

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY
OF VIENNA, AND EMMANUELLE CHARPENTIER**
Junior Party

(Applications 15/947,680; 15/947,700; 15/947,718; 15/981,807;
15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175;
16/276,361; 16/276,365; 16/276,368; and 16/276,374),

v.

**THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF
TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD
COLLEGE,**
Senior Party

(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,
9,840,713, and Application 14/704,551).

Patent Interference No. 106,115 (DK)

Decision on Motions
37 C.F.R. § 41.125(a)

Interference 106,115

Before, SALLY GARDNER LANE, JAMES T. MOORE, and
DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

1 *I. Introduction*

2 The current interference is between The Regents of the University of
3 California, University of Vienna, and Emmanuelle Charpentier (“CVC”) and The
4 Broad Institute, Inc., Massachusetts Institute of Technology, and President and
5 Fellows of Harvard College (“Broad”) regarding CRISPR-Cas9 systems. A
6 CRISPR-Cas9 system is a combination of protein and ribonucleic acid (“RNA”)
7 that can alter the genetic sequence of an organism. (*See* CVC involved application
8 15/947,680, Ex. 4018, at ¶ 4; Broad involved patent 8,697,359, Ex. 3011, at 1:45-
9 46 and 2:13–20.) In their natural environment, CRISPR-Cas systems protect
10 bacteria against infection by viruses. (*See* Declaration of Randall T. Peterson,
11 Ph.D. (“Randall Decl.”)¹, Ex. 4036, ¶ 37; *see* Declaration of Technical Expert
12 Christoph Seeger (“Seeger Decl.”)², Ex. 3401, ¶¶ 2.1–2.2.) Both CVC’s and

¹ Dr. Peterson testifies that he has extensive experience in the field of genetic engineering and has knowledge and understanding of genome editing tools, having worked with them in zebrafish models. (*See* Peterson Decl., Ex. 4036, ¶ 17.) Dr. Peterson’s *curriculum vitae* (Ex. 4061) supports his testimony, listing grant awards and publications in the field of gene editing. Broad does not contest his qualifications. We find Dr. Peterson to be qualified to present opinions on the technical issues of this interference.

² Dr. Seeger testifies that he has many years of experience in the field of virology and is familiar with the use of CRISPR-Cas9 systems, having used them to target hepatitis B virus to research drug resistance in liver and pancreatic cancer therapy.

Interference 106,115

1 Broad's involved claims are limited to cells, systems, and methods using CRISPR-
2 Cas9 systems to modify the DNA in the genomes of eukaryotes. (*See* CVC Clean
3 Copy of Claims, Paper 7; *see* Broad Clean Copy of Claims, Paper 14.)

4 This is the second interference between these parties related to CRISPR-
5 Cas9 systems. The first interference, 106,048 ("the '048 interference"), was
6 terminated without a determination of unpatentability under 35 U.S.C. § 102(g)³ to
7 either party because Broad's motion for no interference-in-fact was granted. (*See*
8 Interference 106,048, Decision on Motion, Paper 893.) The only issue decided in
9 the first interference was that the subject matter of none of Broad's involved claims
10 would be obvious over the subject matter of any of CVC's involved claims, under
11 the provisions of 37 C.F.R. § 41.203(a) that CVC's claims be considered to be
12 prior art. (*See id.*) The interference did not determine any other issues and did not
13 hold that any of the parties' claims were unpatentable.

14 CVC subsequently filed new claims in application 15/947,680 and this
15 second interference was declared with the same Broad claims involved in the first

(*See* Seeger Decl., Ex. 3401, ¶ 1.3.) Dr. Seeger's *curriculum vitae* (Ex. 3402) supports his testimony, listing publications on the use of CRISPR-Cas9 technology. CVC does not contest his qualifications. We find Dr. Seeger to be qualified to present opinions on the technical issues of this interference.

³ Patent interferences continue under the relevant statutes in effect on 15 March 2013. *See* Pub. L. 112-29, § 3(n), 125 Stat. 284, 293 (2011).

Interference 106,115

1 interference. (*See* Declaration, Paper 1; *see* Appendix listing the parties' involved
2 patents and applications.)

3 Neither party has raised the issue of no interference-in-fact. Thus, the
4 presence of an interference between the parties' claims is not contested. Instead,
5 Broad argues that this interference is estopped by the judgment in the prior
6 '048 interference. (*See* Broad Motion 1, Paper 72.) We are not persuaded by
7 Broad's arguments, as discussed below, and do not terminate the interference on
8 that basis.

