Washington, DC, argued for appellants. Appellants Regents of the University of California, University of Vienna also represented by GINGER ANDERS; EDWARD GEORGE DANE, ADAM R. LAWTON, Los Angeles, CA.

RAYMOND N. NIMROD, Quinn Emanuel Urquhart & Sullivan, LLP, New York, NY, argued for appellees. Also

represented by MATTHEW D. ROBSON; STEVEN R. TRYBUS, HARRY J. ROPER, Jenner & Block LLP, Chicago, IL.

LI-HSIEN RIN-LAURES, RinLaures LLC, Chicago, IL, for appellant Emmanuelle Charpentier. Also represented by SANDIP PATEL, Marshall, Gerstein & Borun LLP, Chicago, IL.

Before PROST, *Chief Judge,* SCHALL and MOORE, *Circuit Judges.*

MOORE, *Circuit Judge*.

The University of California, the University of Vienna, and Emmanuelle Charpentier, (collectively "UC"), appeal a decision of the Patent Trial and Appeal Board determining there was no interference-in-fact between UC's Application No. 13/842,859, and the claims of twelve patents and one application owned by the Broad Institute, Inc., Massachusetts Institute of Technology, and the President and Fellows of Harvard College, (collectively "Broad"). Because the Board's underlying factual findings are supported by substantial evidence and the Board did not err in concluding that Broad's claims would not have been obvious over UC's claims, we affirm.

BACKGROUND

The involved claims relate to the use of a CRISPR-Cas9[1] system for the targeted cutting of DNA molecules. The system includes three components: (1) a "crRNA"; (2) a "tracrRNA"; and (3) the Cas9 protein. J.A. 4803. The crRNA is an RNA molecule with a variable portion that targets a particular DNA sequence. J.A. 4799–803. The nucleotides that make up the

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[1] "CRISPR" is an acronym for "Clustered Regularly Interspaced Short Palindromic Repeats." J.A. 4682.

variable portion complement the target sequence in the DNA and hybridize with the target DNA. J.A. 4801. Another portion of the crRNA consists of nucleotides that complement and bind to a portion of the tracrRNA. J.A. 4801. The Cas9 protein interacts with the crRNA and tracrRNA and cuts both strands of DNA at the target location. J.A. 4799.

In August 2012, UC researchers published an article ("Jinek 2012") demonstrating that the isolated elements of the CRISPR-Cas9 system could be used in vitro in a non-cellular experimental environment. J.A. 4799–804. In February 2013, Broad researchers published an article describing the use of CRISPR-Cas9 in a human cell line. J.A. 4682–86. Both parties sought patent protection. CRISPR-Cas systems occur naturally in prokaryotes such as bacteria, J.A. 4799, but have not been found to naturally exist in eukaryotes, such as plants and animals, J.A. 5488; *see also* J.A. 5006, 5029. It is undisputed that the Jinek 2012 article did not report the results of experiments using CRISPR-Cas9 in a eukaryotic cell, and the claims in UC's '859 application do not refer to a particular cell type or environment. J.A. 13, 9665–66. Claim 165 of the '859 application is representative:

> 165. A method of cleaving a nucleic acid comprising
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> contacting a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)— CRISPR associated (Cas) (CRISPR-Cas) system comprising
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> a) a Cas9 protein; and
>
> b) a single molecule DNA-targeting RNA comprising

> i) a targeter-RNA that hybridizes with the target sequence, and
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> ii) an activator-RNA that hybridizes with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,
>
> wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides,
>
> wherein the single molecule DNA-targeting RNA forms a complex with the Cas9 protein,
>
> whereby the single molecule DNA-targeting RNA targets the target sequence, and the Cas9 protein cleaves the target DNA molecule.

J.A. 9665. The claims in Broad's patents and application are limited to use in eukaryotic cells. Claim 1 of U.S. Patent No. 8,697,359 is representative:

> 1. A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising:
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> a) a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and

> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II Cas9 protein,
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> wherein components (a) and (b) are located on same or different vectors of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

J.A. 1831.

