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Filed: February 15, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE,
(Patents 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641 and Application 14/704,551),

Junior Party,

v.

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, and EMMANUELLE CHARPENTIER
(Application 13/842,859),

Senior Party.

Patent Interference No. 106,048 (DK)

DECISION ON MOTIONS

37 C.F.R. § 41.125(a)

Before RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

Per curiam.

I. Summary

Broad has persuaded us that the parties claim patentably distinct subject matter, rebutting the presumption created by declaration of this interference. Broad provided sufficient evidence to show that its claims, which are all limited to CRISPR-Cas9 systems in a eukaryotic environment, are not drawn to the same invention as UC's claims, which are all directed to CRISPR-Cas9 systems not restricted to any environment. Specifically, the evidence shows that the invention of such systems in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or *in vitro*, because one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment. This evidence shows that the parties' claims do not interfere. Accordingly, we terminate the interference.

II. Introduction

A.

A CRISPR-Cas9[1] system is a combination of protein and ribonucleic acid ("RNA") that can alter the genetic sequence of an organism. In their natural environment, CRISPR-Cas systems protect bacteria against infection by viruses. (Simons Decl., Exh. 2001, at ¶ 2.1; Greider Decl., Exh. 1022, at ¶ 51.) The

[1] "CRISPR-Cas" is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) system. (*See* UC involved application 13/842,859, Exh. 1001, at ¶ 4; Broad involved patent 8,697,359, Exh. 1007, at 1:45-46.)

CRISPR-Cas9 system is now being developed as a powerful tool to modify specific deoxyribonucleic acid ("DNA") in the genomes of other organisms, from plants to animals. "With CRISPR, scientists can create mouse models of human diseases much more quickly than before, study individual genes much faster, and easily change multiple genes in cells at once to study their interactions." (Pennisi, Exh. 2231[2], at 834.)

Both parties claim CRISPR-Cas9 systems and methods of using them, though none of their claims are identical. Senior Party, the Regents of the University of California, University of Vienna, and Emmanuelle Charpentier (collectively "UC"), suggested this interference between its involved application and multiple patents issued to Senior Party, the Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College (collectively "Broad"). (*See* Application 13/842,859, Suggestion for Interference Pursuant to 37 C.F.R. § 41.202, filed 13 April 2015; *see* Appendix.) The interference was declared based in part on the representations made by UC during *ex parte* prosecution of its involved application.

When the interference was declared, all of the claims of UC's involved application and all of the claims of each of Broad's involved patents were designated as corresponding to Count 1, the single count of the interference. (*See* Declaration, Paper 1.) The interference was later redeclared to add Broad application 14/704,551, which was found by the examiner to contain allowable

[2] Pennisi, 341 Science 833-836 (2013) (Exh. 2231).

subject matter after the declaration of this interference. (Redeclaration, Paper 32; *see* Order Authorizing Motions and Setting Times, Paper 33, at 13:9-12.)

B.

Both parties rely on the opinion testimony of witnesses with experience in the field of their inventions – molecular biology.

Broad presents Paul Simons, Ph.D., as a witness in its motions. Dr. Simons is a Reader in Experimental Genetics and Molecular Medicine with tenure at the University College of London. (*See* Declaration of Technical Expert Paul Simons in Support of Broad et al. ("Simons Decl."), Exh. 2001, at ¶ 1.3.) Dr. Simons testifies that he has 35 years of research experience in the development of genetic manipulation methods and has published many research papers in peer reviewed journals. (*Id.*; *see also* Curriculum Vitae, Exh. 2002.) We find Dr. Simons to be qualified to provide opinion testimony on the subject matter of this interference.

UC relies on the testimony of two witnesses, Carol Greider, Ph.D. (*see., e.g.,* Second Declaration of Carol Greider, Ph.D. ("Greider Decl."), Exh. 1534) and Dana Carroll, Ph.D. (*see., e.g.,* Second Declaration of Dana Carroll, Ph.D. ("Carroll Decl."), Exh. 1535). We note that much of the direct testimony of Drs. Greider and Carroll is substantially identical.

Dr. Greider testifies that she is a Professor of Molecular Biology and Genetics and Professor of Oncology, Daniel Nathans Professor and Director in the Department of Molecular Biology & Genetics and Bloomberg Distinguished Professor in the Department of Biology at The Johns Hopkins University School of Medicine. (Declaration of Carol Greider, Ph.D., Exh. 1022, at ¶ 15.) She testifies that since 1990 she has directed research focused on biochemistry and molecular

and cell biology, has published many peer-reviewed articles on her research, and has been invited to author reviews and book chapters on those topics. (*Id.* at ¶¶ 16 and 24.) We find Dr. Greider to be qualified to provide opinion testimony on the subject matter of this interference.

Dr. Carroll testifies that he is a Distinguished Professor of Biochemistry at the University of Utah School of Medicine. (Declaration of Dana Carroll, Ph.D., Exh. 1024, at ¶ 15.) He testifies that he has authored many original peer-reviewed publications on his research in the fields of biochemistry, molecular biology, genetics, and genome editing, as well as invited reviews and book chapters on those topics. (*Id.* at ¶ 18.) We find Dr. Carroll to be qualified to provide opinion testimony on the subject matter of this interference.

C.

The Type II[3] CRISPR-Cas system comprises three components: (1) a crRNA molecule, which is called a "guide sequence" in Broad's claims[4] and a "targeter-RNA" in UC's claims, (2) a "tracr RNA," which is called an "activator-RNA" in UC's claims, (3) and a protein called Cas9. (Simons Decl., Exh. 2001, at ¶ 2.9; Greider Decl., Exh. 1022, at ¶ 50.) To alter a DNA molecule, the system must achieve three interactions: (1) crRNA binding by specific base pairing to a specific sequence in the DNA of interest ("target DNA"), (2) crRNA binding by specific

[3] Type I and Type III CRISPR-Cas systems were also known to be present in bacteria, but these other systems use different molecular mechanisms for nucleic acid cleavage. (Greider Decl., Exh. 1022, ¶ 49.)

[4] Some of Broad's claims recite a "guide RNA." Broad's patents explain: "The invention comprehends the guide RNAs comprising a guide sequence fused to a tracr sequence." Broad patent 8,697,359, Exh. 1007, at 2:53-54.

base pairing at another sequence to a tracr RNA, and (3) tracr RNA interacting with a Cas9 protein, which then cuts the target DNA at the specific site. These interactions are depicted in Figure 5A of Jinek 2012[5] (Exh. 1155), which is reproduced below.

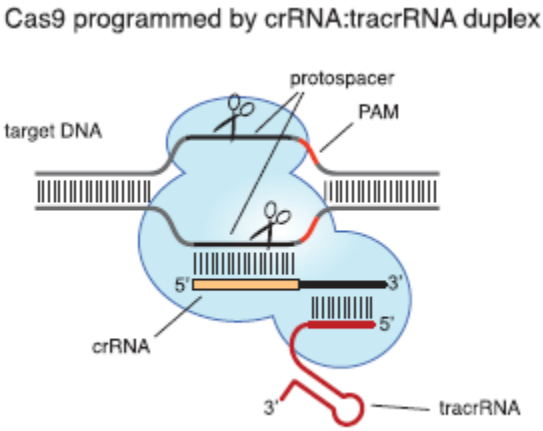

Figure 5A depicts a double-stranded target DNA sequence that is bound to a crRNA (as indicated by the vertical black lines showing nucleic acid base pairing). A different part of the crRNA is bound to a tracrRNA. The tracrRNA interacts with a Cas9 protein that cuts the target DNA in a site-specific matter. By linking a DNA-cutting enzyme to a specific site on the target DNA, the CRISPR-Cas9 system achieves specific, targeted manipulation of DNA.

The CRISPR-Cas9 system occurs naturally in bacteria, which are in the category of living organisms called "prokaryotes." CRISPR-Cas9 is not known to occur naturally in the category of living things that includes plants and animals –

[5] Jinek *et al.*, 337 SCIENCE 816-21 (2012) (Exh. 1155).

the "eukaryotes." (*See* Declaration of Carol Greider, Ph.D., Exh. 1022, at ¶ 51; Simons Decl., Exh. 2001, at ¶ 2.1.)

D.

Several motions authorized for this phase of the interference are before us. Motions for priority of invention have not yet been authorized.

Broad filed a motion arguing that the interference should not have been declared because there is no interference-in-fact between the parties' claims. (*See* Broad Motion 2, Paper 77.) Broad also filed a motion to argue that even if some of the parties' claims interfere, other Broad claims do not correspond to Count 1 because they are not anticipated or rendered obvious by it. (Broad Motion 5, Paper 67.)

Both parties claim the benefit of earlier filed applications and have filed motions to be accorded these earlier filing dates as constructive reductions to practice of Count 1. (*See* Broad Motion 3, Paper 66, and UC Motion 4, Paper 57.)

UC filed a motion arguing that Count 1 should be replaced by Proposed Count 2. (UC Motion 3, Paper 56.) Broad filed a motion responsive to UC Motion 3, arguing that if Count 1 is replaced by Proposed Count 2, Broad should be accorded the benefit of the filing date of its earlier filed applications as to the new count. (Broad Motion 6, Paper 570.)