9 The parties' other motions before us relate to preliminary matters that set the
10 proceeding for a determination of priority, if one is necessary, in a second phase.
11 Each party has the burden of proof in persuading us by a preponderance of the
12 evidence that they are entitled to the relief sought in their motions. *See* 37 C.F.R.
13 § 41.121(b) ("The party filing the motion has the burden of proof to establish that
14 it is entitled to the requested relief."); *see also* 37 C.F.R. § 41.208(b) ("The burden
15 of proof is on the movant."). We take up motions in the order that secures a just,
16 speedy, and inexpensive determination of the proceeding. *See* 37 C.F.R.
17 § 41.125(a).

18 Broad has filed the following substantive motions, which are opposed by
19 CVC:

20 a motion to change the count (Broad Motion 2, Paper 271), which we deny;

21 a motion to change the designation of claims corresponding to the count

22 (Broad Motion 3, Paper 268), which we deny; and

Interference 106,115

1 a motion to be accorded benefit of the filing date of its earlier application
2 (Broad Motion 4, Paper 269), which we grant.

3 CVC has filed the following substantive motions, which are opposed by
4 Broad:

5 a motion to be accorded benefit of the filing date of its earlier applications
6 (CVC Motion 1, Paper 212), which we grant-in-part; and

7 a motion to be accorded benefit of the filing date of its earlier application,
8 responsive to the grant of Broad's motion to change the count (CVC Motion 2,
9 Paper 437), which we dismiss as moot because we deny Broad Motion 2.

10 We address each of the parties' motions and relevant issues in detail below.

11 *II. Broad Motion 1 - Estoppel*

12 In its Substantive Motion 1, Broad requests judgment against CVC, arguing
13 that the interference is barred under estoppel by the Board decision in the prior
14 '048 interference. (*See* Broad Motion 1, Paper 72, 1:2–7.) According to Broad,
15 CVC's claims should be finally refused because claims limited to a eukaryotic
16 environment have already been awarded to Broad and, thus, cannot be awarded to
17 CVC without an interference, which CVC is estopped from pursuing. (*See id.* at
18 27:2–9.)

19 We are not persuaded by Broad's arguments and decline to terminate the
20 interference because of estoppel. Although we agree that resolving the parties'
21 disputes in one proceeding may have been preferable, we do not agree that
22 estoppel allows CVC's claims to be canceled in this proceeding. The
23 '048 interference ended without an award of priority or a determination of

Interference 106,115

1 unpatentability for either party. As stated in the judgment, it “neither cancels nor
2 finally refuses either parties’ claims.” (Judgment in ’048 Interference, Paper 894,
3 2:2–3.) Thus, the resolution at the end of the ’048 interference was that
4 interference between the claims presented at that time did not deprive either party
5 of its claims. This decision was upheld by the Federal Circuit. *See Regents of*
6 *Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286 (Fed. Cir. 2018). Broad
7 fails to persuade us that CVC is estopped because the subject matter of the current
8 interference is the same as the subject matter of the prior ’048 Interference.

9 Broad now argues that different CVC claims should be finally refused
10 because Broad was awarded claims that interfere with these new CVC claims.
11 (*See* Broad Motion 1, Paper 72, 27:6–8.) According to Broad, CVC is estopped
12 under 37 C.F.R. § 41.127(a)(1). (*See id.* at 1:11–21.) That rule applies to
13 judgment in an interference, stating:

14 *Estoppel.* A judgment disposes of all issues that were, or by motion
15 could have properly been, raised and decided. A losing party who
16 could have properly moved for relief on an issue, but did not so move,
17 may not take action in the Office after the judgment that is
18 inconsistent with that party's failure to move, except that a losing
19 party shall not be estopped with respect to any contested subject
20 matter for which that party was awarded a favorable judgment.