The Board instituted an interference, and Broad moved to terminate the interference, arguing its claims are patentably distinct from UC's claims because a person of ordinary skill in the art would not have had a reasonable expectation that the CRISPR-Cas9 system would work successfully in a eukaryotic cell. J.A. 7, 13. The Board determined there was no interference-in-fact because, given the differences between eukaryotic and prokaryotic systems, a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the CRISPR-Cas9 system in eukaryotes. J.A. 48–49. It determined, therefore, that UC's claims to the use of CRISPR-Cas9 did not render obvious Broad's claims to its use in eukaryotes. J.A. 49.

UC timely appeals. We have jurisdiction over appeals of interferences under 28 U.S.C. § 1295(a)(4)(A) as it existed prior to changes made by the America Invents Act ("AIA"). *See* Technical Corrections—Leahy–Smith America Invents Act, Pub. L. No. 112-274, 126 Stat. 2456, 2458 (2013).

DISCUSSION

If two parties claim patentably indistinct subject matter, under pre-AIA 35 U.S.C. § 102(g), a patent may only

be awarded to the first inventor.[2] Whether an interference occurs is determined by comparing the involved claims. *Noelle v. Lederman*, 355 F.3d 1343, 1352 (Fed. Cir. 2004). The Board applies a two-way test to determine whether the claims are patentably distinct, asking whether "the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa." 37 C.F.R. § 41.203(a). If the two-way test is not met, no interference-in-fact exists.

When an interference-in-fact turns on whether one set of claims renders obvious the subject matter of another set of claims, the standard of review mirrors that in an obviousness review. *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 932 (Fed. Cir. 2003). Obviousness is a question of law based on underlying facts. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1326 (Fed. Cir. 2016). In *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966), the Supreme Court set forth factors for assessing obviousness. The *Graham* factors—(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 nonobviousness—are questions of fact reviewed for substantial evidence. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1358 (Fed. Cir. 2017).

An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art

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[2] The AIA replaced the first-to-invent rule with a first-inventor-to-file rule, but the prior rule continues to apply in this interference. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, sec. 3(n)(2), 125 Stat. 284, 293 (2011); *Storer v. Clark*, 860 F.3d 1340, 1342 (Fed. Cir. 2017).

and would have had a reasonable expectation of success in doing so. *In re Stepan Co.*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017). "Whether a person of ordinary skill in the art would have been motivated to modify or combine teachings in the prior art, and whether he would have had a reasonable expectation of success, are questions of fact." *Id.* at 1346. We review the Board's ultimate conclusion of obviousness de novo, and the underlying factual findings for substantial evidence. *In re Mouttet*, 686 F.3d 1322, 1330–31 (Fed. Cir. 2012).

This 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. J.A. 48–49. 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. UC argues 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. For the reasons set forth below, we hold the Board did not err in its analysis.

Reasonable Expectation of Success

The Board found 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 a eukaryotic cell. J.A. 48–49. It concluded, therefore, that if UC's claims were prior art, they would not have rendered Broad's claims obvious, so there was no interference-in-fact. J.A. 49. Substantial evidence supports the Board's finding that there would not have been a reasonable expectation of success.

Broad's expert Dr. Paul Simons testified as to the differences between prokaryotic systems and eukaryotic systems that rendered the application of the CRISPR-

Cas9 system in eukaryotic cells unpredictable. He explained that the function of the CRISPR-Cas9 system is dependent on the proper folding of the Cas9 protein. J.A. 5526 at ¶ 6.9. He explained that folding is particularly important for the CRISPR-Cas9 system because of the conformational changes the Cas9 protein undergoes in performing its function. *Id.* He further explained that differences in cellular conditions can cause differences in protein folding, *id.*, and elaborated on some of the differences between prokaryotic and eukaryotic cellular conditions that would make the functionality of CRISPR-Cas9 in eukaryotes unpredictable, J.A. 5527 at ¶ 6.13. These included: 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. *Id.*

