Appeal No. 2017-1907

United States Court of Appeals

for the

Federal Circuit

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

Appellants,

– v. –

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

Appellees.

APPEAL FROM THE PATENT TRIAL AND APPEAL BOARD
OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
IN INTERFERENCE NO. 106,048

REPLY BRIEF FOR APPELLANTS

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Certificate Of Interest

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1. The full name of every party represented by me is:

Regents of the University of California
University of Vienna

2. The name of the real parties in interest represented by me are:

Regents of the University of California
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3. All parent corporations and any publicly held companies that own 10% or more of stock in the parties represented by me are:

None

4. The names of all law firms and the partners or associates that appeared for the parties now represented by me before the Patent Trial and Appeal Board or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal are:

None

Respectfully submitted,

Dated: November 22, 2017

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Counsel for Appellant Emmanuelle Charpentier certifies the following:

1. The full name of every party represented by me is:

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2. The names of the real party in interest represented by me is:

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N/A

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal are:

None

Respectfully submitted,

Dated: November 22, 2017 /s/ *Li-Hsien Rin-Laures*
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Table Of Abbreviations

Parties	
UC	Regents of the University of California, University of Vienna, and Emmanuelle Charpentier, collectively
Broad	The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College, collectively
Patents and Applications	
the '859 Application	Patent Application No. 13/842,859 (UC)
the Kim Application	U.S. Patent Application No. 14/685,568
the Kim Provisional	Provisional Patent Application No. 61/717,324
Defined Terms	
PTAB	Patent Trial and Appeal Board of the United States Patent and Trademark Office
PTO	United States Patent and Trademark Office
Jinek 2012	Jinek et al., A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity, 337(6096) SCIENCE 816-821 (August 17, 2012; published online June 28, 2012) (Appx04799-04804)
TALEN	Transcription activator-like effector nuclease

Introduction

The core issue in this case is whether UC's claims applying CRISPR-Cas9 to cleave DNA in all environments, including eukaryotic cells, address the same subject matter as, and therefore interfere with, Broad's later claims applying CRISPR-Cas9 in eukaryotic cells. The answer turns on whether Broad's eukaryotic claims are obvious in light of UC's all-environment claims and the prior art. Broad's brief makes the answer clear: never once does Broad suggest that it attempted or achieved any innovation over UC's disclosures, or that inventive problem-solving was necessary to employ CRISPR-Cas9 in eukaryotes once UC disclosed the components of the system and directed its use in eukaryotes. Rather, Broad simply did what five other research groups did: it engaged in a "predictable use of prior art elements according to their established functions" to achieve success in a matter of months—the very definition of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

Unable to show that its own claims reflect innovation, Broad instead offers a tendentious alternative history that seeks to obscure the pathbreaking innovation of UC's inventors. Broad insinuates that UC merely performed narrow experiments on CRISPR-Cas9 in a test-tube environment while Broad achieved earlier success using

CRISPR-Cas9 in eukaryotic cells.[1] The record conclusively demonstrates, however, that UC achieved *the* inventive breakthrough that made the subsequent employment of CRISPR-Cas9 in eukaryotes not only possible, but obvious. Before Jinek 2012, researchers had not comprehended the critical role that tracrRNA plays in the CRISPR-Cas9 cleavage complex. Appx04900. UC's disclosure of that breakthrough—and concomitant demonstration that CRISPR-Cas9 could function outside of its native prokaryotic cells, could be modified to use a streamlined chimeric RNA, and could be reprogrammed to cleave DNA of choice, as well as its suggestion that CRISPR-Cas9 could supplant existing methods of cleaving DNA in eukaryotes—immediately redirected the course of CRISPR-Cas9 research and gene editing.

The scientific community's reaction to Jinek 2012 makes this crystal clear, while exposing the mischaracterizations that litter Broad's account. Publications hailed Jinek 2012 for demonstrating how to use CRISPR-Cas9 to cleave DNA *outside* of prokaryotic cells. Appx04871, Appx04898-04901. And the other research groups who rushed to employ CRISPR-Cas9 in eukaryotes acknowledged their debt to UC's

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[1] For instance, Broad depicts as fact the purported experimental results that Broad has presented to the PTO's examiners when in reality Broad's results are hotly disputed and do not show success. Appx04944-04972; Appx00244-00248. And the "Heroes of CRISPR" article on which Broad relies (Appx09310) was written by Broad's president and was widely criticized for its many inaccuracies. *See Heroes of CRISPR Disputed*, www.the-scientist.com/?articles.view/articleNo/45119/.

invention. The Kim group credited Jinek 2012 with "elegantly" demonstrating how CRISPR-Cas9 could be used and "raising the possibility of using [it] for genome editing in cells and organisms," Appx05187, and others, including Broad, used Jinek 2012's RNA designs in their experiments.[2] Appx04930-04931, Appx04684, Appx04714, Appx05201, Appx04778, Appx04792.

Ultimately, however, Broad's revisionist history merely distracts from the issue on which this appeal turns. Broad's narrative is about priority—the issue that the PTAB should have adjudicated in the interference. The PTAB, however, prematurely terminated the proceeding based on a threshold finding of nonobviousness that reflected clear legal errors.

First, the PTAB required specific instructions and virtual certainty in the prior art, contravening *KSR* and this Court's precedents. Broad does not attempt to defend that standard, instead claiming that the PTAB did not actually apply it—but the plain text of the decision refutes that argument.

