

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**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)

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**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.*

1           I.        *Summary*

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

14

15           II.       *Introduction*

16

A.

17           A CRISPR-Cas9<sup>1</sup> system is a combination of protein and ribonucleic acid  
18 (“RNA”) that can alter the genetic sequence of an organism. In their natural  
19 environment, CRISPR-Cas systems protect bacteria against infection by viruses.  
20 (Simons Decl., Exh. 2001, at ¶ 2.1; Greider Decl., Exh. 1022, at ¶ 51.) The

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<sup>1</sup> “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.)

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

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

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

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<sup>2</sup> Pennisi, 341 Science 833-836 (2013) (Exh. 2231).

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

3 B.

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

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

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

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

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

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

12 C.

13 The Type II<sup>3</sup> CRISPR-Cas system comprises three components: (1) a crRNA  
14 molecule, which is called a “guide sequence” in Broad’s claims<sup>4</sup> and a “targeter-  
15 RNA” in UC’s claims, (2) a “tracr RNA,” which is called an “activator-RNA” in  
16 UC’s claims, (3) and a protein called Cas9. (Simons Decl., Exh. 2001, at ¶ 2.9;  
17 Greider Decl., Exh. 1022, at ¶ 50.) To alter a DNA molecule, the system must  
18 achieve three interactions: (1) crRNA binding by specific base pairing to a specific  
19 sequence in the DNA of interest (“target DNA”), (2) crRNA binding by specific

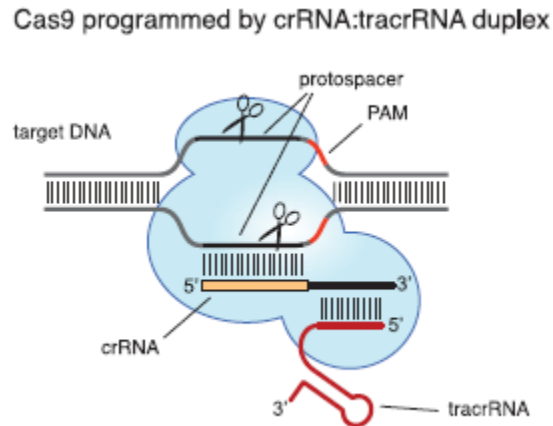
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<sup>3</sup> Type I and Type III CRISPR-Cas systems were also known to be present in bacteria, but these other systems use different molecular mechanisms for nucleic acid cleavage. (Greider Decl., Exh. 1022, ¶ 49.)

<sup>4</sup> 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.

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



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

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

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<sup>5</sup> Jinek *et al.*, 337 SCIENCE 816-21 (2012) (Exh. 1155).

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

3 D.

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

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

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

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

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

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

4           We use our discretion to take up these motions in the order that secures the  
5 just, speedy, and inexpensive determination of this proceeding. *See* 37 C.F.R.  
6 § 41.125(a) (“The Board may take up motions for decisions in any order, may  
7 grant, deny, or dismiss any motion, and may take such other action appropriate to  
8 secure the just, speedy, and inexpensive determination of the proceeding.”).

9

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

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

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

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<sup>6</sup> 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).



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1 (“if the Board is to compare two inventions [in a determination of interference-in-  
2 fact], the Board must only compare the parties' claims.”) To make this  
3 comparison, we use a “two-way test” wherein “the subject matter of a claim of one  
4 party would, if prior art, have anticipated or rendered obvious the subject matter of  
5 a claim of the opposing party and vice versa.” 37 C.F.R. §41.203(a). *See Eli Lilly*  
6 *& Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003)  
7 (holding that the Board committed no error in interpreting its own rule to apply the  
8 “two-way test” when determining if an interference-in-fact existed between junior  
9 party’s genus claims and senior party’s claims to a species within that genus); *see*  
10 *also Noelle*, 355 F.3d at 1350–51 (“In order to determine whether the two parties  
11 claim the same patentable invention, the USPTO has promulgated a “two-way”  
12 test, which has been approved by this court.”).