21
22 37 C.F.R. § 41.127(a)(1). First, Broad argues that CVC is estopped because CVC
23 provoked an interference with the same opponent for the same subject matter. (*See*
24 Broad Motion 1, Paper 72, 2:1–19.) According to Broad, there can be no dispute
25 that CVC has provoked a second interference for the same subject matter “because

Interference 106,115

1 *each and every* Broad eukaryotic claim that was at issue in the prior interference is
2 at issue once again here.” (*See id.* at 15:19–21; *see also* 16:10–14.) We are not
3 persuaded that Broad’s claims alone determine the interfering subject matter in
4 either this interference or the prior one. CVC’s claims in the prior interference are
5 different from CVC’s claims involved in this interference. The prior CVC claims
6 did not interfere with Broad’s claims, whereas Broad does not contest that the
7 currently involved CVC claims do. (*See* CVC Opp. 1, Paper 428, 9:13–22.) Thus,
8 it is not clear that the subject matter of the interference is the same, even if the
9 subject matter of Broad’s claims is the same.

10 Broad fails to provide a sufficient comparison of the subject matter of the
11 two interferences to persuade us that the current interference is, or will be, the
12 same subject matter of the ’048 interference and will raise the same issues. For
13 example, Broad fails to compare the count in the current interference, or Broad’s
14 proposed counts, with either parties’ claims in the prior interference. Broad states
15 that “[t]he textual differences between Count 1 of this interference and the count of
16 the 048 Interference are likewise irrelevant,” but then acknowledges that the
17 current count in the current interference recites a limitation on the RNA
18 configuration that is not recited in the count of the ’048 interference. (Broad
19 Motion 1, Paper 72, 17:6–18:2 (referring to the limitation to a single molecule
20 RNA “covalently linked” or “fused” in Count 1 of current interference).) As
21 Broad acknowledges, whether the prior count and the current count are drawn to
22 the same subject matter is a disputed issue, which is not sufficiently addressed in
23 Broad’s Motion 1. (*See* CVC Opp. 1, Paper 428, 2:21–22 (“Broad’s first estoppel

Interference 106,115

1 theory is based on the false assumption that this interference concerns the same
2 subject matter as the '048 proceeding. . . . It does not.”); *see also id.* 9:13–22.)
3 Accordingly, we are not persuaded that CVC is estopped and should have
4 judgment entered against it because the interference involves the same parties and
5 the same subject matter.

6 Broad also argues that CVC is estopped under the provision of 37 C.F.R.
7 § 41.127(a)(1) that “[a] judgment disposes of all issues that were, or by motion
8 could have properly been, raised and decided.” (*See* Broad Motion 1, Paper 72,
9 1:18–4:19, 19:8–21:22.) According to Broad, CVC should have requested
10 authorization to file a motion to add claims limited to a eukaryotic environment in
11 the '048 interference if it wanted to address the issues of the current interference.
12 (*See id.* at 2:25–3:9.) Broad argues further that CVC knew it should file such a
13 responsive motion because this scenario was discussed during a conference call in
14 the '048 interference. (*See id.* at 3:10–17, citing Transcript of 10 March 2016 in
15 the '048 interference, Ex. 3103, 23:3–24:22.)

16 Broad argues that estoppel for failure to move in the prior interference is
17 applicable to CVC because the first sentence of 37 C.F.R. § 41.127(a)(1) contains
18 no limitation on the type of judgment entered in the first proceeding. (*See* Broad
19 Motion 1, Paper 72, 13:3–22; *see* Broad Reply 1, Paper 433, 4:14–6:3.) According
20 to Broad, the judgment of no interference-in-fact triggers estoppel against CVC.
21 (*See* Broad Motion 1, Paper 72, 4:1–2; *see* Broad Reply 1, Paper 433, 5:26–6:3.)

22 CVC opposes this interpretation of Rule 127(a)(1), arguing that the first
23 sentence sets forth the general principle of finality and the second sentence

Interference 106,115

1 clarifies the effect of the first by specifying the failure-to-move estoppel is
2 confined to the losing party. (*See* CVC Opp. 1, Paper 428, 14:2–16:5.)

3 We agree with CVC. Although section (a)(1) of 37 C.F.R. § 41.127 is
4 entitled “Estoppel,” a plain reading of the first sentence does not mention estoppel.
5 Instead, the first sentence explains the effect of a judgment as disposing all issues
6 of the proceeding. But a judgment of no interference-in-fact does not dispose of
7 any issue other than interference-in-fact. For example, the Board may not decide a
8 motion regarding unpatentability over the prior art after a determination of no
9 interference-in-fact. (*Cf. Berman v. Housey*, 291 F.3d 1345, 1352 (Fed. Cir. 2002)
10 (holding that if “a condition precedent to the declaration of an interference,” in this
11 case 35 U.S.C. § 135(b), is not met, the Board did not err in refusing to consider
12 Berman’s patentability motion.) Thus, a judgment based on no interference-in-fact
13 would not dispose of a prior art issue that was fully briefed. Accordingly, we are
14 not persuaded that a judgment of no interference-in-fact is necessarily
15 contemplated in the first sentence of 37 C.F.R. § 41.127(a)(1), particularly, for
16 example, if the same subject matter is not at issue in a later challenge.