Second, the PTAB refused to consider compelling evidence of simultaneous invention demonstrating that employing CRISPR-Cas9 in eukaryotes was well within the ordinary skill in the art. Broad seeks to obscure the force of this argument by

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[2] Broad's article states that its experiments used the chimeric RNA disclosed in Jinek 2012. Appx04683.

contending—incorrectly—that UC failed to raise it below. And on the merits, Broad cannot reconcile the PTAB's unwillingness to consider the evidence with this Court's holdings that what others actually did is strong evidence of both skilled artisans' capabilities and obviousness. Here, the evidence is particularly compelling. The research groups that applied CRISPR-Cas9 in eukaryotes designed experiments using only conventional techniques and Jinek 2012's guidance. None of these skilled artisans viewed the hypothetical concerns later identified by Broad as significant enough to warrant applying novel techniques. Had they thought otherwise, surely they would have designed their experiments accordingly. But none did. This evidence of what skilled artisans actually did exposes Broad's arguments for what they are—post hoc obfuscations designed to mask the fact that Broad achieved no genuine innovation.

Third, the PTAB refused to consider the Kim Application as prior art under 35 U.S.C. § 102(e) demonstrating that Broad's claims are obvious in light of UC's. Broad's defense of that refusal based solely on an inapposite inventorship decision and a facially inadequate effort to antedate the Kim Application is meritless.

The PTAB's legal errors skewed its evaluation of the record—and led it to disregard the most compelling evidence of obviousness. When considered under the correct standards and in light of all evidence, the record supports only one outcome: Broad's claims are obvious in light of UC's claims, and this Court should reverse the

PTAB's holding that there is no interference-in-fact. At a minimum, the Court must vacate and remand because the PTAB's decision is unsupported by substantial evidence. The PTAB's erroneous legal analysis led it to place inordinate weight on a few out-of-context public statements, including post hoc quotations given to the press, while discounting or ignoring the overwhelming objective evidence of a reasonable expectation of success.

The weakness of Broad's defense of the PTAB's decision underscores just how indefensible that decision is. Broad first seeks to create the impression of substantial record support by identifying five "categories" of evidence. But that is a rhetorical trick. Broad has identified two types of evidence—the statements mentioned above and the hypothetical obstacles that Broad claims undermined any expectation of success—and broken them into five categories to make them seem more substantial. Making matters worse, Broad then mischaracterizes the standard of review, claiming that the PTAB's ruling must be upheld if more than a scintilla of evidence exists in any of the five categories, without regard to contradictory evidence in either that category or the other four. But an agency's decision must be supported by substantial evidence when considered in light of the whole record, including countervailing evidence. *Universal Camera Corp. v. NLRB*, 340 U.S. 474, 488 (1951).

The PTAB's decision is erroneous and unjust. Instead of determining priority with respect to one of the most important inventions of our time, the PTAB effectively

permitted Broad to patent an obvious subset within UC's earlier broader invention. The decision perpetuates uncertainty about the parties' rights, and impedes commercial development of CRISPR-Cas9 applications. To further the overriding public interest in resolving competing claims to this groundbreaking technology, this Court should conclude that there is an interference-in-fact and direct the PTAB to adjudicate priority.

Argument

I. The PTAB applied an erroneous legal standard that distorted its evaluation of the evidence.

Under *KSR*, the obviousness analysis focuses on whether a claimed invention is "the product not of innovation but of ordinary skill and common sense." 550 U.S. at 421. Broad does not contend that employing CRISPR-Cas9 in eukaryotes required any ingenious techniques or specialized measures. It acknowledges that none of the potential difficulties that *could have arisen* in transferring CRISPR-Cas9 to the eukaryotic environment actually *did arise*. Once UC disclosed how CRISPR-Cas9 functioned and directed its use in eukaryotes, all that was necessary to achieve Broad's purported invention was to apply conventional techniques for introducing prokaryotic molecules into eukaryotes. Broad, moreover, failed to demonstrate that skilled artisans would have expected its hypothesized difficulties to impede success using conventional techniques. Indeed, that the simultaneous inventors saw no need to account for those difficulties in designing their experiments refutes Broad's

arguments. Thus, Broad's claimed advance—one simultaneously achieved by five other research groups, and for which Broad is merely one of several entities, and not even the first after UC, to seek patent protection—required no innovation over UC's disclosures. Appx00240.

The PTAB nonetheless found Broad's eukaryotic application nonobvious because it applied the "reasonable expectation of success" standard in a manner totally divorced from what the obviousness analysis must focus on: innovation. The PTAB relied on a lack of specific instructions in the prior art and a pre-experimentation lack of certainty to transform Broad's performance of methods suggested by Jinek 2012, using existing techniques in a routine manner, into a nonobvious invention. But the "reasonable expectation of success" standard must take into account the pre-experimentation lack of certainty that is intrinsic to fields grounded in experimentation.