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

- 16 1) that, if considered to be prior art to UC’s claims, Broad’s involved  
17 claims would not anticipate or render obvious UC’s involved claims, or
- 18 2) that, if considered to be prior art to Broad’s claims, UC’s involved  
19 claims would not anticipate or render obvious Broad’s claims.

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

1 such that, if un rebutted, it would justify the relief sought. The burden of proof is  
2 on the movant.”).

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

6 A.

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

10 A method of cleaving a nucleic acid comprising  
11 contacting a target DNA molecule having a target sequence  
12 with an engineered and/or non-naturally-occurring Type II Clustered  
13 Regularly Interspaced Short Palindromic Repeats (CRISPR)—  
14 CRISPR associated (Cas) (CRISPR-Cas) system comprising  
15 a) a Cas9 protein; and  
16 b) a single molecule DNA-targeting RNA comprising  
17 i) a targeter-RNA that hybridizes with the target  
18 sequence, and  
19 ii) an activator-RNA that hybridizes with the targeter-  
20 RNA to form a double-stranded RNA duplex of a  
21 protein-binding segment,  
22 wherein the activator-RNA and the targeter-RNA are covalently  
23 linked to one another with intervening nucleotides,  
24 wherein the single molecule DNA-targeting RNA forms a  
25 complex with the Cas9 protein,  
26 whereby the single molecule DNA-targeting RNA targets the  
27 target sequence, and the Cas9 protein cleaves the target DNA  
28 molecule.

29  
30 (Senior Party Clean Copy of Claims, Paper 12, at 2.) UC also has claims drawn to

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

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

4 A method of altering expression of at least one gene product  
5 comprising introducing into a *eukaryotic cell* containing and  
6 expressing a DNA molecule having a target sequence and encoding  
7 the gene product an engineered, non-naturally occurring Clustered  
8 Regularly Interspaced Short Palindromic Repeats (CRISPR)--CRISPR  
9 associated (Cas) (CRISPR-Cas) system comprising one or more  
10 vectors comprising:

11 a) a first regulatory element operable in a eukaryotic cell  
12 operably linked to at least one nucleotide sequence encoding a  
13 CRISPR-Cas system guide RNA that hybridizes with the target  
14 sequence, and

15 b) a second regulatory element operable in a eukaryotic cell  
16 operably linked to a nucleotide sequence encoding a Type-II Cas9  
17 protein,

18 wherein components (a) and (b) are located on same or different  
19 vectors of the system, whereby the guide RNA targets the target  
20 sequence and the Cas9 protein cleaves the DNA molecule, whereby  
21 expression of the at least one gene product is altered; and, wherein the  
22 Cas9 protein and the guide RNA do not naturally occur together.  
23

24 (Replacement Broad Clean Copies of Claims, Paper 17, at 3 (emphasis added).)

25 Like UC, Broad also has claims to CRISPR-Cas systems that are involved in this  
26 interference. Unlike UC's claims, all of Broad's claims are limited to the method  
27 or system being used in eukaryotic cells.

28 B.

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

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

9 C.

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

18 “The consistent criterion for determination of obviousness is whether the  
19 prior art would have suggested to one of ordinary skill in the art that this process  
20 should be carried out and would have a reasonable likelihood of success, viewed in  
21 the light of the prior art.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir.  
22 1988). Although the definition of “reasonable expectation” is somewhat vague, the  
23 case law makes clear that a *certainty* of success is not required. *Medichem, S.A. v.*  
24 *Rolabo, S.L.*, 437 F.3d 1157, 1165–66 (Fed. Cir. 2006), *citing In re O’Farrell*, 853

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

6 1.

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

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

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

3 We pay particular attention to the statements made contemporaneously to  
4 Jinek 2012 because where such statements conflict with testimony prepared for  
5 litigation, contemporaneous statements have been considered to be stronger  
6 evidence of a particular situation. *See United States v. U.S. Gypsum Co.*, 333 U.S.  
7 364, 395–96 (1948) (determining that oral testimony in conflict with  
8 contemporaneous documentary evidence deserves little weight in a litigation  
9 regarding price fixing of patented products); *see also Cucuras v. Sec'y of Dep't of*  
10 *Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993) (holding no error  
11 by the trial court or special master when greater weight was accorded to  
12 contemporaneous medical records than to later, conflicting oral testimony).  
13 Accordingly, we give significant weight to the statements by those in the art at the  
14 time of Jinek 2012 regarding expectation of success in using a CRISPR-Cas9  
15 system in eukaryotic cells.