17 Broad cites to comments by the Office in support of its argument that the
18 first sentence of 37 C.F.R. § 41.127(a)(1) estops CVC from presenting its currently
19 involved claims. These comments do not persuade us of Broad’s argument.
20 During the proposed rulemaking in 2003 the Office noted that “[w]hile the second
21 sentence of the proposed paragraph would continue to focus on the losing party, a
22 decision of no interference-in-fact could estop a party from provoking an
23 interference with the same opponent for the same subject matter.” (*See* Broad

Interference 106,115

1 Motion 1, Paper 72, 13:15–22, citing 68 Fed. Reg. 66648, 66661 (26 Nov. 2003);
2 *see* Broad Reply 1, Paper 433, 5:18–21.) As explained above, though, Broad fails
3 to persuade us that the current interference is for the same subject matter as the
4 prior '048 interference. Thus, the explanation in the proposed rulemaking of 2003
5 does not support Broad's argument that judgment should be entered against CVC.

6 We note that in contrast to Broad's interpretation of Rule 127(a)(1), the
7 MPEP states that "[a] judgment of no interference-in-fact means that no
8 interference is needed to resolve priority between the parties. Neither party has lost
9 the interference for the purpose of estoppel consistent with 37 CFR 41.127(a)(1),
10 even if one of the parties suggested the interference." (MPEP § 2308.03(b).) We
11 agree with this understanding because a judgment of no interference-in-fact ends
12 the proceeding without an award of priority to either party. Thus, there is no losing
13 party.

14 Because we are not persuaded that 37 C.F.R. § 41.127(a)(1) applies to either
15 party where patentably distinct subject matter is claimed after a judgment of no
16 interference-in-fact, we are not persuaded that CVC is estopped from its current
17 claims even though they were not presented during the '048 interference.

18 We note further that 37 C.F.R. § 41.127(a)(1) does not provide any
19 guarantees that a party is protected from other interfering claims. Broad cites no
20 other rule, statute, or common law principle that provides such guarantees.
21 Instead, Broad cites to the Manual of Patent Examining Procedure ("MPEP")
22 § 2308.03(b), which states, in part: "A judgment of no interference-in-fact bars any
23 further interference between the same parties for claims to the same invention as

Interference 106,115

1 the count of the interference.” It is not entirely clear to which claims the MPEP
2 refers – a further interference between the same claims of both parties or involving
3 each parties’ claims individually. This confusion is compounded by the lack of
4 support for the statement in the MPEP.

5 The MPEP further states: “No second interference should occur between the
6 same parties *on patentably indistinct subject matter*. If the Board ... held that there
7 is no interference-in-fact between the parties for the subject matter of the count,
8 that holding may not be reopened in further examination.” MPEP § 2308.03(c)
9 (emphasis added). This MPEP statement reinforces that the portion of the MPEP
10 cited by Broad is relevant only when the second interference is about the same
11 subject matter, an issue Broad acknowledges is in dispute here. Again, Broad does
12 not persuade us that the interfering subject matter between CVC’s currently
13 involved claims and Broad’s claims is patentably indistinct from the subject matter
14 of the prior ’048 Interference. Thus, Broad’s reliance on the MPEP is
15 unpersuasive.

16 The Federal Circuit has explained that interference estoppel by judgment
17 rests on the principle that a “judgment in an action precludes relitigation of claims
18 or issues that were ... raised in [the earlier] proceeding.” *In re Deckler*, 977 F.2d
19 1449, 1452 (Fed.Cir.1992); *see also Biogen MA, Inc. v. Japanese Found. for*
20 *Cancer Research*, 785 F.3d 648, 657–58 (Fed. Cir. 2015). Broad desires to clear
21 the “cloud of uncertainty” that it asserts surrounds its claims, but Broad fails to
22 sufficiently explain why the subject matter of either the current or prior
23 interference is defined solely by the subject matter of its claims. (*See Broad*

Interference 106,115

1 Motion 1, Paper 72, 25:15–26:1.) Broad has failed to persuade us that under
2 37 C.F.R. § 41.127(a)(1) CVC is estopped because Broad fails to persuade us that
3 the subject matter of the current interference is the same as the subject matter of
4 the prior '048 Interference.