A. The PTAB's "specific instructions" standard is wrong.

KSR and this Court's decisions reject a "rigid" test for obviousness that finds innovation whenever the prior art lacks "precise teachings directed to the specific subject matter of the challenged claim." 550 U.S. at 418-19; *In re Kubin*, 561 F.3d 1351, 1359-61 (Fed. Cir. 2009). The PTAB did exactly what *KSR* forbids. It required "instructions . . . that [are] *specifically relevant to* CRISPR-Cas9 and [that] would instruct those of ordinary skill how to achieve activity with that system in eukaryotic

cells." Appx00028-00029 (emphasis added). Further, the PTAB effectively required, again contrary to *KSR*, that the specific instructions be found in a single reference, rather than in the prior art as a whole. UC Opening Br. 31-32. It concluded that each reference in isolation did not contain sufficient specificity to support an expectation that CRISPR-Cas9 "could be used in eukaryotic cells successfully." Appx00041-00045. Employing that erroneous standard to evaluate the evidence, the PTAB found insufficiently "specific" the extensive prior-art guidance—including Jinek 2012's direction to use CRISPR-Cas9 in eukaryotes; previous successes using prokaryotic proteins to manipulate DNA in eukaryotes; and the existence of well-established techniques that the PTAB acknowledged were "routine and known to be useful in achieving activity of prokaryotic proteins in eukaryotic cells." Appx00035. And it did so despite the fact that skilled artisans could (and *did*) use those techniques to employ CRISPR-Cas9 in eukaryotes, as expected. These legal errors warrant reversal.

Rather than defend what the PTAB did, Broad mischaracterizes (Br. 54) the PTAB's legal error as a "factual inquir[y]" into whether the prior art contained specific instructions relevant to CRISPR-Cas9. But the PTAB undertook that "factual inquiry" because it believed such instructions were *legally required*. The PTAB stated unambiguously that "we look to whether or not there were instructions in the prior art that would be specifically relevant to CRISPR-Cas9" to assess a "reasonable expectation of success." Appx00028. And in holding that Broad's claims were

nonobvious, the PTAB confirmed that it would have found a reasonable expectation of success only if there were instructions specifically relevant to CRISPR-Cas9: "there would not have been *specific instructions* relevant to CRISPR-Cas9 to give one . . . a reasonable expectation of success." Appx00045 (emphasis added). Those statements remove any doubt that the PTAB viewed instructions specifically relevant to CRISPR-Cas9 as legally required.

Broad also argues (Br. 53) that the PTAB looked for "specific instructions" only because it concluded that skilled artisans would have expected CRISPR-Cas9 to require "its own set of unique conditions" to function in eukaryotes. Appx00039. But the skilled artisans who employed CRISPR-Cas9 in eukaryotes did not think it necessary to deploy any innovative techniques to account for such "unique conditions." In all events, it was still error to effectively require that a single reference contain instructions specifically directed to those conditions. The proper inquiry would remain whether a skilled artisan, considering prior-art guidance, could have applied ordinary inferences and skill to a finite set of predictable solutions, or instead would have needed to "vary all parameters" in the prior art without meaningful guidance. *Kubin*, 561 F.3d at 1359-60; *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Broad also appears to contend (Br. 56) that the PTAB's application of a "specifically relevant instructions" legal standard was harmless error because "it

would not apply" to the Carroll and Doudna statements on which Broad relies so heavily. Broad provides no support for the surprising proposition that this Court could affirm based solely on these statements, without regard to the objective examination of the prior art and other objective evidence that is fundamental to the obviousness inquiry. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *KSR*, 550 U.S. at 418. Broad's suggestion is also contrary to the rule that an agency's decision must be supported by substantial evidence in light of the *whole* record. *Universal Camera*, 340 U.S. at 487-88; Part III, *infra*.

B. The PTAB committed an additional legal error by requiring a virtual certainty of success.

The PTAB's legal standard was divorced from the overarching question of innovation in another respect: it disregarded this Court's holding that a reasonable expectation of success exists, despite a pre-experimentation lack of certainty, when the prior art teaches a finite set of approaches to a well-defined problem and there is reason to anticipate success using those approaches. *Kubin*, 561 F.3d at 1359-60; UC Opening Br. 29-30. Properly understood, the "reasonable expectation of success" standard is tightly connected to the ultimate question of whether a purported invention actually reflects innovation. If the artisan must "vary all parameters" or explore a new field "without guidance," then she lacks an expectation of success and must innovate. *O'Farrell*, 853 F.2d at 902-04. Conversely, where she need only apply prior-art guidance in a predictable manner rather than innovating, ex ante uncertainty does not

preclude a reasonable expectation of success. *Kubin*, 561 F.3d at 1359-60. Broad ignores these precedents, asserting (Br. 51-52) that a "reasonable expectation of success" requires virtual certainty before reduction to practice, divorced from whether the advance required innovation rather than ordinary skill.

The PTAB erroneously accepted that argument. The clearest illustration is the inordinate importance the PTAB gave to the Doudna and Carroll statements: before considering any prior art, the PTAB concluded from those statements that a skilled artisan would have lacked a reasonable expectation of success. Appx00023. That conclusion distorted the PTAB's analysis: the PTAB dismissed multiple directly relevant prior-art successes primarily because of Dr. Carroll's statement that there was "no guarantee that Cas9 will work effectively." Appx00045, Appx00033. But those examples provided precisely the guidance that is crucial in determining whether there are "a finite number of identified, predictable solutions" and reason to anticipate success. *Kubin*, 561 F.3d at 1359-60; *KSR*, 550 U.S. at 421. In substance, the PTAB required virtual certainty: it used one practitioner's statement that there was "no guarantee" to dismiss actual guidance in the prior art that skilled artisans would have considered.