Dr. Simons identified additional concerns involving the CRISPR-Cas9 system which he testified would have caused a skilled artisan not to have a reasonable expectation that it would work in eukaryotic cells. The CRISPR-Cas9 system relies on two RNA components, crRNA and tracrRNA. J.A. 5528 at ¶ 6.15. Eukaryotic cells contain a number of molecules, known as ribonucleases, which are not present in prokaryotic cells, that cut up RNA molecules. J.A. 5528–29 at ¶¶ 6.15–6.16. Eukaryotic cells also contain systems that degrade double-stranded RNA. The CRISPR-Cas9 system contains a section of double-stranded RNA where the crRNA binds with the tracrRNA, adding additional uncertainty. J.A. 5529–30 at ¶¶ 6.17–6.20. Dr. Simons suggested a person of ordinary skill in the art would have been concerned that the CRISPR-Cas9 system could result in an 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. J.A. 5530–32 at ¶¶ 6.22–6.27. He testified that these differences made it such that a skilled artisan would not have had a reasona-

ble expectation of success in applying CRISPR-Cas9 in eukaryotic cells. J.A. 5532 at ¶ 6.27.

In a September 2012 article, UC's expert witness Dr. Dana Carroll recognized many of the same issues that could arise in attempting to apply the CRISPR-Cas9 system in eukaryotic cells. These included the possibility that CRISPR-Cas9 might be degraded by nucleases in eukaryotic cells and that toxicity could result from its use in eukaryotic cells. J.A. 4797. He also noted potential problems arising from the fact that, unlike prokaryotic DNA, eukaryotic DNA exists in a chromatin complex, in which the DNA is wrapped around protein structures. J.A. 4797. He stated that "[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." J.A. 4797; *accord* J.A. 9111. He further noted that the efficacy of prior systems relying on gene editing through base pairing "remains discouragingly low in most cases." J.A. 4797. Ultimately, Dr. Carroll concluded 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." J.A. 4797. This is substantial evidence that skilled artisans believed many problems could arise in implementing the CRISPR-Cas9 system in eukaryotes, which the Board viewed as indicating that an ordinarily skilled artisan would have lacked a reasonable expectation of success.

The Board was also presented evidence of statements by the UC inventors acknowledging doubts and frustrations about engineering CRISPR-Cas9 systems to function in eukaryotic cells and noting the significance of Broad's success. One of the named inventors, Dr. Jennifer Doudna, acknowledged the "huge bottleneck" in making genetic modifications in animals and humans, J.A. 5911, and after the publication of the initial UC research, she stated "[o]ur 2012 paper was a big success, but there was a problem. We weren't sure if CRISPR/Cas9 would work in

eukaryotes," J.A. 5880. She also explained that she had "many frustrations" in getting CRISPR-Cas9 to work in human cells, and that she thought success in doing so would be "a profound discovery." J.A. 5908. Evidence in the record also suggested her colleagues recognized Broad's development was significant. When a colleague contacted Dr. Doudna to inform her of Broad's success he stated "I hope you're sitting down," "CRISPR is turning out to be absolutely spectacular in [Broad researcher] George Church's hands." J.A. 5908. The Board viewed this evidence as indicating that an ordinarily skilled artisan would have lacked a reasonable expectation of success.[3]

The Board also considered evidence regarding the development of other gene editing systems. It found several of these were not particularly informative in assessing the reasonable expectation of success of CRISPR-Cas9. Specifically, it found that the prior art TALEN and zinc finger nuclease ("ZFN") systems were not analogous to CRISPR-Cas9 because they have their origins in eukaryotic domains and that the adaptability of small prokaryotic protein systems like Cre would not have informed the expectation of success for the larger CRISPR-Cas9 complex. J.A. 17 (citing J.A. 4797), 41, 43. Broad presented

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[3] UC also argues the Board erred in giving "near-dispositive weight" to statements by Dr. Doudna and Dr. Carroll, which it claims were misinterpreted by the Board. The Board considered a variety of statements made by both Dr. Doudna and Dr. Carroll. In doing so, it afforded the statements weight depending on the contexts in which they were made and their relevance to its analysis. *See* J.A. 14–23. To the extent UC argues the Board erred in its reading of these statements in the contexts in which they arose, we conclude substantial evidence supports the Board's interpretation.