5 Broad argues that the revisions to the estoppel rules have been intended to
6 improve proceedings and prevent re-litigations in multiple interferences. (*See*
7 Broad Motion 1, Paper 72, 25:6–14, citing 49 Fed. Reg. 48416 at 48440
8 (preventing “delays and litigation” by imposing estoppel rules where “[i]t may be
9 stated that this rule works no hardship to him who is diligent in pursuit of his
10 rights. When an interference is declared, the files of his contestants are open to
11 him. He has full cognizance of their disclosures and claims. So advised, it becomes
12 his duty to put forward every claim he has. [Rule 1.633(e)] ... affords him this
13 opportunity.”).) We construe our rules “to secure the just, speedy, and inexpensive
14 resolution of every proceeding before the Board.” (37 C.F.R. § 41.1(b).) Although
15 we are mindful of the comments made by the Commissioner regarding the reasons
16 for applying estoppel for subsequent interferences, under the facts before us now
17 there is no estoppel rule that we can enforce because CVC did not lose on priority
18 or on any patentability issues in the prior interference. Instead, the judgment of no
19 interference-in-fact neither cancels nor finally refuses either parties’ claims.

20 In addition, although Broad argues that CVC could have filed a responsive
21 motion to add its current claims in the prior '048 Interference (*see* Broad Motion 1,
22 Paper 72, 19:24–21:12), CVC argues that it had no claims limited to a eukaryotic
23 environment that were in condition for allowance. (*See* CVC Opp. 1, Paper 428,

Interference 106,115

1 18:10–12.) According to Broad, such claims would not have been patentable to
2 CVC. (*See* Broad Reply 1, Paper 433, 3:12–13.) Because the patentability of such
3 claims to CVC was not certain at the time of the '048 Interference, we agree with
4 CVC that allowing ex parte examination to conclude was preferable. (*See* CVC
5 Opp. 1, Paper 428, 18:12–14.) Indeed, the Board expressed this view in response
6 to a request to file a preliminary, as opposed to responsive, motion to add a claim
7 and substitute the count, stating:

8 UC was not authorized to file [a motion to add a claim as contingent
9 on a motion to substitute a count where none of the parties' claims
10 correspond to the proposed count]. Under the facts and circumstances
11 of this interference, where UC believes all of its current claims
12 interfere with all of Broad's claims, there is no reason why UC should
13 need to add a new claim. *If UC's claims in other applications are*
14 *ultimately found to be allowable, UC may suggest additional*
15 *interferences to the examiner.* At this point in the proceeding, though,
16 a determination of priority may proceed on the subject matter
17 commonly and currently claimed by the parties. A priority
18 determination does not require the addition of any other claims.

19

20 (Order of 11 May 2016 in '048 Interference, Paper 48, 5:5–15 (emphasis added).)
21 Thus, even if allowability is not a requirement for filing a motion to add a claim to
22 an interference under Standing Order ¶ 208.5.1, as Broad argues (*see* Broad Reply,
23 Paper 433, 10:3–9), CVC was informed in the last interference that other
24 interferences may be declared if its then pending claims were deemed allowable.
25 We agree with Broad that the refusal of a CVC motion to add a claim in the
26 previous interference was not in regard to the type of motion Broad now argues

Interference 106,115

1 CVC should have sought. (*See* Broad Reply 1, Paper 433, 10:23–11:7.)

2 Nevertheless, the explanation quoted above could have been interpreted to mean
3 that the Board would entertain future interferences on different, but related subject
4 matter and that Rule 127(a)(1) estoppel would not apply to that subject matter.

5 Because we are not persuaded by Broad’s arguments that CVC is estopped
6 from participating in this interference, we DENY Broad Motion 1.⁴

7 Having determined that the interference will not be terminated at this point,
8 we turn to the substantive issues of the parties’ other motions.