Broad contends (Br. 51) that the PTAB's boilerplate recitation that "*certainty* of success is not required" (Appx00012) inoculates its ruling from challenge on this basis. But the crucial question is what the PTAB *did*, not what it said. What the

PTAB did—use Dr. Carroll's statement to discount abundant prior-art guidance—is flatly inconsistent with *KSR* and this Court's precedents. Tellingly, Broad identifies no other case in which statements to the effect that there was "no guarantee" of success were used to discount actual prior-art guidance or establish that there was no expectation of success.

Finally, Broad attacks a strawman, contending that UC sought presumptions that a "decision to undertake experiments automatically proves an expectation of success," and that "when success is eventually achieved using 'well-known conventional techniques,' the claimed invention must be . . . obvious." Br. 52, 55. Not so: the point is that the fact and nature of the experiments actually undertaken constitute compelling evidence of obviousness in *this* case, and the PTAB ignored them because of its legally erroneous focus on specific instructions and near-certainty. The objective evidence shows that Broad and five other groups, guided by Jinek 2012, chose to use only conventional techniques in testing CRISPR-Cas9 in eukaryotes. Appx05258, Appx05261, Appx05266. None viewed the hypothetical, litigation-driven concerns later identified by Broad as significant enough to warrant applying novel techniques. Instead, their experimental designs assumed that conventional techniques would succeed. As *KSR* put it, the prior art provided a "finite number of identified, predictable solutions" and reason to believe that they would work, and Broad's implementation required nothing beyond "the predictable use of prior art

elements according to their established functions." *KSR*, 550 U.S. at 417, 421. The PTAB failed to apply that well-established legal standard.

II. The PTAB committed legal error in failing to consider evidence of simultaneous invention.

The PTAB committed a further legal error when it dismissed the evidence that six research groups (including Broad and UC) independently used only Jinek 2012's disclosures and conventional techniques to apply CRISPR-Cas9 in eukaryotic cells in a matter of months. "Simultaneous invention" evidence is considered particularly strong evidence of obviousness. *Ecolochem, Inc. v. S. Cal. Edison Co*., 227 F.3d 1361, 1376 (Fed. Cir. 2000).

A. The PTAB erroneously disregarded evidence that six groups independently applied CRISPR-Cas9 in eukaryotes within months of UC's disclosures.

1. As an initial matter, Broad is wrong (Br. 62) that UC failed to raise this argument. UC argued below, as here, that the evidence of simultaneous invention is relevant in two respects.

First, as Broad acknowledges (Br. 62), UC argued below that multiple "independent" groups were able to "quickly adapt" CRISPR-Cas9 to eukaryotes, and that this success demonstrates a reasonable expectation of success. Appx00235, Appx00244-00246. That is because it "is strong evidence of what constitutes the level of ordinary skill in the art," *Ecolochem*, 227 F.3d at 1379, and because it "demonstrates what others in the field *actually* accomplished" in view of the state of

the art. *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 Fed. App'x 916, 930 (Fed. Cir. 2015). Evidence of the skill and methods actually used are critical in determining whether skilled artisans would have reasonably expected success.

Second, and relatedly, UC argued below that evidence of what others actually achieved following Jinek 2012 was a relevant secondary consideration. It was, as UC stated, "objective evidence" that Broad's eukaryotic application was "obvious" in light of UC's disclosure because it showed that other skilled artisans "w[ere] able to quickly adapt" "routine" conventional techniques to employ CRISPR-Cas9 in eukaryotes. Appx00235, Appx00246. That is precisely how this Court has described the probative value of simultaneous invention as a secondary consideration of obviousness. *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1306 (Fed. Cir. 2010) (simultaneous invention is "objective evidence"); *In re GPAC Inc.*, 57 F.3d 1573, 1550 (Fed. Cir. 1995) ("objective evidence of nonobviousness must be considered if present"); *Alarm.com v. iControl Networks, Inc.*, 2015 WL 1871503, at *23 (P.T.A.B. Mar. 31, 2015) ("objective evidence" relevant in determining interference-in-fact). Broad is left to argue that UC did not use the precise words "secondary considerations." But this Court often discusses "objective" considerations without calling them "secondary." *E.g.*, *Woods v. DeAngelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1286 (Fed. Cir. 2012). This Court should reject Broad's attempt to turn preservation of arguments into a game of magic words.

2. Broad next argues (Br. 65) that the PTAB actually considered and rejected UC's simultaneous invention arguments. Again, Broad misstates what the PTAB did. The PTAB entirely failed to consider simultaneous invention as objective evidence of obviousness. And the PTAB refused to consider simultaneous invention as evidence of the capabilities of skilled artisans in light of prior-art guidance, and therefore probative of an expectation of success. The PTAB gave three reasons, all erroneous.

First, the PTAB held that the evidence is relevant only to the uncontested question of motivation. That is contrary to this Court's decisions recognizing that simultaneous invention is strong evidence that the claimed invention is the product only of ordinary skill.

Second, the PTAB held that the simultaneous inventions were at first "unpublished" and therefore not known to skilled artisans. Appx00023. But that is irrelevant. The point is not that others could have learned from those results, but that skilled artisans *themselves* obtained the same results using conventional techniques.

Third, the PTAB reasoned that considering the success achieved in mere months by multiple groups would constitute impermissible hindsight. Broad defends that reasoning as "unremarkable." Br. 66. It is anything but. This Court has repeatedly held that what skilled artisans achieve, even after the claimed invention, must be considered in evaluating both the level of skill and obviousness itself. *See Geo. M. Martin*, 618 F.3d at 1305-06; *In re Farrenkopf*, 713 F.2d 714, 720 (Fed. Cir.