evidence regarding three other systems derived from prokaryotes that had been adapted for use in eukaryotes: riboswitches, ribozyme systems, and group II introns. The Board found that in each instance there was either limited efficacy or the technology required a specific strategy to adapt it for use in eukaryotic cells. J.A. 36–38. Broad presented expert testimony that only a few riboswitches had been successfully adapted to work in eukaryotes, and a prior art article explained that differences in RNA folding in vivo versus in a cellular environment may prevent the riboswitches from working. J.A. 36 (citing J.A. 5537–38 at ¶ 6.47; J.A 5893). Based on expert testimony and an earlier publication, the Board found that although some success was achieved using ribozyme systems, "that success required a specific strategy developed particularly for ribozymes." J.A. 38 (citing J.A. 5889–90). As to group II introns, there was evidence before the Board that despite 16 years of experimental efforts and the development of a specific strategy to increase the likelihood of success for that system, their use in eukaryotes remained limited. J.A. 5535–36 at ¶¶ 6.37–39; J.A. 8653–56 at ¶¶ 1.45–53. This substantial evidence supports the Board's finding that the success in applying similar prokaryotic systems in eukaryotes was unpredictable and had relied on tailoring particular conditions to the technology. J.A. 37–39. The Board also found that "one skilled in the art would have expected that the CRISPR-Cas9 system would have also required its own set of unique conditions." J.A. 39. We conclude the record evidence is sufficient to support that finding.

In light of the record evidence, which includes expert testimony, contemporaneous statements made by skilled artisans, statements by the UC inventors themselves, and prior art failures, we conclude that the Board's fact-finding as to a lack of reasonable expectation of success is supported by substantial evidence.

UC expended substantial time and effort to convince this court that substantial evidence supports the view it would like us to adopt, namely, that a person of ordinary skill would have had a reasonable expectation of success in implementing the CRISPR-Cas9 system in eukaryotes. There is certainly evidence in the record that could support this position. The prior art contained a number of techniques that had been used for adapting prokaryotic systems for use in eukaryotic cells, obstacles adopting other prokaryotic systems had been overcome, and Dr. Carroll suggested using those techniques to implement CRISPR-Cas9 in eukaryotes. 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.

Specific Instructions

UC argues the Board erred in adopting a test requiring that there be specific instructions in the prior art to establish a reasonable likelihood of success. Appellants' Opening Br. 19 ("its requirement that the art contain 'specific instructions'"), 21 ("expressly refused to find obviousness because the prior art lacked 'specific instructions'"), 31 ("requiring that the prior art contain 'specific instructions'"; "insisted that the prior art must contain 'instructions that are *specifically relevant*'"; "fell short because it did not provide specific instructions"). It argues that instead of asking whether the claimed invention is "the product not of innovation but of ordinary skill and common sense," the Board adopted a rigid test for obviousness that formalistically looked for specific instructions in the prior art while ignoring "the inferences and creative steps that a person of ordinary skill in the art would employ" without the need for specific guidance. Appellants' Opening Br. 27 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 420 (2007)). The Board

did not adopt a test requiring there be specific instructions in the art in order to make a finding of a reasonable expectation of success, and we see no error in its analysis.

The Board acknowledged that certainty in the art is not required, J.A. 12, and performed a factual analysis based on the correct legal standard. In considering whether there was a reasonable expectation of success, it stated that it "look[ed] to whether or not there were instructions in the prior art that would be specifically relevant to CRISPR-Cas9," as well as "whether there are examples in the prior art of the success or failure of similar systems." J.A. 28–29. The Board noted 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." J.A. 28. It further noted that in other cases the combination of only generalized instructions *and* evidence of failures with similar subject matter indicated there was not a reasonable likelihood of success. J.A. 28. It made clear that the determination "depends on the specific nature of what was known from the prior art about closely related subject matter." J.A. 28. We see no error in these statements of law—the Board did *not* hold specific instructions were needed.

In this case, the Board found there would not have been specific instructions in the art as to CRISPR-Cas9 that would have given one of ordinary skill in the art a reasonable expectation of success, and it was "persuaded that the failure demonstrated with other systems would have indicated the lack of a reasonable expectation of success." J.A. 45–46. At no point did the Board suggest it found there would not have been a reasonable expectation of success solely because there were not specific instructions in the art describing how to apply CRISPR-Cas9 in eukaryotes. We see no error in the Board's consideration of the lack of specific instructions in conjunction with

prior failures at adapting prokaryotic systems to eukaryotic cells based on general instructions.