The parties each also filed motions to exclude evidence of the other. (*See* Broad Miscellaneous Motion 8, Paper 878; UC Miscellaneous Motion 5, Paper 880.)

Broad was authorized to file a motion arguing that UC does not have written description support for its claims under 35 U.S.C. § 112. Broad elected not to file that motion. (*See* Paper 565.)

We use our discretion to take up these motions in the order that secures the just, speedy, and inexpensive determination of this proceeding. *See* 37 C.F.R. § 41.125(a) ("The Board may take up motions for decisions in any order, may grant, deny, or dismiss any motion, and may take such other action appropriate to secure the just, speedy, and inexpensive determination of the proceeding.").

III. Broad Motion 2 – No Interference-in-Fact

We first consider Broad Motion 2, which argues that there is no interference-in-fact, because it will determine if the interference should have been declared and if it should continue. An interference determines whether claims are patentable under 35 U.S.C. § 102(g)[6], wherein "[a] person shall be entitled to a patent unless . . . during the course of an interference . . . . another inventor involved therein establishes . . . that before such person's invention thereof the invention was made by such other inventor. . . ." Thus, if two parties claim patentably indistinct subject matter, a patent can be awarded to only the first inventor under 35 U.S.C. § 102(g).

Whether an interference occurs is determined by comparing the parties' involved claims. *See Noelle v. Lederman*, 355 F.3d 1343, 1352 (Fed. Cir. 2004)

[6] Interferences continue under the statutes that were in effect on March 15, 2013. *See* Pub. L. 112-29, § 3(n), 125 Stat. 284, 293 (2011).

("if the Board is to compare two inventions [in a determination of interference-in-fact], the Board must only compare the parties' claims.") To make this comparison, we use a "two-way test" wherein "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). *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003) (holding that the Board committed no error in interpreting its own rule to apply the "two-way test" when determining if an interference-in-fact existed between junior party's genus claims and senior party's claims to a species within that genus); *see also Noelle*, 355 F.3d at 1350–51 ("In order to determine whether the two parties claim the same patentable invention, the USPTO has promulgated a "two-way" test, which has been approved by this court.").

In this proceeding, to prevail on its argument that there is no interference, Broad must show that the parties' claims do *not* meet at least one of the following two conditions:

1) that, if considered to be prior art to UC's claims, Broad's involved claims would not anticipate or render obvious UC's involved claims, or

2) that, if considered to be prior art to Broad's claims, UC's involved claims would not anticipate or render obvious Broad's claims.

Broad will prevail and a determination of no interference-in-fact will be made if a preponderance of the evidence indicates one of these conditions is not met. *See Yorkey v. Diab*, 605 F.3d 1297, 1300 (Fed. Cir. 2010) (no interference-in-fact must be shown by a preponderance of the evidence); *see* 37 C.F.R. § 41.208(b) ("To be sufficient, a motion must provide a showing, supported with appropriate evidence,

such that, if unrebutted, it would justify the relief sought. The burden of proof is on the movant.").

Broad's argument is that the second of these conditions is not met, wherein UC's claims would not anticipate or render obvious Broad's claims if UC's claims were considered to be prior art.

A.

For the purposes of evaluating the arguments relating to Broad's Motion 1, the following claims are representative. Claim 165 of UC's involved '859 application recites:

> A method of cleaving a nucleic acid comprising
> 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
> a) a Cas9 protein; and
> b) a single molecule DNA-targeting RNA comprising
> i) a targeter-RNA that hybridizes with the target sequence, and
> 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.

(Senior Party Clean Copy of Claims, Paper 12, at 2.) UC also has claims drawn to

CRISPR-Cas9 systems. None of UC's claims are limited to any particular environment.

Claim 1 of Broad's involved patent 8,697,359 recites:

> 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:
>
> 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,
>
> 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.

(Replacement Broad Clean Copies of Claims, Paper 17, at 3 (emphasis added).) Like UC, Broad also has claims to CRISPR-Cas systems that are involved in this interference. Unlike UC's claims, all of Broad's claims are limited to the method or system being used in eukaryotic cells.

B.

"Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently." *Atofina v. Great Lakes Chem.*

Corp., 441 F.3d 991, 999 (Fed. Cir. 2006). UC admits that if treated as prior art, none of its involved claims anticipate Broad's involved claims. (UC Opp. 2, Paper 652, at App'x 2-2, admitting Broad Statement of Material Fact 7.) We agree because none of UC's claims recite a limitation to a eukaryotic environment and each of Broad's claims contains this limitation. Thus, to prevail on its argument of no interference-in-fact, Broad need only provide persuasive argument supported by a preponderance of the evidence that UC's claims would not render Broad's claims obvious if UC's claims are considered to be prior art to Broad's claims.

C.

To determine obviousness, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." G*raham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). In our analysis we assume that UC's claimed CRISPR-Cas9 system in a generic environment is the "prior art." This subject matter is compared to Broad's narrower claimed eukaryotic cell environment. We ascertain the level of ordinary skill in the art by examining the evidence cited by the parties, as discussed below.

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Although the definition of "reasonable expectation" is somewhat vague, the case law makes clear that a *certainty* of success is not required. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165–66 (Fed. Cir. 2006), *citing In re O'Farrell*, 853

F.2d 894, 903–04 (Fed.Cir.1988) ("Obviousness does not require absolute predictability of success . . . [A]ll that is required is a reasonable expectation of success."). The question of whether there would have been a reasonable expectation of success is a question of fact. *See Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed.Cir.2014).

1.

Broad argues that UC's involved claims would not render Broad's involved claims obvious, either alone or in view of the available prior art, because a skilled artisan would not have had a reasonable expectation that the CRISPR-Cas9 system would work successfully in a eukaryotic cell. (Broad Motion 2, Paper 77, at 2:13-16.) Broad's argument is based in part on evidence of the contemporaneous statements made by those in the art at the time CRISPR-Cas9 was shown to work outside of a prokaryotic environment.

To make its argument, Broad acknowledges that the UC inventors published results in Jinek 2012 using the prokaryotic CRISPR-Cas9 system *in vitro*, that is, in a non-cellular experimental environment, before Broad filed its claims directed to the eukaryotic cell environment. (Broad Motion 2, Paper 77, at 3:15-4:2, citing Jinek 2012, Exh. 1155.) Jinek 2012 demonstrates that isolated components of the CRISPR-Cas9 system worked to contact and cleave a DNA target in an *in vitro* system. (Jinek 2012, Exh. 1155, at abstract.) It is undisputed that Jinek 2012 does not report the results of experiments using the CRISPR-Cas9 system in a eukaryotic cell. Broad's argument is that the statements by those in the field made contemporaneously to Jinek 2012 show that after it was known CRISPR-Cas9 is active in a non-eukaryotic, *in vitro* environment, ordinarily skilled artisans did not

have a reasonable expectation that it would also work in eukaryotic cells. (Broad Motion 2, Paper 77, at 4:3-11.)

We pay particular attention to the statements made contemporaneously to Jinek 2012 because where such statements conflict with testimony prepared for litigation, contemporaneous statements have been considered to be stronger evidence of a particular situation. *See United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395–96 (1948) (determining that oral testimony in conflict with contemporaneous documentary evidence deserves little weight in a litigation regarding price fixing of patented products); *see also Cucuras v. Sec'y of Dep't of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993) (holding no error by the trial court or special master when greater weight was accorded to contemporaneous medical records than to later, conflicting oral testimony). Accordingly, we give significant weight to the statements by those in the art at the time of Jinek 2012 regarding expectation of success in using a CRISPR-Cas9 system in eukaryotic cells.

Broad cites to statements written by UC inventors Jinek and Doudna that although their findings in Jinek 2012 suggested the "exciting possibility" that CRISPR-Cas9 complexes might constitute a simple and versatile RNA-directed system for site-specific genome editing, "it was not known whether such a bacterial system would function in eukaryotic cells." (Exh. 1057[7], at 1-2; *see* Broad Motion 2, Paper 77, at 4:3-8.)

[7] Jinek et al. 2 eLIFE e00471 (2013), DOI: 10.7554/eLife.00471 (Exh. 1057).

Broad also cites to statements reportedly made by UC inventor Doudna after Jinek 2012 that the publication "was a big success, but there was a problem. We weren't sure if CRISPR/Cas9 would work in eukaryotes—plant and animal cells." (Exh. 2207[8], at 3; *see* Broad Motion 2, paper 77, at 4:8-11.) In another report, Doudna was quoted as stating that she had experienced "many frustrations" getting CRISPR to work in human cells and that she knew that if she succeeded, CRISPR would be "a profound discovery." (Exh. 2230[9], at 3; *see* Broad Motion 2, Paper 77, at 8:1-4.)