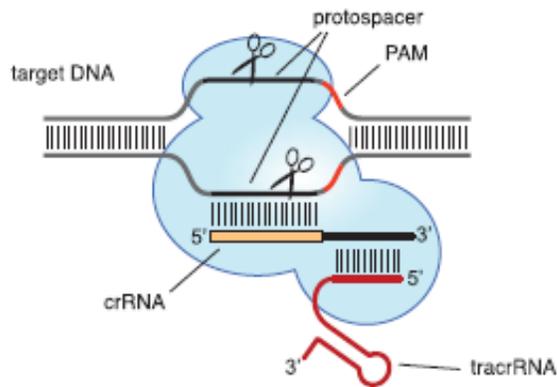
9 *III. Claim Construction*

10 Some of the issues in Broad’s motions, particularly Motions 2 and 3, are
11 related to the scope of Broad’s claims regarding the configuration of the CRISPR-
12 Cas9 system. The CRISPR-Cas systems of the parties’ claims comprise two RNA
13 components and one protein component to achieve site specific cleavage of a
14 double-stranded DNA. (*See* Seeger Decl., Ex. 3401, ¶ 2.10.) Figure 5A of Jinek
15 2012⁵ depicts a schematic diagram of the components of a CRISPR-Cas9 system
16 and is reproduced, in part, below.

⁴ CVC requested authorization to file a sur-reply to Broad’s Reply 1. (*See* Order, Paper 443, 2:3–17.) Because we deny Broad Motion 1, the issues raised by CVC are moot and no sur-reply is necessary.

⁵ Jinek et al., “A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity,” *Science* 337:816–21 (2012) (Ex. 3202).

Cas9 programmed by crRNA:tracrRNA duplex



1
2 Figure 5A depicts a (1) a Cas9 protein shown as blue connected circular shapes in
3 the background, (2) a “crRNA”⁶ shown as bonded to a target DNA (vertical black
4 lines indicating nucleic acid base pairing)⁷, and (3) a “tracrRNA”⁸ shown as a red
5 curved line bonded to the crRNA. (See Jinek 2012, Ex. 3202, 820.) In a CRISPR-
6 Cas9 system, the tracrRNA interacts by base-pairing with the crRNA to form a
7 crRNA:tracrRNA complex, which then directs the Cas9 protein to target and cut

⁶ CVC uses the term “targeted RNA” for this component in its involved claims. (See, e.g., CVC Clean Copy of Claims, Paper 7, 3.)

⁷ We note that Broad defines sub-portions of crRNA component, including a “guide sequence” and a “tracr mate” sequence that together make up the crRNA. (See ’359 patent, Ex. 3011, 16:32–42 (“In general, ‘CRISPR system’ refers collectively to transcripts and other elements involved in the expression of or directing the activity of CRISPR-associated (“Cas”) genes, including sequences encoding a Cas gene, a tracr (transactivating CRISPR) sequence . . . , a tracr-mate sequence . . . a guide sequence . . . , or other sequences and transcripts from a CRISPR locus.”).)

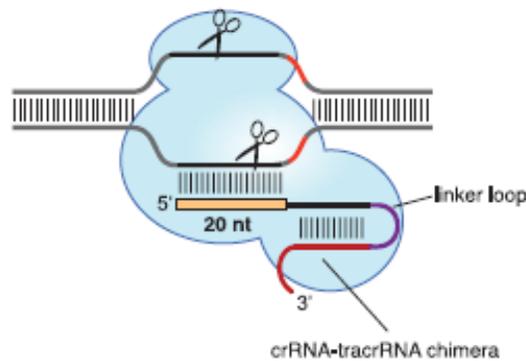
⁸ CVC uses the term “activator-RNA” for this component in its involved claims. (See, e.g., CVC Clean Copy of Claims, Paper 7, 3.)

Interference 106,115

1 DNA in a site-specific matter. (See Seeger Decl., Ex. 3401, ¶ 2.10.) In Figure 5A
2 depicted above, the crRNA and the tracrRNA are separate RNAs, not linked or
3 fused, in a configuration we refer to as a dual- or double-molecule RNA
4 configuration.

5 Figure 5A of Jinek 2012 provides another schematic diagram that contrasts
6 with part of Figure 5A shown above. This part of Figure 5A is reproduced below.

7 Cas9 programmed by single chimeric RNA



12 The figure depicts the same components as the portion of Figure 5A reproduced
13 above, but the crRNA and the tracrRNA are joined with a linker loop. (See Jinek
14 2012, Ex. 3202, 820.) This is an alternate RNA molecule configuration for a
15 CRISPR-Cas9 system, which we refer to a single-molecule RNA configuration.
16 This configuration is in contrast to the one depicted above, in which the crRNA
17 and tracrRNA are separate, not linked, joined, or fused.