1983). The course pursued by *multiple* practitioners demonstrates that skilled artisans, considering the problem ex ante, understood how to employ CRISPR-Cas9 in eukaryotes in light of the prior art—and that they independently designed their experiments using only conventional techniques and the RNA designs described in Jinek 2012. They saw no need to address the hypothetical difficulties that Broad argues preclude a reasonable expectation of success. The researchers reasonably expected success at the outset, and Broad's claimed invention was thus well within the routine application of ordinary skill. The PTAB erred in disregarding this critical evidence.[3]

3. Broad next contends (Br. 41-42) that the groups' activities do not qualify as simultaneous-development evidence. Broad first argues that the researchers had extraordinary skill because the lead investigators in some groups had sought patents concerning TALEN-based systems. But in the genome-editing field, the ordinarily skilled artisan was a highly-trained scientist who could design such experiments. That some contributed to patented advances simply demonstrates the high level of skill in

[3] Broad is wrong in contending (Br. 66) that this evidence was irrelevant because the parties did not dispute the level of ordinary skill. The parties disputed the expectations, "inferences[,] and creative steps" of a skilled artisan. *KSR*, 550 U.S. at 418; Appx00250; Appx00306. The simultaneous invention evidence was directly related to those disputes.

this art. *See, e.g.*, *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1566 (Fed. Cir. 1984). Importantly, Broad does not suggest that any extraordinary skill was needed to design and perform experiments using techniques the PTAB found to be routine. That so many groups succeeded so quickly thus confirmed that the skill level was sufficiently high for the ordinarily skilled artisan to expect to achieve success in eukaryotes.

Broad also suggests (Br. 41) that the fact that some groups sought patents indicates that they "belie[ved]" that their work was "inventive." But Broad cites no authority for the proposition that a researcher's subjective belief in possible patentability establishes nonobviousness. Accepting that assertion would render every claimed invention nonobvious. And, as Broad argued, the prospect of a "huge reward" motivated everyone to patent whatever they could. Appx00304.

Finally, Broad asserts (Br. 25) that some groups were not independent because they were "members" of the Broad community, which comprises scientists from multiple institutions. But each group published and sought patent protection separately, representing that they achieved their results independently. UC Opening Br. 40-41.

B. The PTAB erroneously disregarded the Kim Provisional and Application.

In defending the PTAB's failure to consider the Kim Application, Broad argues without support that section 102(e) prior art of others is unavailable to support

obviousness in the context of an interference-in-fact determination. Broad is incorrect.

Broad argues (Br. 58) that the interference-in-fact inquiry "determine[s] whether two parties claim the same patentable invention," implying that the inventions must be mutually anticipatory. However, the phrase "'same patentable invention' means that the invention of one party anticipates *or renders obvious* the other party's invention." *Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash.*, 334 F.3d 1264, 1268 (Fed. Cir. 2003) (emphasis added).

In *In re Bartfield*, 925 F.2d 1450, 1451 n.4 (Fed. Cir. 1991), this Court confirmed that section 102(e) art, even though not publicly available when created, is relevant to obviousness. Broad's attempt to distinguish *Bartfield* as involving invalidity rather than an interference is misplaced. The interference-in-fact test of obviousness parallels the section 103 analysis, considering "whether *the prior art* would . . . have revealed that in . . . making or carrying out [the invention], those of ordinary skill would have a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006). The party arguing against an interference-in-fact thus must demonstrate that "*the universe of relevant prior art* would not provide a basis or reason for modifying the 'primary reference' to account for [any] differences." *Alarm.com*, 2015 WL 1871503, at *24 (emphasis added).

This is precisely why the PTAB erred in failing to consider Kim with regard to expectation of success. The Kim Application was objective prior-art evidence that, before Broad's earliest arguable filing date, a skilled artisan had *already* taken Jinek 2012's guidance and applied UC's invention in eukaryotes. Even as of the December 2012 date Broad asserted in the obviousness inquiry, then, a skilled artisan reasonably would have expected to implement UC's CRISPR-Cas9 genus invention in the eukaryotic species. *See Medichem*, 437 F.3d at 1167 (affirming interference-in-fact where prior art provided a reasonable expectation of success in making species in light of genus); Manual of Patent Examining Procedure § 2301.03 (9th ed. 2015) (Example 6; third-party art may render species obvious in interference-in-fact test).

Although Broad argues that UC is using Kim to remedy omissions in its invention, UC's claims are not limited to a test-tube environment, but instead are genus claims encompassing use of CRISPR-Cas9 in any environment—extracellular, prokaryotes, and eukaryotes. Thus, UC's claims *already* cover use of CRISPR-Cas9 in eukaryotic cells; indeed, UC's application teaches implementing the invention in eukaryotes. *See, e.g.*, Appx00812-00813, Appx00818-00821, Appx04920-04923. The question is therefore whether a skilled artisan reasonably would have expected to implement UC's invention in one of the claimed environments—eukaryotes. Kim provides that answer, overcoming any purported differences between UC's genus and Broad's species claims. Contrary to Broad's argument (Br. 60), Kim does not render

UC's claims irrelevant to the interference-in-fact analysis. Because both parties' claims must anticipate or render each other's claims obvious, 37 C.F.R. § 41.203(a), there would be no interference-in-fact if UC's claims concerned unrelated subject matter. Broad has not contended that its claims, if prior art, would not anticipate or render obvious UC's claims. Appx00009-00010.