Broad cites to other statements attributed to Dr. Doudna regarding the difficulties of genetic modification techniques in eukaryotes. (Broad Motion 2, Paper 77, at 9:5-22.) One author quoted Dr. Doudna as saying: "The ability to modify specific elements of an organism's genes has been essential to advance our understanding of biology, including human health. . . . However, the techniques for making these modifications in animals and humans have been a huge bottleneck in both research and the development of human therapeutics." (Sanders[10], Exh. 2259, at 2.) According to Broad, the contemporaneous statements of the UC inventors demonstrate that one of ordinary skill in the art lacked a reasonable expectation of success. (Broad Motion 2, Paper 77, at 4:14-17.)

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[8] 9 Catalyst Magazine 1-32, College of Chemistry, University of California, Berkeley (2014) (available at http://catalyst.berkeley.edu/slideshow/the-crispr-revolution/) (Exh. 2207).

[9] Pandika, OZY (2014) (http://www.ozy.com/rising-stars/jennifer-doudna-crispr-code-killer/4690) (Exh. 2230).

[10] Sanders, Berkeley News (2013) (http://news.berkeley.edu/2013/01/07/ cheap-and-easy-technique-to-snip-dna-could-revolutionize-gene-therapy/) (Exh. 2259).

In opposition to Broad's arguments, UC attempts to characterize these statements as demonstrating the UC inventors "fully expected that the system could be successfully used in eukaryotic cells" and that the inventors were simply indicating that the confirmatory experimental results had not yet been reported. (UC Opp. 2, Paper 652, at 27:6-28:13, citing Greider Decl., Exh. 1534, ¶¶ 30, 35-36, and 68-70, and Carroll Decl., Exh. 1535, ¶¶ 30, 35-36, and 68-70.)

UC also argues that Jinek 2012 itself provided an expectation of success using the CRISPR-Cas9 system in eukaryotic cells because it predicted "the potential to exploit the system for RNA-programmable genome editing." (Jinek 2012, Exh. 1155, at abstract.) UC cites to a similar statement in Jinek 2012 that the results reported therein "rais[e] the exciting possibility of developing a simple and versatile RNA-directed system to generate dsDNA breaks for genome targeting and editing." (*Id.* at 816; *see* UC Opp. 2, Paper 652, at 8:9-22.) The UC inventors conclude Jinek 2012 by stating:

> Zinc-finger nucleases and transcription-activator–like effector nucleases have attracted considerable interest as artificial enzymes engineered to manipulate genomes. . . . We propose an alternative methodology based on RNA-programmed Cas9 that could offer considerable potential for gene-targeting and genome-editing applications.

(Jinek 2012, Exh. 1155, at 820 (citations omitted).) UC argues that because zinc-finger nucleases (ZFNs) and transcription-activator-like enzymes (TALENs) were the state of the art for DNA cleavage and genome editing in eukaryotic cells at the time, these statements in Jinek 2012 would have been understood to be an explicit

proposal to use Type II- CRISPR-Cas system for eukaryotic gene editing. (UC Opp. 2, Paper 652, at 8:16-9:3.)

We agree with Broad that the statements by and attributed to the UC inventors do not demonstrate a reasonable expectation of success. Although the statements express an eagerness to learn the results of experiments in eukaryotic cells and the importance of such results, none of them express an expectation that such results would be successful. The contemporaneous commentary by the UC inventors cited by Broad do not indicate that at the time of Jinek 2012 the ordinarily skilled artisan would have reasonably expected the CRISPR-Cas9 system to work in eukaryotic cells.

UC also argues that the selected quotations from inventors Doudna and Jinek are irrelevant because determination of interference-in-fact is from the viewpoint of a person of ordinary skill, not an inventor. (UC Opp. 2, Paper 652, at 27:12-14.) Although this may be true, UC's argument only tends to persuade us more because if the inventors themselves were uncertain, it seems that ordinarily skilled artisans would have been even more uncertain.

To further support its argument of the lack of an expectation of success, Broad cites to statements made by Dr. Carroll, UC's witness in this interference, to demonstrate that those of skill in the art had doubts about using CRISPR-Cas9 in eukaryotic cells. (Broad Motion 2, Paper 77, at 5:4-25.) Dr. Carroll wrote:

> What about activity of the system in eukaryotic cells? Both zinc fingers and TALE modules come from natural transcription factors that bind their targets in a chromatin context. This is not true of the CRISPR components. There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA–RNA

> hybrid can be stabilized in that context. This structure may be a substrate for RNA hydrolysis by ribonuclease H and/or *FEN1*, both of which function in the removal of RNA primers during DNA replication. Only attempts to apply the system in eukaryotes will address these concerns.

(Carroll[11], Exh. 1152, at 1660.) Dr. Carroll also raised technical questions about whether CRISPR-Cas9 could be used successfully in eukaryotic cells in the same commentary. Dr. Carroll discussed ways to potentially enhance the activity of CRISPR cleavage in eukaryotic cells, while cautioning about the risk of undesirable side effects. (*Id.*) Dr. Carroll concluded:

> Gene editing through base pairing has been attempted many times and is still being pursued. The efficiency of modification by introduction of simple oligonucleotides, chemically modified oligos, or oligo mimics such as peptide nucleic acids remains discouragingly low in most cases. Triplex-forming oligonucleotides have shown activity, but with a limited range of targets and less efficiency than ZFN or TALEN cleavage. Whether the CRISPR system will provide the next-next generation of targetable cleavage reagents remains to be seen, but it is clearly well worth a try. Stay tuned.

(*Id.* (citations omitted).) Although Dr. Carroll indicated there was reason to try using the CRISPR system in eukaryotic cells, we do not discern any expectation that it would work before results of the actual studies were known.

UC argues that Dr. Carroll's statements were discussed by Broad out of context. (UC Opp. 2, Paper 652, at 14:6-15:6.) According to UC, Dr. Carroll's conclusion to "[s]tay tuned," indicates that he clearly recognized the obviousness

[11] Carroll, 20 MOLECULAR THERAPY 1658-60 (2012) (Exh. 1152).

of using the CRISPR-Cas9 system in eukaryotic cells, suggested doing so, and expected that it would be done. (UC Opp. 2, Paper 652, at 15:2-6.)

UC also cites to Dr. Carroll's and Dr. Greider's direct testimony in support of this interpretation. (*See* Greider Decl., Exh. 1534, ¶¶ 34-36 and Carroll Decl., Exh. 1535, ¶¶ 34-36.) When questioned about his contemporaneous commentary on cross-examination, Dr. Carroll explained that he was "expressing thoughts about what -- if the CRISPR-Cas system did not work in eukaryotic cells, what might be the -- the reasons." (Carroll Depo., Exh. 2012, 28:11-13).

After considering all of the evidence, we are persuaded that Dr. Carroll did not express an expectation that the CRISPR-Cas9 system could be used successfully in eukaryotic cells. Although we agree that Dr. Carroll expressed a suggestion and an expectation that the necessary experiments would be done, he did not state any expectation of what the results would be. Instead, Dr. Carroll pointed to differences between CRISPR-Cas9 and systems that work in eukaryotic cells (ZFNs and TALENs) and wrote: "There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA-RNA hybrid can be stabilized in that context." (Carroll, Exh. 1152, at 1660.) We fail to see how "no guarantee" indicates an expectation of success. Although there need not be absolute predictability for a conclusion of obviousness (*see In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985), at best, Dr. Carroll's statement highlights some specific reasons why the CRISPR-Cas9 system might fail in eukaryotes. Thus, the only conclusion we draw from Dr. Carroll's statement is that at the time, he did not have a reasonable expectation that the system would work.

To further oppose Broad's arguments, UC cites to other commentary that accompanied Jinek 2012 when it was published. (UC Opp. 2, Paper 652, at 9:3-24.) In one article the author stated:

> Jinek *et al*. realized that a highly specific, customizable RNA-directed DNA nuclease could be useful to edit whole genomes. Based on the 20-nucleotide guide section of the crRNA, the enzyme could theoretically introduce breaks at unique sites in any eukaryotic genome. As a proof of concept, the authors programmed Cas9 to cleave a plasmid carrying the gene encoding green fluorescent protein at predetermined loci using a single chimeric crRNA containing just the critical segment of the tracrRNA. DNA breaks induce cellular DNA repair pathways . . . and this can be harnessed to disrupt, insert, or repair specific genes of cells. Introducing DNA breaks at desired loci using just Cas9 and a chimeric crRNA would be a substantial improvement over existing gene-targeting technologies, such as zinc finger nucleases and transcription activator–like effector nucleases, as these require protein engineering for every new target locus . . . . Efficient gene repair strategies in cells from patients, and the reintroduction of repaired cells, could become increasingly important for treating many genetic disorders.

(Brouns[12], Exh. 1471, at 2 (citations omitted).) UC argues that because this commentary presents a prediction that the CRISPR-Cas9 system would be an important tool for treating genetic disorders, it demonstrates a contemporaneously expressed expectation of success. UC's witnesses, Drs. Greider and Carroll support this view, testifying that the statements in this commentary (Exh. 1471) and in Jinek 2012 would have given one of ordinary skill in the art a reasonable

[12] Brouns, 337 SCIENCE 808-09 (2012) (Exh. 1471).

expectation that the Type-II CRISPR-Cas system would cleave DNA in eukaryotic cells. (Greider Decl., Exh. 1534, ¶¶ 30-32 and Carroll Decl., Exh. 1535, ¶¶ 30-32.)