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

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

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

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

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<sup>8</sup> 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).

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

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

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

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

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

21  
22 (Jinek 2012, Exh. 1155, at 820 (citations omitted).) UC argues that because zinc-  
23 finger nucleases (ZFNs) and transcription-activator-like enzymes (TALENs) were  
24 the state of the art for DNA cleavage and genome editing in eukaryotic cells at the  
25 time, these statements in Jinek 2012 would have been understood to be an explicit



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

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

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

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

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

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

6  
7 (Carroll<sup>11</sup>, Exh. 1152, at 1660.) Dr. Carroll also raised technical questions about  
8 whether CRISPR-Cas9 could be used successfully in eukaryotic cells in the same  
9 commentary. Dr. Carroll discussed ways to potentially enhance the activity of  
10 CRISPR cleavage in eukaryotic cells, while cautioning about the risk of  
11 undesirable side effects. (*Id.*) Dr. Carroll concluded:

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

21  
22 (*Id.* (citations omitted).) Although Dr. Carroll indicated there was reason to try  
23 using the CRISPR system in eukaryotic cells, we do not discern any expectation  
24 that it would work before results of the actual studies were known.

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

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<sup>11</sup> Carroll, 20 MOLECULAR THERAPY 1658-60 (2012) (Exh. 1152).

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

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

9 After considering all of the evidence, we are persuaded that Dr. Carroll did  
10 not express an expectation that the CRISPR-Cas9 system could be used  
11 successfully in eukaryotic cells. Although we agree that Dr. Carroll expressed a  
12 suggestion and an expectation that the necessary experiments would be done, he  
13 did not state any expectation of what the results would be. Instead, Dr. Carroll  
14 pointed to differences between CRISPR-Cas9 and systems that work in eukaryotic  
15 cells (ZFNs and TALENs) and wrote: "There is no guarantee that Cas9 will work  
16 effectively on a chromatin target or that the required DNA-RNA hybrid can be  
17 stabilized in that context." (Carroll, Exh. 1152, at 1660.) We fail to see how "no  
18 guarantee" indicates an expectation of success. Although there need not be  
19 absolute predictability for a conclusion of obviousness (*see In re Longi*, 759 F.2d  
20 887, 897 (Fed. Cir. 1985), at best, Dr. Carroll's statement highlights some specific  
21 reasons why the CRISPR-Cas9 system might fail in eukaryotes. Thus, the only  
22 conclusion we draw from Dr. Carroll's statement is that at the time, he did not have  
23 a reasonable expectation that the system would work.

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

4           Jinek *et al.* realized that a highly specific, customizable RNA-directed  
5 DNA nuclease could be useful to edit whole genomes. Based on the  
6 20-nucleotide guide section of the crRNA, the enzyme could  
7 theoretically introduce breaks at unique sites in any eukaryotic  
8 genome. As a proof of concept, the authors programmed Cas9 to  
9 cleave a plasmid carrying the gene encoding green fluorescent protein  
10 at predetermined loci using a single chimeric crRNA containing just  
11 the critical segment of the tracrRNA. DNA breaks induce cellular  
12 DNA repair pathways . . . and this can be harnessed to disrupt, insert,  
13 or repair specific genes of cells. Introducing DNA breaks at desired  
14 loci using just Cas9 and a chimeric crRNA would be a substantial  
15 improvement over existing gene-targeting technologies, such as zinc  
16 finger nucleases and transcription activator–like effector nucleases, as  
17 these require protein engineering for every new target locus . . . .  
18 Efficient gene repair strategies in cells from patients, and the  
19 reintroduction of repaired cells, could become increasingly important  
20 for treating many genetic disorders.