Broad strays far afield in arguing by analogy that the prior-invention provisions of section *102(g)*, 35 U.S.C. § 102(g), do not apply to the interference-in-fact obviousness analysis (Br. 59-60). First, section 102(g) is not at issue. Second, pre-AIA section 102(g)(1) is limited to the claims of parties to the interference, and thus cannot apply to third-party art. And while section 102(g)(2) can apply to third-party inventions, Broad cites no authority suggesting that such prior art could not be used to support obviousness in the interference-in-fact test.

Broad's reliance on an inventorship decision, *CardiAQ Valve Technologies, Inc. v. Neovasc Inc.*, No. 2017-1302, 2017 WL 3833209 (Fed. Cir. Sept. 1, 2017), is similarly misplaced. An inventor's contribution cannot consist of "merely explaining well-known concepts and/or the current state of the art." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998). In *CardiAQ*, the Court merely held that this rule does not foreclose inventorship to those whose contributions, although present in section 102(e) prior art, were "not contemporaneously available to an ordinary skilled artisan." *CardiAQ*, 2017 WL 3833209, at *3. Obviousness, in contrast, involves an

objective analysis based on a hypothetical artisan who is aware of all prior art, including 102(e) art. Kim's application was directly relevant to that analysis.

Finally, Broad argues that the Kim Provisional was filed after Broad submitted an article allegedly disclosing its invention. However, the PTAB never found that Broad had disqualified Kim as 102(e) art, and Broad never presented any evidence to antedate Kim. Broad's reference to declarations it submitted in *prosecution* is irrelevant. To rely on "affidavits filed during examination," Appx00145 (¶ 154.1.1), specifically, "swear-behind" declarations, 37 C.F.R. § 1.131, Broad was required to submit them in the interference, which would have allowed UC to cross-examine the declarants (a procedure not available during prosecution). UC Opening Br. 46 n.12; Appx00308. Broad did not, and thus no record evidence disqualifies Kim as prior art. Nor did UC admit that Broad had disqualified Kim by properly antedating it. The record excerpts Broad cites do not address antedating Kim. UC Opening Br. 11; Appx008342.

III. Substantial evidence in the record considered as a whole does not support the PTAB's decision.

Broad staked its entire argument for nonobviousness (on which Broad bore the burden of proof) on the proposition that a skilled artisan seeking to employ CRISPR-Cas9 to cleave DNA in eukaryotes would have lacked a reasonable expectation that its effort would succeed. Broad did *not* argue that it took any innovative steps in investigating, or designing or performing its experiments. The PTAB accepted

Broad's reasonable-expectation-of-success argument only because it applied the wrong legal standards and erroneously refused to consider compelling simultaneous-development evidence. Considered under the correct standards and in light of the whole record, the undisputed evidence permits only one conclusion: Broad's claims are obvious. At the very least, the PTAB's decision is not supported by substantial evidence.

A. Broad misstates the substantial evidence standard.

Broad suggests that this Court must affirm if it finds *any* evidence supporting the decision below—regardless of any countervailing evidence in the record considered as a whole. Broad thus argues that cherry-picked pieces of evidence each would support the decision—while ignoring the rest of the record. Br. 34-36. That is not how substantial-evidence review works.

That review requires an "examination of the record as a whole, taking into account both the evidence that justifies and detracts from [the] agency's opinion." *Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006); *Universal Camera*, 340 U.S. at 477-78. Broad's attempt to urge this Court to ignore compelling evidence in UC's favor that the PTAB erroneously disregarded thus falls flat. An "agency cannot ignore evidence contradicting its position"; that is the very definition of arbitrary agency action. *Butte Cty. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010).

B. The record demonstrates that Broad's eukaryotic implementation is obvious in light of UC's claims.

The record establishes that Broad's eukaryotic claims are obvious in light of UC's generic-environment claims. The PTAB wrongly discounted, and Broad ignores, compelling evidence that, considered in light of the whole record, precluded any finding of nonobviousness.

First, the PTAB itself found that the prior art taught methods of implementing prokaryotic DNA-manipulating proteins in eukaryotic cells, and that any skilled artisan would know how to use them. Appx00035 (techniques were "routine" and "known" to skilled artisans); Appx00039. Broad suggests (Br. 44) that "other" techniques were also required—but it has never identified, either here or below, those techniques. There are no such "other" techniques: Broad's successful experiments, like those performed by the five other groups, used only the conventional techniques identified by UC. Broad's argument that researchers did not *know* in advance that those techniques would work falls far short of proving that the eukaryotic application was not obvious *despite* the PTAB's finding that only conventional techniques were necessary. Broad nowhere identifies any nonobvious selection among conventional techniques or any other ingenuity—because none was necessary. Broad's argument thus reduces to the proposition that researchers lacked ex ante certainty. But such certainty would be impossible, and does not vitiate the expectation of success arising from the prior successful uses of those routine techniques.

Second, the six instances of simultaneous invention are powerful objective real-world evidence confirming that Broad's purported invention was merely an incremental step—one that many others achieved in the "ordinary course." *KSR*, 550 U.S. at 419. That is compelling evidence of what skilled artisans actually expected—and did—in applying CRISPR-Cas9 in eukaryotes.