While we agree that Jinek 2012 proposed using the system of UC's involved claims in eukaryotic cells, we do not agree that, on their face, discussion of a "potential," a "possibility," or what Cas9 could "theoretically" do indicates that the system was expected to work in eukaryotic cells. Similarly, while the commentary accompanying Jinek 2012 discussed the potential for using the system in eukaryotic cells, we are not persuaded that the plain meaning of the language in the commentary would have provided those in the art with a reasonable expectation of success.

In addition, UC cites to a portion of a publication by Dr. Fei Ran, an inventor named on some of Broad patents, describing her thoughts while undertaking experiments of the CRISPR-Cas9 system in eukaryotes. (UC Opp. 2, Paper 652, at 13:5-15.) Dr. Ran recounted that "[w]e built upon these exciting discoveries [the identification of the CRISPR-Cas9 tracrRNA and use of a single RNA in an *in vitro* system from Dr. Charpentier's and Dr. Dounda's labs], *but at the same time, nobody knew if this was going to work in mammalian cells*." (Exh. 1561, at 73 (emphasis added).) Dr. Ran's full statement does not demonstrate a reasonable expectation of success. We acknowledge that Dr. Ran's reported statement was made as a reflection, not contemporaneously, but we also note that it was not made for the purposes of this proceeding and thus, we have no reason to doubt that it reflects her understanding at the time.

UC cites to other statements by those in the art regarding the results reported in Jinek 2012. In one commentary, the author observed that "[i]t was immediately

obvious that such a system might be repurposed for genome engineering, similar to ZFNs and TALENs." (Golic[13], Exh. 1473, at 304; *see* UC Opp. 2, Paper 652, at 15:18-21.) In another article, it was observed that UC inventor Doudna and her colleagues were in the process of gathering more details on how the RNA-guided cleavage reaction works and were testing whether the system would work in eukaryotic organisms. (Yarris[14], Exh. 1546, at 3; *see* UC Opp. 2, Paper 652, at 28:22-29:12.) Doudna was quoted as saying that "Although we've not yet demonstrated genome editing, given the mechanism we describe it is now a very real possibility." (Yarris, Exh. 1546, at 3.) Doudna also reportedly said: "Our results could provide genetic engineers with a new and promising alternative to artificial enzymes for gene targeting and genome editing in bacteria and other cell types." (*Id.*, at 1.)

We agree with UC that these are "positive, forward-looking" statements apparently published before the filing of Broad's earliest provisional application. (UC Opp. 2, Paper 652, at 28:22-29:12.) We do not agree, though, that as such they indicate Dr. Doudna or more importantly, the person having ordinary skill in the art, had a reasonable expectation of success that CRISPR-Cas9 would work in eukaryotic cells. Statements of a "possibility" that the system might work and that it "could" provide a "promising" alternative are not statements that it would be

[13] Golic, 195 GENETICS 303-308 (2013) (Exh. 1473).
[14] Yarris, NEWS CENTER, (2012) (http://newscenter.lbl.gov/2012/06/28/programmable-dna-scissors/) (Exh. 1546).

expected to do so. UC does not cite to statements that the system was "expected" to work or that it would "likely" work or other more definite language.

The contemporaneous statements cited by both parties persuade us that one of ordinary skill in the art would not have reasonably expected success before experiments in eukaryotic cells were done.

2.

According to UC, the alleged fact that many independent research groups were "immediately" able to use the CRISPR-Cas9 system in eukaryotic cells after publication of Jinek 2012 is evidence there was a reasonable expectation of success in doing so. (UC Opp. 2, Paper 652, at 30:10-21; *see also* 10:5-11:16.)

Regardless of how many groups achieved success in eukaryotic cells, we are not persuaded that such success indicates there was an *expectation* of success before the results from these experiments were known. The unpublished results of research groups are not necessarily an indication of whether ordinarily skilled artisans would have expected the results achieved. Instead of viewing such work as evidence of an expectation of success, we consider the number of groups who attempted to use CRISPR-Cas9 in eukaryotic cells to be evidence of the motivation to do so, an issue that is not in dispute. We agree with Broad's argument that a large reward might motivate persons to try an experiment even if the likelihood of success is very low. (*See* Broad Reply 2, Paper 866, at 6:6-7.) *See Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) ("The desire for that payoff could motivate pursuit of the method, but 'knowledge of the goal does not render its achievement obvious,' . . . ." (citing *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed.Cir.2008).).

UC argues that the research groups that were reportedly successful after publication of Jinek 2012 "could not have undertaken the use of UC's Type II CRISPR-Cas9 system in eukaryotic cells unless there was sufficient motivation and expectation of success." (UC Opp. 2, Paper 652, at 11:5-7; *see also* 11:15-16.) UC's witnesses Greider and Carroll testify that "the Doudna laboratory would not have pursued and succeeded had they had no reasonable expectation of success in moving the CRISPR-Cas9 complex into eukaryotic cells." (Greider Decl., Exh. 1534, ¶ 69; Carroll Decl., Exh. 1535, at ¶ 69; *see* UC Opp. 2, Paper 866, at 11:11-16.) UC also argues, citing to the cross-examination testimony of Broad's witness, that "[o]ne never does an experiment without the belief that it might work under certain circumstances." (UC Opp. 2, Paper 652, at 30:1-2 citing Simons Depo., Exh. 1555, at 178:10-12.)

We are not persuaded by these arguments or evidence that because research groups, including Dr. Doudna's, undertook experiments to determine if CRISPR-Cas9 could work in eukaryotic cells, an ordinarily skilled artisan would have necessarily expected these experiments to be successful. We are not persuaded that a scientist's "belief" in the success of his or her own experiments is necessarily a reasonable expectation of success that indicates obviousness. Were this true, the requirement for a reasonable expectation of success or predictability in the context of subject matter that would have been obvious to try would be rendered meaningless.

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007), the Court determined that

> [w]hen there is a design need or market pressure to solve a problem

> and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Thus, the "anticipated" success of a solution to a problem when there are "a finite number of identified, predictable solutions" may show that claimed subject matter would have been obvious. *See KSR,* 550 U.S. at 421. If we were to accept that success is reasonably expected for every experiment, under the framework provided in *KSR,* subject matter would always be obvious under 35 U.S.C. § 103 when there is a design need or market pressure to solve a problem, a finite number of solutions, and those of ordinary skill had the technical capability. Instead of creating a presumption of obviousness when researchers attempt experiments to advance a field, the Federal Circuit has recognized:

> The methodology of science and the advance of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each 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.

Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008). Thus, we look to the specific context of the art at the time.

3.

To determine if under the facts of this case there would have been an expectation of success in using CRISPR-Cas9 in eukaryotic cells, we compare the

specific evidence before us to the facts of the precedential case law. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) ("Undue dependence on mechanical application of a few maxims of law, such as 'obvious to try,' that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case."). For example, in *In re Droge*, 695 F.3d 1334, 1337-38 (Fed. Cir. 2012), a reasonable expectation of success of a method mediating sequence specific recombination of DNA in eukaryotic cells with a modified enzyme was found because the normal enzyme had previously been used to mediate similar recombination.

In *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009), a reasonable expectation of success of nucleic acids encoding a specific protein was found because the prior art taught the same protein and also a five-step protocol for cloning nucleic acid molecules encoding the protein.

In *Velander v. Garner*, 348 F.3d 1359, 1379 (Fed. Cir. 2003), a reasonable expectation of success for challenged claims directed to producing a particular protein in the milk of an animal was found because all of the elements were known in the prior art and it was known that several other proteins had been produced in a similar way.

In *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014), a reasonable expectation of success in the use of nanoparticle technology in formulation chemistry was found because that technology had become fairly reliable and had produced consistent results.

In *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166–67 (Fed. Cir. 2006), a reasonable expectation of success in optimizing a reaction was found because

there were not too many parameters to vary and the principle parameter, concentration of tertiary amine, was known. Furthermore, the prior art gave more than merely general guidance, indicating that low concentrations were best.

In *Pfizer*, a reasonable expectation of success was found because there was only one parameter to vary to obtain the specific salt of the drug claimed. (*Pfizer*, 480 F.3d at 1366.) In addition, one skilled in the art had several references available to use for direction and was capable of narrowing the possible salts previously approved to a small group from which to choose and verify by routine trial-and-error procedures. (*Id.* at 1367-68.)

In contrast, in *In re Rinehart*, 531 F.2d 1048, 1054 (CCPA 1976), a reasonable expectation of success was not found because the problem encountered by the claimed method of commercial scale production of polyesters was not the same problem addressed in the prior art and there was evidence that a combination of the prior art steps could not be commercially scaled up successfully.

In *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003), a reasonable expectation of success was not found for the claimed method of growing and isolating a particular virus with monkey cells because the prior art reported failure with other viruses isolated with monkey kidney cells.