21  
22 (Brouns<sup>12</sup>, Exh. 1471, at 2 (citations omitted).) UC argues that because this  
23 commentary presents a prediction that the CRISPR-Cas9 system would be an  
24 important tool for treating genetic disorders, it demonstrates a contemporaneously  
25 expressed expectation of success. UC’s witnesses, Drs. Greider and Carroll  
26 support this view, testifying that the statements in this commentary (Exh. 1471)  
27 and in Jinek 2012 would have given one of ordinary skill in the art a reasonable

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<sup>12</sup> Brouns, 337 SCIENCE 808-09 (2012) (Exh. 1471).

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

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

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

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

1 obvious that such a system might be repurposed for genome engineering, similar to  
2 ZFNs and TALENs.” (Golic<sup>13</sup>, Exh. 1473, at 304; *see* UC Opp. 2, Paper 652, at  
3 15:18-21.) In another article, it was observed that UC inventor Doudna and her  
4 colleagues were in the process of gathering more details on how the RNA-guided  
5 cleavage reaction works and were testing whether the system would work in  
6 eukaryotic organisms. (Yarris<sup>14</sup>, Exh. 1546, at 3; *see* UC Opp. 2, Paper 652, at  
7 28:22-29:12.) Doudna was quoted as saying that “Although we’ve not yet  
8 demonstrated genome editing, given the mechanism we describe it is now a very  
9 real possibility.” (Yarris, Exh. 1546, at 3.) Doudna also reportedly said: “Our  
10 results could provide genetic engineers with a new and promising alternative to  
11 artificial enzymes for gene targeting and genome editing in bacteria and other cell  
12 types.” (*Id.*, at 1.)

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

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<sup>13</sup> Golic, 195 GENETICS 303-308 (2013) (Exh. 1473).

<sup>14</sup> Yarris, NEWS CENTER, (2012) (<http://newscenter.lbl.gov/2012/06/28/programmable-dna-scissors/>) (Exh. 1546).

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

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

6 2.

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

11 Regardless of how many groups achieved success in eukaryotic cells, we are  
12 not persuaded that such success indicates there was an *expectation* of success  
13 before the results from these experiments were known. The unpublished results of  
14 research groups are not necessarily an indication of whether ordinarily skilled  
15 artisans would have expected the results achieved. Instead of viewing such work  
16 as evidence of an expectation of success, we consider the number of groups who  
17 attempted to use CRISPR-Cas9 in eukaryotic cells to be evidence of the motivation  
18 to do so, an issue that is not in dispute. We agree with Broad’s argument that a  
19 large reward might motivate persons to try an experiment even if the likelihood of  
20 success is very low. (*See* Broad Reply 2, Paper 866, at 6:6-7.) *See Institut Pasteur*  
21 *& Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir.  
22 2013) (“The desire for that payoff could motivate pursuit of the method, but  
23 ‘knowledge of the goal does not render its achievement obvious,’ . . . .” (citing  
24 *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed.Cir.2008).).

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1 UC argues that the research groups that were reportedly successful after  
2 publication of Jinek 2012 “could not have undertaken the use of UC’s Type II  
3 CRISPR-Cas9 system in eukaryotic cells unless there was sufficient motivation  
4 and expectation of success.” (UC Opp. 2, Paper 652, at 11:5-7; *see also* 11:15-16.)  
5 UC’s witnesses Greider and Carroll testify that “the Doudna laboratory would not  
6 have pursued and succeeded had they had no reasonable expectation of success in  
7 moving the CRISPR-Cas9 complex into eukaryotic cells.” (Greider Decl., Exh.  
8 1534, ¶ 69; Carroll Decl., Exh. 1535, at ¶ 69; *see* UC Opp. 2, Paper 866, at 11:11-  
9 16.) UC also argues, citing to the cross-examination testimony of Broad’s witness,  
10 that “[o]ne never does an experiment without the belief that it might work under  
11 certain circumstances.” (UC Opp. 2, Paper 652, at 30:1-2 citing Simons Depo.,  
12 Exh. 1555, at 178:10-12.)