Third, the prior art as a whole showed that multiple prokaryotic systems in the prior art—protein-only, RNA-only, and protein-RNA systems—had successfully functioned in eukaryotes. Appx00033-00035, Appx05031-05037. Although Broad identified specialized measures that were necessary with certain prokaryotic systems—discussed further below—those purported obstacles had been overcome years earlier. Those solutions provided additional guidance for applying prokaryotic systems in eukaryotes.

This evidence demonstrates that a skilled artisan considering UC's claims in light of the prior art would have had a reasonable expectation of success—indeed, the research groups who immediately designed experiments using conventional techniques and guidance provided by Jinek 2012 acted on precisely that expectation. Broad itself confirms the obviousness of its claims, as it does not contend that it needed to overcome any obstacles arising from the eukaryotic environment, or that any problem-solving or innovation was necessary. Appx05257-05263, Appx05266-

05267. Broad simply did what Jinek 2012 and the prior art suggested. It thus did not make any inventive contribution.

C. The evidence on which Broad relies does not provide substantial evidence for the PTAB's decision.

The evidence upon which Broad relies (Br. 35-50) does not constitute substantial evidence supporting the PTAB's decision. That is so whether one considers it in isolation as Broad improperly seeks to do, or considers it in light of the record as a whole as is required.

1. Dr. Doudna's and Dr. Carroll's statements do not speak to the question of obviousness.

The PTAB gave the statements on which Broad relies so heavily near-dispositive weight only because it applied an erroneous legal standard that sought affirmative expressions of virtual certainty and specific instructions in the prior art. Under the correct standard, the PTAB could not have discounted prior-art guidance based solely on what it viewed as expressions of pre-experimentation uncertainty. *See* Part I.B, *supra*. Broad has identified no case treating post-hoc inventor statements as near-dispositive evidence of nonobviousness. The one opinion on which Broad relies is a *dissent*. Br. 36 (citing *NantKwest, Inc. v. Lee*, 686 Fed. App'x 864, 875 (Fed. Cir. 2017) (Stoll, J., dissenting)).

Broad first relies on statements by Dr. Doudna, one of the four UC inventors, that the inventors saw a "promising" and "very real possibility" that CRISPR-Cas9

would function in eukaryotes. Br. 35; Appx00014-00015. That the PTAB viewed such statements as "positive"—in a field inherently requiring experimentation—yet failing to show a reasonable expectation of success demonstrates how gravely the PTAB misunderstood that standard as requiring near-certainty. It also shows that the PTAB, by requiring "statements that the system was 'expected' to work," effectively shifted the burden to UC to prove the near-certainty that the PTAB sought. Appx00023. But Broad bore the burden of proof, 37 C.F.R. § 41.208(b), and therefore had to show that skilled artisans *lacked* a reasonable expectation of success. Statements that the PTAB merely viewed as insufficiently affirmative to demonstrate an expectation of success do not satisfy that burden.[4]

Likewise unavailing is Broad's reliance (Br. 38-40) on Dr. Carroll's article observing that there was "no guarantee that Cas9 w[ould] work effectively" in eukaryotic cells and that "attempts to apply the system in eukaryotes" were "well worth a try" and necessary. Appx04797. All of Dr. Carroll's supposed concerns simply contributed to his conclusion that there was "no guarantee" that CRISPR-Cas9

[4] Broad also mischaracterizes some statements, arguing that Dr. Doudna asserted that applying CRISPR-Cas9 in eukaryotes represented a "huge bottleneck," when the context indicates that she was discussing the time-consuming, expensive nature of *previous* gene-targeting techniques and describing how CRISPR-Cas9, by contrast, can be used by "essentially anybody." Appx05911.

would function "effectively" in eukaryotes—an unremarkable conclusion about the need for experimentation or optimization. None of those concerns dissuaded him from correctly predicting how CRISPR-Cas9 could be implemented in eukaryotes, or providing detailed instructions on using the standard techniques that could be—and were—used. *Id.* Like the Doudna statements, this article does not speak to obviousness, and certainly does not show that Broad's claims were nonobvious.

2. Broad's evidence that adapting prokaryotic systems to work in eukaryotes required experimentation does not speak to obviousness.

Broad's final attempt to defend the PTAB's decision rests on differences between prokaryotic and eukaryotic environments (Br. 43-46) and the challenges allegedly experienced when implementing prior-art prokaryotic systems in eukaryotes (Br. 47-50). This attempt fares no better.

As an initial matter, Broad's argument misleadingly suggests that Broad's burden is to show a patentable distinction between CRISPR-Cas9 in a eukaryotic environment and CRISPR-Cas9 in a prokaryotic environment. As noted above, however, UC's genus claims cover *all* cells and environments, and UC's application describes implementing CRISPR-Cas9 in eukaryotes. *E.g.*, Appx00786, Appx00807, Appx00812-00813. Broad therefore must show a patentable distinction between claims directed to CRISPR-Cas9 in a eukaryotic environment and claims directed to CRISPR-Cas9 regardless of environment.