In *Noelle v. Lederman*, 355 F.3d 1343, 1352–53 (Fed. Cir. 2004), a reasonable expectation of success was not found for a method of isolating human CD40CR antibodies using mouse CD40CR antibodies because expert witnesses testified to the unpredictability in the state of the art at the relevant time.

In *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08 (Fed. Cir. 1991), a reasonable expectation of success in claims to a specific protein was not found because none of the prior art references suggested that screening a human genomic library would be likely to succeed in pulling out the gene of interest and no one else had successfully used the technique for that purpose. Furthermore, patentee provided a witness who testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. (*Id.* at 1208.)

In *Institut Pasteur*, 738 F.3d at 1346, a reasonable expectation of success for claims to methods of site directed double-stranded break in chromosomal DNA with a "Group I intron" nuclease was not found because the prior art did not teach using the nuclease on chromosomal DNA within a yeast cell and because the Board failed to given proper weight to prior art teaching toxic effects of the nuclease in cells.

These cases instruct us that whether or not one of ordinary skill in the art would have had a reasonable expectation of success for the purposes of determining obviousness depends on the specific nature of what was known from the prior art about closely related subject matter. Specific 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. The availability of only generalized instructions and evidence of failures with similar subject matter have indicated the opposite. Thus, we look to whether or not there were instructions in the prior art that would be specifically relevant to CRISPR-Cas9 and would instruct those of ordinary skill how to achieve activity with that system

in eukaryotic cells. We also look to whether there are examples in the prior art of the success or failure of similar systems.

4.

Broad argues that Dr. Simons reviewed the relevant prior art and found no basis for a person of ordinary skill to have had a reasonable expectation of successfully using CRISPR-Cas9 in eukaryotic cells. (Broad Motion 2, Paper 77, at 19:14-16, citing Simons Decl., Exh. 2001, ¶¶ 2.10-2.12.) Broad's witness, Dr. Simons, testifies:

> Prior to December 12, 2012, it was not known whether or not it would be possible to ensure appropriate ratios of Cas9 to guide RNA with appropriate timing and co-localization for complex formation and activity in a eukaryotic cell while minimizing or avoiding toxicity is an aspect of translating the CRISPR-Cas9 system to eukaryotic cells. The outcome could not be predicted from experiments in a biochemical system with purified components as in Jinek 2012. Thus, the skilled person had no reasonable expectation of success in ensuring a functional CRISPR-Cas9 system in eukaryotes.

(Simons Decl., Exh. 2001, at ¶ 6.26.) In addition, Broad points to specific evidence of prior work in the field. (Broad Motion 2, Paper 77, at 4:14-7:23 and 14:10-18:2.)

Broad cites to Dr. Simons's testimony to explain that ordinarily skilled artisans knew of several differences between prokaryotic and eukaryotic systems that would make use of CRISPR-Cas9 in a eukaryotic system unpredictable even though it was known to work endogenously in prokaryotes. (Broad Motion 2, Paper 77, at 6:4-7:23, citing Simons Decl., Exh. 2001, at ¶¶ 6.28; *see also* Broad Motion 2, Paper 77, at 15:14-16:2.) Dr. Simons explains that differences in gene

expression, protein folding, cellular compartmentalization, chromatin structure, cellular nucleases, intracellular temperature, intracellular ion concentrations, intracellular pH, and the types of molecules in prokaryotic versus eukaryotic cells, would contribute to this unpredictability. (Simons Decl., Exh. 2001, at ¶¶ 6.28.)

Dr. Simons explains in more detail that eukaryotic DNA is divided into chromosomes composed of chromatin – tightly packed structures of DNA bound to proteins called histones. (*See* Simons Decl., Exh. 2001, at ¶ 6.29.) In contrast to this tight packing, the DNA of prokaryotes exists as a single circle that is not structured as chromatin. (*Id.*) Dr. Simons also contrasts the tightly packed and structured chromatin of eukaryotes with the even simpler, naked plasmid DNA used in Jinek 2012. (*Id.*) According to Dr. Simons, a person of ordinary skill in the art at the time could not have been predicted Cas9 would be able to access the tightly packed eukaryotic genome from the prior art uses of CRISPR-Cas9 with more relaxed DNA. (*Id.*)

Broad argues further that it was known that differences in the cellular conditions between prokaryotes and eukaryotes could affect protein folding and could have prevented the CRISPR-Cas9 system from undergoing the conformational changes that allow it to work. (Broad Motion 2, Paper 77, at 15:14-16:2, citing Simons Decl., Exh. 2001, ¶¶ 6.13 and 6.33.) In support, Dr. Simons testifies that the prior art showed protein folding to be critical because it is inextricably linked to function, noting that in eukaryotes misfolded proteins may be degraded through a pathway not present in prokaryotes. (Simons Decl.,

Exh. 2001, ¶ 6.33, citing Goldberg[15], Exh. 2242 (*e.g.* "In eukaryotic cells, the large ATP-dependent proteolytic machine . . . prevents the accumulation of non-functional, potentially toxic proteins." (abstract).) Dr. Simons testifies that conditions such as temperature, pH, and ion (*e.g.* magnesium) concentration could affect protein folding. (*Id.* at ¶ 6.13.) According to Dr. Simons, because of these differences in prokaryotic and eukaryotic environments, skilled artisans would not have been able to predict with any reasonable certainty how the prokaryotic system would act in a eukaryotic cell. (*Id.*)

Broad argues further that the possible degradation of foreign RNA in eukaryotic cells would have presented one of ordinary skill in the art with another uncertainty about using the CRISPR-Cas9 system in eukaryotes. (Broad Motion 2, Paper 77, at 15:17-22, citing Simons Decl., Exh. 2001, at ¶ 6.15.) Broad argues that even more uncertainty existed because bacterial proteins and RNA can be toxic to eukaryotic cells. (Broad Motion 2, Paper 77, at 15:22-16:2, citing Simons Decl., Exh. 2001, at ¶ 6.60.) For example, Loonstra[16] (Exh. 2224), cited by Dr. Simons, teaches that the prokaryotic protein Cre can be toxic at high levels, requiring careful titration for gene modification in mammalian cells. (Loonstra, Exh. 2224, at abstract.)

In opposition to Broad's arguments, UC argues that one of ordinary skill in the art would not have considered any of the issues identified by Broad to be impediments for the Type-II CRISPR-Cas9 system in eukaryotic cells. (UC

[15] Goldberg, 426 NATURE 895 (2003).
[16] Loonstra, 98 PROC. NAT'L ACAD. SCI 9209 (2001).

Opp. 2, Paper 652, at 21:10-23:23, citing Greider Decl., Exh. 1534, at ¶¶ 93-109, and Carroll Decl., Exh. 1535, at ¶¶ 93-109.) UC cites to the cross-examination testimony of Broad's witness, Dr. Simons, who explained that none of the differences noted by Broad actually presented any difficulty in using CRISPR-Cas9 in eukaryotic cells. (UC Opp. 2, Paper 652, at 21:6-20, citing Simons Depo., Exh. 1555, at 179:8-180:9, 192:10-193:16, 202:2-22, and 203:16-21.)

Dr. Simons's testimony about the lack of actual impediments in eukaryotes is not persuasive because the relevant question before us is whether those of skill in the art would have *expected* there to be problems *before* the experiments were done. We note that despite Dr. Simons's testimony about the eventual results of using CRISPR-Cas9, he reiterated his opinion that "a person of ordinary skill in the art would have been concerned about [issues such as toxicity]." (Simons Depo., Exh. 1555, at 194:11-13.) We are not persuaded that the ultimate success is indicative of the expectation of success before the experiments were completed.

Similarly, we are not persuaded by UC's arguments that because the ultimate success in using CRISPR-Cas9 in eukaryotic cells was achieved with only conventional and routine materials and techniques, there would have been a reasonable expectation of success. (*See* UC Opp. 2, Paper 652, at 1:13-22, 11:17-12:12, and 16:14-17:20.) The ultimate results of an experiment do not indicate what one of ordinary skill in the art would have thought before the experiment was performed. "That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success." *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

UC also relies on its witnesses to argue that those of skill in the art would not have expected the generalized issues Broad cites to be impediments to using the CRISPR-Cas9 system in eukaryotic cells. (UC Opp. 2, Paper 652, at 21:13-23:23.) For example, Drs. Greider and Carroll testify that protein folding would not have been expected to be an impediment because other prokaryotic proteins were known to fold properly and because those of skill in the art knew that functional proteins could be injected directly into eukaryotic cells. (UC Opp. 2, Paper 652, at 21:13-22:4, citing Greider Decl., Exh. 1534, at ¶¶ 78-79, and Carroll Decl., Exh. 1535, at ¶¶ 78-79.) Drs. Greider and Carroll also cite to statements in the prior art that deemphasize the overall impact of misfolding and protein degradation on activity. (*See* Greider Decl., Exh. 1534, at ¶ 78, and Carroll Decl., Exh. 1535, at ¶ 78, both citing Goldberg, Exh. 2242, at 896.)