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

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

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



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

7  
8       Thus, the “anticipated” success of a solution to a problem when there are “a finite  
9       number of identified, predictable solutions” may show that claimed subject matter  
10       would have been obvious. *See KSR*, 550 U.S. at 421. If we were to accept that  
11       success is reasonably expected for every experiment, under the framework  
12       provided in *KSR*, subject matter would always be obvious under 35 U.S.C. § 103  
13       when there is a design need or market pressure to solve a problem, a finite number  
14       of solutions, and those of ordinary skill had the technical capability. Instead of  
15       creating a presumption of obviousness when researchers attempt experiments to  
16       advance a field, the Federal Circuit has recognized:

17                    The methodology of science and the advance of technology are  
18                    founded on the investigator's educated application of what is known, to  
19                    intelligent exploration of what is not known. Each case must be  
20                    decided in its particular context, including the characteristics of the  
21                    science or technology, its state of advance, the nature of the known  
22                    choices, the specificity or generality of the prior art, and the  
23                    predictability of results in the area of interest.

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

26   3.

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

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

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

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

19 In *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir.  
20 2014), a reasonable expectation of success in the use of nanoparticle technology in  
21 formulation chemistry was found because that technology had become fairly  
22 reliable and had produced consistent results.

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

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

4 In *Pfizer*, a reasonable expectation of success was found because there was  
5 only one parameter to vary to obtain the specific salt of the drug claimed. (*Pfizer*,  
6 480 F.3d at 1366.) In addition, one skilled in the art had several references  
7 available to use for direction and was capable of narrowing the possible salts  
8 previously approved to a small group from which to choose and verify by routine  
9 trial-and-error procedures. (*Id.* at 1367-68.)

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

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

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

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

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

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

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

3 4.

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

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

18  
19 (Simons Decl., Exh. 2001, at ¶ 6.26.) In addition, Broad points to specific  
20 evidence of prior work in the field. (Broad Motion 2, Paper 77, at 4:14-7:23 and  
21 14:10-18:2.)

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

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

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

15 Broad argues further that it was known that differences in the cellular  
16 conditions between prokaryotes and eukaryotes could affect protein folding and  
17 could have prevented the CRISPR-Cas9 system from undergoing the  
18 conformational changes that allow it to work. (Broad Motion 2, Paper 77, at  
19 15:14-16:2, citing Simons Decl., Exh. 2001, ¶¶ 6.13 and 6.33.) In support,  
20 Dr. Simons testifies that the prior art showed protein folding to be critical because  
21 it is inextricably linked to function, noting that in eukaryotes misfolded proteins  
22 may be degraded through a pathway not present in prokaryotes. (Simons Decl.,

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

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

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

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<sup>15</sup> Goldberg, 426 NATURE 895 (2003).

<sup>16</sup> Loonstra, 98 PROC. NAT’L ACAD. SCI 9209 (2001).

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

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

15 Similarly, we are not persuaded by UC’s arguments that because the  
16 ultimate success in using CRISPR-Cas9 in eukaryotic cells was achieved with only  
17 conventional and routine materials and techniques, there would have been a  
18 reasonable expectation of success. (*See* UC Opp. 2, Paper 652, at 1:13-22, 11:17-  
19 12:12, and 16:14-17:20.) The ultimate results of an experiment do not indicate  
20 what one of ordinary skill in the art would have thought before the experiment was  
21 performed. “That the inventors were ultimately successful is irrelevant to whether  
22 one of ordinary skill in the art, at the time the invention was made, would have  
23 reasonably expected success.” *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d  
24 1320, 1326 (Fed. Cir. 2000).