The differences between prokaryotic and eukaryotic environments concerning DNA packaging, protein folding, and CRISPR-Cas9 stability upon which Broad relies do not suffice. *Cf. Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1379 (Fed. Cir. 2014) (species may be patentable over genus "if the species manifests unexpected properties or produces unexpected results"). Broad describes (Br. 43) these differences as raising "questions" that could not be answered "absent experiments" in eukaryotic cells. To be sure, there would be no *certainty* until researchers performed experiments demonstrating that CRISPR-Cas9 would cleave DNA in eukaryotes. But such pre-experimentation lack of certainty does not render a purported advance nonobvious, particularly if obtaining confirmation required only applying prior-art techniques according to their established functions. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1349-50 (Fed. Cir. 2009); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014); *Procter & Gamble Co. v. Teva Pharm. USA, Inc*., 566 F.3d 989, 996 (Fed. Cir. 2009); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007); *O'Farrell*, 853 F.2d at 903-04. And the "variables that would need to be identified" that Broad hypothesizes (Br. 44) would not suggest nonobviousness unless the prior art gave "*no* direction as to which of many possible choices is likely to be successful." *Kubin*, 561 F.3d at 1359 (emphasis added). Here, of course, the prior art provided established techniques of introducing prokaryotic systems into eukaryotes, and researchers immediately

demonstrated their confidence in those techniques by designing experiments using only those techniques.

Nor does the PTAB's decision find support in Broad's analogies to scientists' efforts to implement riboswitch, ribozyme, and Group II intron systems in eukaryotes. Scientists had long since overcome such obstacles to employing these systems in eukaryotes, and that guidance had become part of the prior art. Appx00037-00039. Thus, although the PTAB observed that the systems "require[d] a unique set of conditions" to function in eukaryotes, Appx00039, the PTAB did not explain why that observation, in light of the prior art *as a whole*, would have led a skilled artisan to conclude that CRISPR-Cas9 would require unique conditions that would impede success. The uniform record of success in employing prokaryotic systems in eukaryotes, and the existence of previously successful conventional techniques, powerfully indicated otherwise.

IV. The PTAB used a December 12, 2012 prior art cut-off date without finding that Broad was entitled to that date.

The PTAB erred in assuming a December 12, 2012 effective filing date for Broad's claims, after having accorded neither party benefit of applications filed before their respective nonprovisional applications. The PTAB improperly excused Broad's burden to establish and overcome post-December 2012 art, and ignored additional art that clearly rendered Broad's claims obvious.

Broad's contention that UC forfeited this argument is incorrect. UC noted below that Broad had "made no showing" of entitlement to the December 2012 filing date. Appx00238.

Broad wrongly suggests that the PTAB's error was harmless because UC did not rely on post-December 2012 prior art. UC argued both that pre- and post-December 2012 art rendered Broad's claims obvious, and that, post-December 2012 art aside, pre-December 2012 art still rendered Broad's claims obvious. Appx00238-00240. UC made both arguments because it could not know which date the PTAB would select as the cut-off. The declaration of interference accorded Broad benefit only of its October 2013 nonprovisional filing date. But simultaneously with the no-interference-in-fact motion, Broad sought benefit of its December 2012 provisional application. In the interference-in-fact briefing, therefore, UC argued—correctly—that Broad had not established a prior art cut-off date of December 2012 for its claims, while also arguing that pre-December 2012 prior art rendered Broad's claims obvious.

That UC deemed the pre-December 2012 prior art *sufficient* to render Broad's claims obvious does not mean that UC considered later art irrelevant. As UC argued, using the presumptive October 2013 filing date, the teachings and eukaryotic examples in UC's '859 Application, filed in March 2013 and published in 2014 (Publication No. 2014/0068797), as well as the other groups' articles, published by January 2013, constituted section 102(e) and section 102(a) (prior printed publication)

prior art, respectively. Appx00240, Appx00288-00289.[5] The PTAB thus erred in failing to require Broad to demonstrate its effective filing date. As of the presumed October 2013 date, Broad's claims were clearly obvious.

V. Broad's jurisdictional contentions are meritless.

In passing, Broad argues (Br. 1-2) that UC lacks standing and that the PTAB proceedings were unconstitutional. Those arguments are meritless.

UC has standing. UC provoked this interference because Broad's patents and application claim exclusive rights to subject matter that UC invented first and should possess instead. That injury is concrete and particularized. *Phigenix, Inc. v. Immunogen, Inc.*, 845 F.3d 1168 (Fed. Cir. 2017), is inapposite because it concerned inter partes reviews, which may be brought by persons whose interests are not affected by the patent. 35 U.S.C. § 311(a). Interferences, by contrast, entail conflicting claims on both sides. UC therefore has a concrete interest in its rights in CRISPR-Cas9 that, absent the PTAB's erroneous decision, would have been resolved in the interference—and thus it has a concrete interest here.

The Supreme Court will not address the constitutionality of interferences in *Oil States Energy Services v. Greene's Energy Group* (No. 16-712), because the only question presented there concerns the constitutionality of inter partes review. *Granted*

[5] As noted at p. 21, Broad did not properly antedate these references.

Cases, https://www.supremecourt.gov/qp/16-00712qp.pdf. Moreover, Broad forfeited any constitutional challenge by failing to present it below.

Conclusion

For the foregoing reasons, the PTAB's judgment should be reversed, and the case remanded for further proceedings.

Respectfully submitted,

Dated: November 22, 2017

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CERTIFICATE OF SERVICE

I hereby certify that on November 22, 2017, I caused the foregoing brief to be filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit through the Court's CM/ECF system and served on counsel of record who have registered for such service.

/s/ Donald B. Verrilli, Jr.
DONALD B. VERRILLI, JR.

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because it contains 6,999 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

Dated: November 22, 2017

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