UC argues further that chromatin structure would not have been a reason for those of ordinary skill to have doubted the success of using CRISPR-Cas9 in eukaryotic cells because other prokaryotic DNA-targeting proteins were known to act on eukaryotic chromatin successfully. (UC Opp. 2, Paper 652, at 22:5-22, citing Greider Decl., Exh. 1534, at ¶¶ 55 and 95-97, and Carroll Decl., Exh. 1535, at ¶¶ 55 and 95-97.) We consider these arguments to be less persuasive because of the statement Dr. Carroll made contemporaneously with the publication of Jinek 2012. (*See* Carroll, Exh. 1152, at 1660.) Dr. Carroll wrote: "There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA–RNA hybrid can be stabilized in that context." (Carroll, Exh. 1152, at 1660.) Because we give contemporaneous evidence more weight than evidence prepared for litigation (*see U.S. Gypsum Co.*, 333 U.S. at 395–96), we are

persuaded that one of skill in the art would not have dismissed the possibility that chromatin structure could prevent CRISPR-Cas9 from working successfully in a eukaryotic cell.

Furthermore, we give UC's witnesses' testimony less weight because Dr. Carroll agreed that prior successes with prokaryotic proteins would only indicate that "the next prokaryotic protein that somebody was studying might or might not work in a chromatin context . . . ." (Carroll Depo., Exh. 2012, at 27:12-15.) Thus, on balance, the evidence supports Broad's argument that success with select prokaryotic proteins and systems would not have provided those of ordinary skill with a reasonable expectation that any of the thousands of prokaryotic system, including the CRISPR-Cas9 system, would work in the context of eukaryotic chromatin. (Broad Reply 2, Paper 866, at 11:15-12:6.)

UC argues that the other potential problems in achieving the activity of a prokaryotic system in eukaryotic cells raised by Broad had routine, well-known solutions at the time, such as codon optimization, targeting of prokaryotic proteins to cellular compartments, such as the nucleus, and the manipulation of ions and pH. (UC Opp. 2, Paper 652, at 22:23-23:23, citing Greider Decl., Exh. 1534, at ¶¶ 98-102, and Carroll Decl., Exh. 1535, at ¶¶ 98-102.) UC argues further that those of ordinary skill in the art would have known there were ways to avoid some of the concerns raised by Broad, citing to studies of directly injecting other prokaryotic systems to achieve genomic DNA modification in eukaryotic cells.

(UC Opp. 2, Paper 652, at 24:1-10, citing Greider Decl., Exh. 1534, at ¶ 104, and Carroll Decl., Exh. 1535, at ¶ 104, and Mastroianni[17], Exh. 1293, at 12.)

We credit Drs. Greider's and Carroll's testimony regarding some of the strategies that were known in the art, including direct injection, codon optimization, and targeting of proteins and RNA to the cell nucleus. According to their testimony, these techniques were routine and known to be useful in achieving activity of prokaryotic proteins in eukaryotic cells. Thus, not all of Broad's arguments regarding the generalized reasons why one of ordinary skill in the art would have lacked an expectation of success using a prokaryotic system in a eukaryotic cell persuade us. Nevertheless, because some techniques for using prokaryotic systems in eukaryotic cells were known to those of ordinary skill, the motivation to try using CRISPR-Cas9 in eukaryotic cells could have been even greater. We discern nothing about the expectation of success merely because there was great motivation to achieve a result. If anything, it is possible that great motivation could encourage artisans to try even when there is little expectation of success. (*See* Broad Reply 2, Paper 866, at 6:6-7.)

In addition to the general reasons for a lack of expectation of success, Broad cites to evidence of failed attempts at transferring other prokaryotic, RNA-based systems into eukaryotic environments. (Broad Motion 2, Paper 77, at 16:3-18:2.) Specifically, Broad focuses on three systems that work in prokaryotic and *in vitro* environments, but do not work well in a eukaryotic environment: riboswitches,

[17] Mastroianni et al., 2 PLOS ONE e3121. doi:10.1371/journal.pone.0003121 (2008) (Exh. 1293).

ribozymes, and group II introns.

The first example, riboswitches, are RNAs that naturally regulate gene expression in bacteria in response to ligands. (Broad Motion 2, Paper 77, at 16:9-19, citing Simons Decl., Exh. 2001, ¶ 6.47.) According to Dr. Simons, even though there was great interest in controlling gene expression in eukaryotes with riboswitches, only a few riboswitches have been successful. (*Id.*) Link[18] (Exh. 2223), cited by Dr. Simons, states: "Given that a few TPP riboswitches are the only validated metabolite-binding riboswitches in eukaryotes, it is not yet clear whether splicing control is a preferential mechanism for the control of gene expression by RNA switches." (Link, Exh. 2223, at 1192.) Link explains further:

> Several early reports involving the grafting of aptamers[19] onto ribozymes or messenger RNAs revealed some of the potential of engineered RNAs to serve as ligand-modulated gene-control systems. Unfortunately, a number of factors intervene to prevent many engineered RNA switches from becoming useful genetic switches. For example, the functions of most aptamers have not been validated in cells, the folding of RNA constructs might differ between test tube and cell, or the ribozyme chosen for RNA switch construction might not be appropriate for controlling gene expression.

(*Id.* at 1190 (citations omitted).) Link demonstrates that those of skill in the art would have known that RNA folding differences between a test tube environment and a cell environment may prevent genome engineering.

Ribozymes, Broad's second example, are RNA molecules that catalyze

[18] Link et al., 16 GENE THERAPY 1189-1201 (2009) (Exh. 2223).
[19] An aptamer can be defined as an oligonucleotide, such as a riboswitch, that binds to a specific target molecule.

biochemical reactions. (Simons Decl., Exh. 2001, ¶ 6.44.) Broad argues that experience with these systems contributes to the lack of a reasonable expectation of success using CRISPR-Cas9 in eukaryotic cells because, like CRISPR-Cas9, they depend on RNAs to work. (Broad Motion 2, Paper 77, at 16:19-17:2.) According to Dr. Simons Koseki[20] (Exh. 2221) teaches that the efficacy of ribozymes *in vitro* is not predictive of its functional activity *in vivo* for a variety of reasons. For example, Koseki states:

> One of the most critical factors determining ribozyme activity in vivo seems to be the association between the ribozyme and its target. A significant fraction of ribozymes must be degraded during transport and also during approach to the target site. For this reason, colocalization of a ribozyme and its target does not, by itself, guarantee the efficacy of ribozymes in vivo.

(Koseki, Exh. 2221, at 1876.) But Koseki also states:

> While we still cannot predict the relative stabilities in vivo of transcripts, we can design ribozymes that can be transported into the cytoplasm by incorporating secondary structures such as those shown in Fig. 1. Since we cannot accurately predict the stability of a transcript, we usually test several constructs and, in the case of various genes tested to date, we have always been able to obtain a cassette that can inactivate the gene of interest with >95% efficiency . . . as long as we follow the rule described above.
>
> The $tRNA^{Val}$ vector may be useful for expression of functional RNAs other than ribozymes whose target molecules are localized in the cytoplasm. Although colocalization in the cytoplasm cannot by itself guarantee effectiveness . . ., we can clearly increase the probability of

[20] Koseki et al., 73 J. VIROL. 1868-77, at 1875-76 (1999) (Exh. 2221).

> success. In our hands, $tRNA^{Val}$ ribozymes have consistently high activities, at least in cultured cells.

(*Id.* (citations omitted).) Thus, although some success was achieved with ribozymes, that success required a specific strategy developed particularly for ribozymes.

Broad's third example cites Group II introns, which are RNA-based, self-splicing nucleic acids found in prokaryotes. (Simons Decl., Exh. 2001, at ¶ 6.37.) Broad cites to Dr. Simons's testimony to argue that using Group II introns in eukaryotic cells is very inefficient, "to the point where it is unusable." (Broad Motion 2, Paper 77, at 17:3-18, citing Simons Decl., Exh. 2001, at ¶ 6.38.) Dr. Simons testifies that the requirement for higher magnesium ion concentration in eukaryotes and the spatial separation of transcription and translation by the nuclear membrane present challenges in eukaryotes. (Simons Decl., Exh. 2001, at ¶ 6.38.) In support of his testimony, Dr. Simons cites to Mastroianni (Exh. 2261), which explains that Group II introns can work in eukaryotes, but only by microinjection along with additional magnesium ions. (Mastroianni, Exh. 2261, at 9.) According to Broad, this limited success was achieved only after 16 years of effort. (Broad Reply 2, Paper 866, at 7:4-12.) As with the ribozyme system discussed above, in the face of the challenges and unpredictability of the Group II intron system a specific strategy was developed to increase the likelihood of success of that system *in vivo*.