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

13 UC argues further that chromatin structure would not have been a reason for  
14 those of ordinary skill to have doubted the success of using CRISPR-Cas9 in  
15 eukaryotic cells because other prokaryotic DNA-targeting proteins were known to  
16 act on eukaryotic chromatin successfully. (UC Opp. 2, Paper 652, at 22:5-22,  
17 citing Greider Decl., Exh. 1534, at ¶¶ 55 and 95-97, and Carroll Decl., Exh. 1535,  
18 at ¶¶ 55 and 95-97.) We consider these arguments to be less persuasive because of  
19 the statement Dr. Carroll made contemporaneously with the publication of  
20 Jinek 2012. (See Carroll, Exh. 1152, at 1660.) Dr. Carroll wrote: “There is no  
21 guarantee that Cas9 will work effectively on a chromatin target or that the required  
22 DNA–RNA hybrid can be stabilized in that context.” (Carroll, Exh. 1152, at  
23 1660.) Because we give contemporaneous evidence more weight than evidence  
24 prepared for litigation (*see U.S. Gypsum Co.*, 333 U.S. at 395–96), we are

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

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

13         UC argues that the other potential problems in achieving the activity of a  
14 prokaryotic system in eukaryotic cells raised by Broad had routine, well-known  
15 solutions at the time, such as codon optimization, targeting of prokaryotic proteins  
16 to cellular compartments, such as the nucleus, and the manipulation of ions and  
17 pH. (UC Opp. 2, Paper 652, at 22:23-23:23, citing Greider Decl., Exh. 1534, at  
18 ¶¶ 98-102, and Carroll Decl., Exh. 1535, at ¶¶ 98-102.) UC argues further that  
19 those of ordinary skill in the art would have known there were ways to avoid some  
20 of the concerns raised by Broad, citing to studies of directly injecting other  
21 prokaryotic systems to achieve genomic DNA modification in eukaryotic cells.

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

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

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

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

1 ribozymes, and group II introns.

2       The first example, riboswitches, are RNAs that naturally regulate gene  
3 expression in bacteria in response to ligands. (Broad Motion 2, Paper 77, at 16:9-  
4 19, citing Simons Decl., Exh. 2001, ¶ 6.47.) According to Dr. Simons, even  
5 though there was great interest in controlling gene expression in eukaryotes with  
6 riboswitches, only a few riboswitches have been successful. (*Id.*) Link<sup>18</sup>  
7 (Exh. 2223), cited by Dr. Simons, states: “Given that a few TPP riboswitches are  
8 the only validated metabolite-binding riboswitches in eukaryotes, it is not yet clear  
9 whether splicing control is a preferential mechanism for the control of gene  
10 expression by RNA switches.” (Link, Exh. 2223, at 1192.) Link explains further:

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

20  
21 (*Id.* at 1190 (citations omitted).) Link demonstrates that those of skill in the art  
22 would have known that RNA folding differences between a test tube environment  
23 and a cell environment may prevent genome engineering.

24       Ribozymes, Broad’s second example, are RNA molecules that catalyze

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<sup>18</sup> Link et al., 16 GENE THERAPY 1189-1201 (2009) (Exh. 2223).

<sup>19</sup> An aptamer can be defined as an oligonucleotide, such as a riboswitch, that binds to a specific target molecule.

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

8           One of the most critical factors determining ribozyme activity *in vivo*  
9           seems to be the association between the ribozyme and its target. A  
10           significant fraction of ribozymes must be degraded during transport  
11           and also during approach to the target site. For this reason,  
12           colocalization of a ribozyme and its target does not, by itself,  
13           guarantee the efficacy of ribozymes *in vivo*.  
14

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

16           While we still cannot predict the relative stabilities *in vivo* of  
17           transcripts, we can design ribozymes that can be transported into the  
18           cytoplasm by incorporating secondary structures such as those shown  
19           in Fig. 1. Since we cannot accurately predict the stability of a  
20           transcript, we usually test several constructs and, in the case of  
21           various genes tested to date, we have always been able to obtain a  
22           cassette that can inactivate the gene of interest with >95% efficiency  
23           . . . as long as we follow the rule described above.  
24

25           The tRNA<sup>Val</sup> vector may be useful for expression of functional RNAs  
26           other than ribozymes whose target molecules are localized in the  
27           cytoplasm. Although colocalization in the cytoplasm cannot by itself  
28           guarantee effectiveness . . . , we can clearly increase the probability of

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<sup>20</sup> Koseki et al., 73 J. VIROL. 1868-77, at 1875-76 (1999) (Exh. 2221).