Treatment of Simultaneous Invention Evidence

UC argues the Board erred in dismissing evidence of simultaneous invention as irrelevant. It argues simultaneous invention can be compelling evidence of obviousness, because it shows the claimed invention "was the product only of ordinary mechanical skill or engineering skill," rather than genuine invention. Appellants' Opening Br. 37 (quoting *Geo. M. Martin Co. v. All Mech. Sys. Int'l*, 618 F.3d 1294, 1305–06 (Fed. Cir. 2010)). It argues simultaneous invention is strong objective evidence of what constituted the level of ordinary skill in the art and is relevant as a secondary consideration under the fourth *Graham* factor. It argues six research groups independently applied CRISPR-Cas9 in eukaryotic cells within months of its disclosures, a secondary consideration which the Board failed to address. The Board, however, did not treat this evidence as irrelevant. Instead, the Board expressly recognized the relevance of simultaneous invention to the question of obviousness. J.A. 23.

Simultaneous invention may serve as evidence of obviousness when considered in light of all of the circumstances. *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1460 (Fed. Cir. 1984). We have recognized that simultaneous invention may bear upon the obviousness analysis in two ways. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998). First, it is evidence of the level of skill in the art. *Id.* Second, it constitutes objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem. *Id.* Inherent in the existence of interference practice is the principle that evidence of simultaneous invention cannot alone show obviousness, otherwise any claims involved in an interference would be unpatentable for

obviousness. *Lindemann*, 730 F.2d at 1460. The weight of evidence of simultaneous invention must, therefore, be carefully considered in light of all the circumstances. *See Monarch Knitting*, 139 F.3d at 883.

In August 2012, the Jinek 2012 paper was published explaining the CRISPR-Cas9 system and its use in vitro using isolated components. There is no dispute that this represented a breakthrough in the art. The fact that six research groups succeeded in applying this technology in eukaryotic cells within a short period of time after this is certainly strong evidence that there was a motivation to combine the prior art in this manner. The Board expressly recognized UC's evidence of simultaneous invention in this context, and it concluded the evidence of simultaneous invention was evidence of the motivation to combine the prior art references but did not "necessarily" indicate an expectation of success prior to the completion of the experiments. J.A. 23.

UC would have the Board read more into this evidence and infer that because several research teams pursued a particular approach, and that approach was ultimately successful, they must have expected that approach to work. It argued to the Board that absent an expectation of success, multiple groups "would not have undertaken the use of UC's Type-II CRISPR-Cas system in eukaryotic cells." J.A. 245. The Board rejected this bright-line rule and instead determined in this instance the evidence of simultaneous invention did not establish a reasonable expectation of success given the "specific context of the art at the time." *See* J.A. 23–25. 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." J.A. 25 (quoting *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008)). We do not see any error in

this analysis. Contrary to UC's claims, the Board recognized that UC's evidence of simultaneous invention is relevant to the obviousness determination. We consider Broad's evidence of simultaneous invention, along with evidence regarding the state of the art, the statements of the inventors, failures involving similar technologies, and the remainder of the record evidence, and conclude the Board's finding is supported by substantial evidence.

CONCLUSION

For the foregoing reasons, we affirm the Board's judgment of no interference-in-fact. The Board performed a thorough analysis of the factual evidence and considered a variety of statements by experts for both parties and the inventors, past failures and successes in the field, evidence of simultaneous invention, and the extent to which the art provided instructions for applying the CRISPR-Cas9 technology in a new environment. In light of this exhaustive analysis and on this record, we conclude that substantial evidence supports the Board's finding that there was not a reasonable expectation of success, and the Board did not err in its determination that there is no interference-in-fact.

We have considered UC's remaining arguments and find them unpersuasive. We note that this case is about the scope of two sets of applied-for claims, and whether those claims are patentably distinct. It is not a ruling on the validity of either set of claims.

AFFIRMED