UC argues that the examples cited by Broad are not evidence of a lack of reasonable expectation of success for CRISPR-Cas9 in eukaryotic cells because, as Dr. Simons admitted on cross-examination, each of the prokaryotic systems were

actually shown to function in eukaryotic cells. (*See* UC Opp. 2, Paper 652, at 25:6-14, citing Simons Depo., Exh. 1556, at 219:21-222:18; and 225:5-13.) But, the systems that Broad highlights each require a unique set of conditions, tailored to the particular system, to achieve any level of success in eukaryotic cells. UC does not point to, and we do not recognize, any commonality between these conditions that could be applied to CRISPR-Cas9. Instead, the evidence cited by Broad shows that because each of the riboswitch, ribozyme, and Group II intron RNA-based systems required specific tailoring of conditions, one skilled in the art would have expected that the CRISPR-Cas9 system would have also required its own set of unique conditions. Thus, even though skilled artisans knew of certain techniques, such as direct injection, codon optimization, and targeting to the cell nucleus, the totality of the evidence cited by both parties does not indicate there was a common set of instructions known to ordinarily skilled artisans that would have given them a reasonable expectation of success with CRISPR-Cas9. In light of the facts of the case law discussed above, the evidence of prokaryotic systems such as riboswitches, ribozymes, and Group II introns that Broad presents indicates ordinarily skilled artisan would not have had a reasonable expectation of success using CRISPR-Cas9 in eukaryotic cells.

In addition to the RNA-based systems to which Broad refers, Broad also addresses the evidence of expectation of success UC presented when it suggested this interference. (Broad Motion 2, Paper 77, at 20:9-22:13, citing UC Suggestion for Interference filed 13 April 2015, Exh. 1529, at 28; *see also* UC Opp. 2, Paper 652, at 17:21-19:2.) According to Broad, none of the protein systems to

which UC's evidence refers resembles the Type II CRISPR-Cas9 system and, therefore, are not informative. (Broad Motion 2, Paper 77, at 20:13-17.)

Broad argues that the ZFN and TALEN systems discussed by UC are not indicative of the expectations of the CRISPR-Cas9 system because they are derived from natural transcription factors that bind targets in a chromatin context. (Broad Motion 2, Paper 77, at 20:18-21:6.) Broad explains that the ZFN and TALENs systems are derived from bacterial proteins that naturally infect plants and, thus, are not purely prokaryotic but are naturally active in eukaryotic cells. (Broad Motion 2, Paper 77, at 20:23-21:3, citing Simons Decl., Exh. 2001 at ¶¶ 6.69-6.70, citing UC Suggestion of Interference, Exh. 1529, at 30:3-6.) Because the RNA-protein complex of the CRISPR-Cas9 system had never been expressed in or shown to be active in a eukaryotic cell before, Broad argues that the ZFNs and TALENs systems are very different from the CRISPR-Cas9 system. (Broad Motion 2, Paper 77, at 21:3-6.)

UC opposes Broad's characterization of the ZFN and TALEN systems, arguing that they use a prokaryotic restriction endonuclease domain and, thus, are relevant. (UC Opp. 2, Paper 652, at 19:4-12.) In support, UC cites to the testimony of its witnesses Drs. Greider and Carroll, which are substantially the same. (*See* Carroll Decl., Exh. 1535, at ¶ 52, and Greider Decl., Exh. 1534, at ¶ 52.) Although this testimony supports UC's argument, it does not address Broad's argument that the entire ZFNs and TALENs proteins are hybrids between prokaryotic domains and eukaryotic domains, which was admitted by UC in its Suggestion of Interference (*see* Exh. 1529, at 30:3-6). Dr. Simons explains that while the nuclease domain may be of prokaryotic origin, the DNA binding

domains of the ZFNs are derived from eukaryotes and the TALE proteins are produced in plants (eukaryotes). (Simons Decl., Exh. 2001, at ¶ 6.70.) Given this more detailed information, we give less weight to Drs. Carroll and Greider testimony that the ZFN and TALEN systems would have provided a person of ordinary skill in the art with reasons to expect that the "analogous" Type-II CRISPR-Cas9 system could be used in eukaryotic cells successfully. (*See* Carroll Decl., Exh. 1535, at ¶ 52, and Greider Decl., Exh. 1534, at ¶ 52.)

Furthermore, Dr. Carroll's testimony in this proceeding appears to contradict the commentary he wrote contemporaneously with publication of Jinek 2012. In that commentary, Dr. Carroll discussed whether CRISPR-Cas9 would work in eukaryotic cells and stated: "Both [ZFNs] and TALE modules come from natural transcription factors that bind their targets in a chromatin context. This is not true of the CRISPR components." (Carroll, Exh. 1152, at 1660.) Thus, at the relevant time, Dr. Carroll did not consider the ZFN or TALEN systems to be analogous or relevant to the question of whether CRISPR-Cas9 would work in eukaryotic cells. As explained above, we give this contemporaneous evidence significant weight. Accordingly, we are not persuaded that the successful use of ZFN and TALEN systems would have given those of skill in the art a reasonable expectation that CRISPR-Cas9 could also have been used successfully in eukaryotic cells.

Broad argues that the other prokaryotic systems cited by UC would not have been predictive of success because they are smaller and less complicated than the CRISPR-Cas9 system. (Broad Motion 2, Paper 77, at 21:7-18, citing Simons Decl., Exh. 2001, at ¶¶6.67-6.68; Broad Reply 2, Paper 866, at 13:9-13.) Specifically, Broad argues that other prokaryotic systems do not involve a complex

of both protein and RNA components. As informed by Dr. Simons, Broad argues that it was not known whether the prokaryotic RNA would be toxic to eukaryotic cells. (*Id*.)

Broad also argues that before use of these other prokaryotic systems was confirmed, researchers expressed doubt that they would work. (Broad Motion 2, Paper 77, at 21:19-22:3.) For example, researchers working with the Cre protein stated:

> [T]he ability of the Cre protein to access a *lox* site placed on a chromosome and then to perform site-specific synapsis of DNA and reciprocal recombination may be highly dependent on surrounding chromatin structure and on the particular location within the genome of the *lox* site. Some regions of the genome may be inaccessible to a bacterial recombinase, for example.

(Sauer 1988[21], Exh. 1336, at 5170; Simons Decl., Exh. 2001, ¶ 6.59.)

UC counters that in the same publication about Cre, the researchers demonstrated site-specific recombination by a prokaryotic protein in mammalian cells. (UC Opp. 2, Paper 652, at 19:13-23, citing Sauer 1998, Exh. 1336, at abstract.) UC argues further that an earlier publication demonstrated the ability of the Cre recombinase to perform precise recombination events on eukaryotic chromosomes unimpaired by chromatin structure. (UC Opp. 2, Paper 652, at 19:13-23 and 22:5-22, citing Sauer 1987[22], Exh. 1335, at abstract; *see also* Carroll Decl., Exh. 1535, at ¶¶ 54-55, and Greider Decl., Exh. 1534, at ¶¶ 54-55.) Thus, according to UC, doubts about access to chromatin were laid to rest.

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[21] Sauer and Henderson, 85 PROC. NAT'L ACAD. SCI. 5166 (1988) (Exh. 1336).
[22] Sauer, 7 Mol. Cell. Biol. 2087 (1987) (Exh. 1335).

Although we agree that the Cre protein is an example of the successful use of a prokaryotic recombinase protein in a eukaryotic cell, UC's opposition does not address Dr. Simons's testimony that the Cre protein is smaller and less complicated than the CRISPR-Cas9 system and so would not have informed those in the art about an expectation of success with CRISPR-Cas9. (*See* Simons Decl., Exh. 2001, at ¶¶ 6.67-6.68.) Accordingly, reports of the success of the Cre protein do not persuade us that those in the art would have expected CRISPR-Cas9 to work.

UC cites to one example of a publication that Drs. Greider and Carroll testify shows is "a multicomponent prokaryotic system including a protein component and a nucleic acid component" functioning in eukaryotic cells. (*See* UC Opp. 2, Paper 652, at 25:22-26:7, citing Chen[23], Exh. 1597, and Carroll Decl., Exh. 1535, at ¶ 80, and Greider Decl., Exh. 1534, at ¶ 80.) Beyond the general statements of Drs. Greider and Carroll that a person of ordinary skill in the art would not have considered the more complicated nature of the CRISPR-Cas9 to be an unpredicatable impediment because of this publication, UC does not direct us to any other explanation of this system (which is apparently a system for encoding unnatural amino acids in mammalian cells) in comparison to the CRISPR-Cas9 system. For example, it is unclear if this system functions in the nucleus of the eukaryotic cells or if it achieves modification of a nucleic acid. Without further explanation, we are not persuaded that this one publication would indicate to an

[23] Chen, et al., 48 ANGEW CHEM INT ED ENGL. 4052 (2009) (Exh. 1597).

ordinarily skilled artisan that the complexity of the CRISPR-Cas9 system would not have impacted the expectation that it would work in eukaryotic cells.

UC argues further that Broad failed to consider other prior art references allegedly suggesting that CRISPR systems in general could be used in eukaryotic cells. UC cites to U.S. patent application publication 2010/0076057 (Exh. 1161, "Sontheimer") to argue that those of skill in the art would have been motivated to use these systems in eukaryotic cells and would have been aware of the conventional techniques, such as expression vectors, nuclear localization signals, and codon optimization, that were available to do so. (UC Opp. 2, Paper 652, at 7:8-20.)