1 success. In our hands, tRNA<sup>Val</sup> ribozymes have consistently high  
2 activities, at least in cultured cells.

3  
4 (*Id.* (citations omitted).) Thus, although some success was achieved with  
5 ribozymes, that success required a specific strategy developed particularly for  
6 ribozymes.

7 Broad's third example cites Group II introns, which are RNA-based, self-  
8 splicing nucleic acids found in prokaryotes. (Simons Decl., Exh. 2001, at ¶ 6.37.)

9 Broad cites to Dr. Simons's testimony to argue that using Group II introns in  
10 eukaryotic cells is very inefficient, "to the point where it is unusable." (Broad  
11 Motion 2, Paper 77, at 17:3-18, citing Simons Decl., Exh. 2001, at ¶ 6.38.)

12 Dr. Simons testifies that the requirement for higher magnesium ion concentration  
13 in eukaryotes and the spatial separation of transcription and translation by the  
14 nuclear membrane present challenges in eukaryotes. (Simons Decl., Exh. 2001, at

15 ¶ 6.38.) In support of his testimony, Dr. Simons cites to Mastroianni (Exh. 2261),  
16 which explains that Group II introns can work in eukaryotes, but only by  
17 microinjection along with additional magnesium ions. (Mastroianni, Exh. 2261, at

18 9.) According to Broad, this limited success was achieved only after 16 years of  
19 effort. (Broad Reply 2, Paper 866, at 7:4-12.) As with the ribozyme system

20 discussed above, in the face of the challenges and unpredictability of the Group II  
21 intron system a specific strategy was developed to increase the likelihood of  
22 success of that system *in vivo*.

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

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

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

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

3 Broad argues that the ZFN and TALEN systems discussed by UC are not  
4 indicative of the expectations of the CRISPR-Cas9 system because they are  
5 derived from natural transcription factors that bind targets in a chromatin context.  
6 (Broad Motion 2, Paper 77, at 20:18-21:6.) Broad explains that the ZFN and  
7 TALENs systems are derived from bacterial proteins that naturally infect plants  
8 and, thus, are not purely prokaryotic but are naturally active in eukaryotic cells.  
9 (Broad Motion 2, Paper 77, at 20:23-21:3, citing Simons Decl., Exh. 2001 at  
10 ¶¶ 6.69-6.70, citing UC Suggestion of Interference, Exh. 1529, at 30:3-6.) Because  
11 the RNA-protein complex of the CRISPR-Cas9 system had never been expressed  
12 in or shown to be active in a eukaryotic cell before, Broad argues that the ZFNs  
13 and TALENs systems are very different from the CRISPR-Cas9 system. (Broad  
14 Motion 2, Paper 77, at 21:3-6.)

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



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

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

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

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

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

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

14

15 (Sauer 1988<sup>21</sup>, Exh. 1336, at 5170; Simons Decl., Exh. 2001, ¶ 6.59.)

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

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<sup>21</sup> Sauer and Henderson, 85 PROC. NAT'L ACAD. SCI. 5166 (1988) (Exh. 1336).

<sup>22</sup> Sauer, 7 Mol. Cell. Biol. 2087 (1987) (Exh. 1335).

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

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

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<sup>23</sup> Chen, et al., 48 *ANGEW CHEM INT ED ENGL.* 4052 (2009) (Exh. 1597).

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

3 UC argues further that Broad failed to consider other prior art references  
4 allegedly suggesting that CRISPR systems in general could be used in eukaryotic  
5 cells. UC cites to U.S. patent application publication 2010/0076057 (Exh. 1161,  
6 “Sontheimer”) to argue that those of skill in the art would have been motivated to  
7 use these systems in eukaryotic cells and would have been aware of the  
8 conventional techniques, such as expression vectors, nuclear localization signals,  
9 and codon optimization, that were available to do so. (UC Opp. 2, Paper 652, at  
10 7:8-20.)