We are not persuaded by this argument because, while Sontheimer demonstrates a motivation for those of skill in the art to use a CRISPR system in eukaryotic cells, an issue the parties do not dispute, UC does not direct us to testimony or other evidence that an ordinarily skilled artisan would have had a reasonable expectation of success in doing so. Drs. Greider and Carroll testify that Sontheimer "suggests" that the Type I and III CRISPR systems could be used successfully in eukaryotic cells (Greider Decl. Exh. 1534, at ¶ 22; Greider Decl. Exh. 1535, at ¶ 22), but counsel for UC stated at oral argument that Sontheimer presents only "a research plan" (Transcript, Paper 892, at 16:11-12). Despite the argument in UC's brief, we are not persuaded that the suggestion in Sontheimer indicates ordinarily skill artisans would have had any expectation of success for the Type II CRISPR-Cas9 system.

Similarly, UC argues that other prokaryotic proteins, the RecA, EcoRI, and Φ31 proteins, had been shown to co-localize with their targets in eukaryotic cells.

(UC Opp. 2, Paper 652, at 26:7-8, citing Greider Decl., Exh. 1534, at ¶ 82, and Carroll Decl., Exh. 1535, at ¶ 82.) UC also argues that none of these proteins were actually hindered by chromatin, citing the testimony of Drs. Greider and Carroll to show that eukaryotic DNA is a dynamic structure, constantly being rearranged and exposed, rather than being fixedly bound in chromatin. According to UC, Broad's argument regarding the expected effects of chromatin structure are incorrect. (UC Opp. 2, Paper 652, at 22:5-22, citing Greider Decl., Exh. 1534, at ¶¶ 95-97, and Carroll Decl., Exh. 1535, at ¶¶ 95-97; also citing Simons Depo., Exh. 1556, at 229:16-230:15 and 232:7-233:6.)

Despite the evidence about the effects of chromatin structure that UC presents for this proceeding, we are still persuaded by Dr. Carroll's statement made contemporaneously to Jinek 2012. (*See* Carroll, Exh. 1152, at 1660: "There is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA–RNA hybrid can be stabilized in that context. . . . Only attempts to apply the system in eukaryotes will address these concerns.") Because the statements Dr. Greider makes in her declaration are substantially identical to Dr. Carroll's in his declaration, we do not give Dr. Greider's statements more weight than Dr. Carroll's.

The preponderance of the evidence cited by Broad persuades us that there would not have been specific instructions relevant to CRISPR-Cas9 to give one of ordinary skill in the art a reasonable expectation of success it would work in eukaryotic cells successfully. Instead, we are persuaded that the failures demonstrated with other systems would have indicated the lack of a reasonable

expectation of success. UC's arguments and evidence do not persuade us otherwise.

5.

In addition to its arguments about Broad's evidence, UC argues that other references must be considered to determine the obviousness of Broad's involved claims over UC's involved claims. Specifically, UC points to documents dated at least by 12 December 2012, the filing date of Broad's earliest provisional application. (UC Opp. 2, Paper 652, at 4:20-5:3.) According to UC, these later references are prior art because Broad did not show its involved claims are deserving of an effective filing date as early as 12 December 2012.

For example, UC argues that US Patent Application 61/717,324 (Exh. 1545, "the Kim provisional"), which was filed 23 October 2012, reports recognition and cleavage of target DNA when Cas9 protein and a guide RNA were introduced into human cells. (UC Opp. 2, Paper 652, at 5:6-6:18, citing Kim provisional, Exh. 1545, at 9[24].) The Kim provisional indicates there was a "possibility" that the CRISPR-Cas9 system taught in Jinek 2012 could be used for genome editing in cells and organisms. (Kim provisional, Exh. 1545, at 7.) UC argues that this provisional application and the non-provisional application based on it, which was filed after the filing date of both UC's and Broad's involved applications and patents, demonstrate that ordinarily skilled artisans had a reasonable expectation of successfully using the CRISPR-Cas9 system in eukaryotic cells. (UC Opp. 2,

[24] Page numbering for Exhibit 1545 reflects the page of the exhibit, not the underlying document.

Paper 652, at 5:24-6:18.) UC argues further that correspondence between the Kim inventors and UC inventor Doudna expressing interest in the results reported in Jinek 2012 is further evidence of this expectation of success. (UC Opp. 2, Paper 652, at 6:2-10, citing Exhs. 1557, 1558, and 1598.)

UC also argues that its own involved '859 application (Exh. 1001) and the provisional application on which it is based, application 61/652,086 (Exh. 1003), filed 25 May 2012, are prior art for the question of obviousness in the no interference-in-fact inquiry. (UC Motion 2, Paper 652, at 6:19-7:9.) According to UC, because these applications teach expression of a Type-II CRISPR-Cas system in eukaryotic cells they anticipate or render obvious Broad's claims. (UC Opp. 2, Paper 652, at 7:1-7, citing, *e.g.* Exh. 1001 at ¶¶ 25, 103-105, 119-120, 244-251, and 277-282; Exh. 1003 at ¶¶ 124-129, 165-177, 186-188, and 216.)

We agree with Broad that the Kim provisional, the non-provisional application based on it, private discussions based on the information in it, and UC's applications are not informative for the no interference-in-fact determination before us. (*See* Broad Reply 2, Paper 866, at 2:4-7.) The parties' claims are the prior art to be considered in an interference-in-fact inquiry. *See* 37 C.F.R. § 41.203(a) ("An interference exists if 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."). Interference-in-fact is a determination of whether there is an interference, not whether the parties' claims are patentable. We do not consider the results presented in the Kim provisional application or any other provisional application to be relevant to the interference-in-fact question before us because this evidence was not available to the public.

Although prior art other than the parties' claims may be considered, it would only be used to show what those of ordinary skill in the art knew at the time. The information in unpublished provisional applications was not available to those of ordinary skill in the art and, therefore, is not relevant to the question of whether one party's claims would have been rendered obvious by the other's.

D.

Both parties filed motions to exclude specific evidence submitted by the other.

Broad argues that UC exhibits 1475, 1548, 1550-1553, 1557-1560, 1598, 1604-10, 1612-18, 1620-28, 1636, and 1637 should be excluded. (Broad Motion 8, Paper 878, at 1:2-4.) Even if we do not exclude this evidence, we do not consider UC's arguments that rely on these exhibits to be persuasive. Accordingly, Broad's request to exclude this evidence is moot.

UC argues that Broad exhibits 2013 (at 169:12-174:24), 2127, 2213, 2268, 2281, 2289, 2291, 2298, 2312, 2404-2407, 2409-2412, 2415, 2416, 2419-2423, and 2426-2428 should be excluded. (UC Motion 5, Paper 880, at 1:2-6.) Because we were able to come to our determination without relying on these exhibits, we dismiss UC's request to exclude them.

In summary, neither party has persuaded us that our decision on Broad's Motion 2 should be different because of the exclusion of evidence.

E.

The preponderance of the evidence, including the contemporaneous statements of the inventors and others in the field, as well as the knowledge of ordinarily skilled artisans, demonstrates that one of ordinary skill would not have

had a reasonable expectation of success that CRISPR-Cas9 could be used in a eukaryotic cell. In light of this finding, we determine that if they were prior art, UC's claims would not have rendered Broad's claims obvious. Because UC's claims would not anticipate Broad's claims either, we conclude that the parties' claims are not drawn to the same patentable subject matter and that there is no interference-in-fact between them. We note that "[i]t is well-settled that a narrow species can be non-obvious and patent eligible despite a patent on its genus." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1379 (Fed. Cir. 2014). An "earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus." *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir. 2003).

Accordingly, we grant Broad's Motion 2 for a determination of no interference-in-fact.

IV. Conclusion

Based on our determination that the preponderance of the evidence shows there is no interference-in-fact between the parties' claims, we need not decide the other pending motions. *Cf. Berman v. Housey*, 291 F.3d 1345, 1352 (Fed. Cir. 2002) (holding that the Board did not err in refusing to consider Berman's patentability motion when Housey's motion under 35 U.S.C. § 135(b), "a condition precedent to the declaration of an interference," was granted). A determination of no interference-in-fact deprives UC of standing to raise other challenges against Broad's claims in this proceeding. *See* 37 C.F.R. § 41.201 (defining no interference-in-fact as an issue that deprives the opponent of the movant of

standing). Accordingly, we terminate the proceeding without entering judgment against either party's claims.

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APPENDIX

Involved Applications and Patents

UC

Application Number	Filing Date
13/842,859	15 March 2013

Broad

Patent Number	Application Number	Filing Date
8,697,359	14/054,414	15 October 2013
8,771,945	14/183,429	18 February 2014
8,795,965	14/183,486	18 February 2014
8,865,406	14/222,930	24 March 2014
8,871,445	14/259,420	23 April 2014
8,889,356	14/183,471	18 February 2014
8,895,308	14/293,498	2 June 2014
8,906,616	14/290,575	29 May 2014
8,932,814	14/258,458	22 April 2014
8,945,839	14/256,912	18 April 2014
8,993,233	14/105,017	12 December 2013
8,999,641	14/226,274	26 March 2014
	14/704,551	5 May 2015