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

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

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1 (UC Opp. 2, Paper 652, at 26:7-8, citing Greider Decl., Exh. 1534, at ¶ 82, and  
2 Carroll Decl., Exh. 1535, at ¶ 82.) UC also argues that none of these proteins were  
3 actually hindered by chromatin, citing the testimony of Drs. Greider and Carroll to  
4 show that eukaryotic DNA is a dynamic structure, constantly being rearranged and  
5 exposed, rather than being fixedly bound in chromatin. According to UC, Broad's  
6 argument regarding the expected effects of chromatin structure are incorrect. (UC  
7 Opp. 2, Paper 652, at 22:5-22, citing Greider Decl., Exh. 1534, at ¶¶ 95-97, and  
8 Carroll Decl., Exh. 1535, at ¶¶ 95-97; also citing Simons Depo., Exh. 1556, at  
9 229:16-230:15 and 232:7-233:6.)

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

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

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

3 5.

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

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

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<sup>24</sup> Page numbering for Exhibit 1545 reflects the page of the exhibit, not the underlying document.

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

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

13 We agree with Broad that the Kim provisional, the non-provisional  
14 application based on it, private discussions based on the information in it, and  
15 UC's applications are not informative for the no interference-in-fact determination  
16 before us. (*See* Broad Reply 2, Paper 866, at 2:4-7.) The parties' claims are the  
17 prior art to be considered in an interference-in-fact inquiry. *See* 37 C.F.R.  
18 § 41.203(a) ("An interference exists if the subject matter of a claim of one party  
19 would, if prior art, have anticipated or rendered obvious the subject matter of a  
20 claim of the opposing party and vice versa."). Interference-in-fact is a  
21 determination of whether there is an interference, not whether the parties' claims  
22 are patentable. We do not consider the results presented in the Kim provisional  
23 application or any other provisional application to be relevant to the interference-  
24 in-fact question before us because this evidence was not available to the public.

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

6 D.

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

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

14 UC argues that Broad exhibits 2013 (at 169:12-174:24), 2127, 2213, 2268,  
15 2281, 2289, 2291, 2298, 2312, 2404-2407, 2409-2412, 2415, 2416, 2419-2423,  
16 and 2426-2428 should be excluded. (UC Motion 5, Paper 880, at 1:2-6.) Because  
17 we were able to come to our determination without relying on these exhibits, we  
18 dismiss UC's request to exclude them.

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

21 E.

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



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1 had a reasonable expectation of success that CRISPR-Cas9 could be used in a  
2 eukaryotic cell. In light of this finding, we determine that if they were prior art,  
3 UC's claims would not have rendered Broad's claims obvious. Because UC's  
4 claims would not anticipate Broad's claims either, we conclude that the parties'  
5 claims are not drawn to the same patentable subject matter and that there is no  
6 interference-in-fact between them. We note that "[i]t is well-settled that a narrow  
7 species can be non-obvious and patent eligible despite a patent on its genus."  
8 *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d  
9 1366, 1379 (Fed. Cir. 2014). An "earlier disclosure of a genus does not necessarily  
10 prevent patenting a species member of the genus." *Eli Lilly & Co. v. Bd. of Regents*  
11 *of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir. 2003).

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

14  
15 *IV. Conclusion*

16 Based on our determination that the preponderance of the evidence shows  
17 there is no interference-in-fact between the parties' claims, we need not decide the  
18 other pending motions. *Cf. Berman v. Housey*, 291 F.3d 1345, 1352 (Fed. Cir.  
19 2002) (holding that the Board did not err in refusing to consider Berman's  
20 patentability motion when Housey's motion under 35 U.S.C. § 135(b), "a condition  
21 precedent to the declaration of an interference," was granted). A determination of  
22 no interference-in-fact deprives UC of standing to raise other challenges against  
23 Broad's claims in this proceeding. *See* 37 C.F.R. § 41.201 (defining no  
24 interference-in-fact as an issue that deprives the opponent of the movant of

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

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**APPENDIX**

Involved Applications and Patents

**UC**

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

**Broad**

<b>Patent Number</b>	<b>Application Number</b>	<b>Filing Date</b>
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