18 Broad uses the term “crRNA” in its specification, but uses the terms “guide
19 RNA,” “chimeric RNA,” and “guide sequence” in its involved claims. (See Broad
20 Clean Copy of Claims, Paper 14; see ’359 patent, Ex. 3001, Fig. 2A.) The

Interference 106,115

1 interpretation and scope of the term “guide RNA” in Broad’s claims is disputed by
2 the parties. Specifically, Broad argues that the majority of its involved claims
3 recite “guide RNA” and are not limited as to a single- or dual-molecule RNA
4 configuration. (See Broad Motion 2, Paper 271, 10:7–9; see Broad Motion 3,
5 Paper 268, 9:2–10:2.) CVC disagrees, arguing that all of Broad’s claims are
6 limited to a single-molecule guide. (See CVC Opp. 2, Paper 575, 13:21–22; see
7 CVC Opp. 3, Paper 591, 17:16–23:10.) Because many of the issues raised in
8 Broad’s motions are related to the interpretation of Broad’s claims, we address the
9 interpretation of the claim term “guide RNA” first.

10 We use the broadest reasonable interpretation to determine the scope of
11 interfering claims and the scope of Broad’s claim term “guide RNA.” See
12 *Bamberger v. Cheruvu*, 55 U.S.P.Q.2d 1523, 1527 (BPAI 1998) (broadest
13 reasonable construction standard applies in interference proceedings), cited with
14 approval in *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2145 (2016). The
15 broadest reasonable interpretation is based on the claim language read in light of
16 the specification as it would be interpreted by one of ordinary skill in the art. See
17 *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004); see
18 *Microsoft Corp. v. Proxycom, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (“[U]nder
19 the broadest reasonable interpretation, the Board’s construction cannot be divorced
20 from the specification and the record evidence, and must be consistent with the one
21 that those skilled in the art would reach.” (internal quotations and citations
22 omitted).)

Interference 106,115

1 Broad argues that the term “guide RNA” includes both single- and dual-
2 molecule RNA configurations and, thus, is a generic term. (See Broad Motion 3,
3 Paper 268, 21:20–21, citing Declaration of Technical Expert Ronald Breaker in
4 Support of Broad (“Breaker Decl.”)⁹, Ex. 3403, ¶¶ 5.8–5.18.) Broad first cites to
5 claims that distinguish between the terms “guide RNA” and “fused” guide RNA.
6 (See Broad Motion 3, Paper 268, 21:22–22:9.) That is, Broad argues that there is a
7 presumption that claims reciting a “guide RNA,” with dependent claims that recite
8 a “fused” guide RNA, are not limited to fused RNA. (See Broad Motion 3,
9 Paper 268, 21:22–22:9.) Broad refers to claim 18 of patent 8,697,359 (“the
10 ’359 patent”), which is part of the Count 1, as an example. Claim 18 recites:

11 The CRISPR-Cas system of claim 15, wherein the *guide RNAs*
12 comprise a guide sequence fused to a tracr sequence.
13 (Broad Clean Copy of Claims, Paper 14, 5 (emphasis added).) Claim 15, from
14 which claim 18 depends, recites:

15 An engineered, programmable, non-naturally occurring Type II
16 CRISPR-Cas system comprising a Cas9 protein and at least one *guide*
17 *RNA* that targets and hybridizes to a target sequence of a DNA

⁹ Dr. Breaker testifies that his research includes advanced functions of nucleic acids, including ribozyme reaction mechanisms, molecular switch technology, and catalytic RNA and DNA engineering and that he co-founded a company that uses bacterial riboswitch technology. (See Breaker Decl., Ex. 3403, ¶ 2.4.) Dr. Breaker’s *curriculum vitae* (Ex. 3404) supports his testimony, listing patents and publications in the field of advanced nucleic acid engineering. CVC does not contest his qualifications. We find Dr. Breaker to be qualified to present opinions on the technical issues of this interference.

Interference 106,115

1 molecule in a eukaryotic cell, wherein the DNA molecule encodes and
2 the eukaryotic cell expresses at least one gene product and the Cas9
3 protein cleaves the DNA molecules, whereby expression of the at
4 least one gene product is altered; and, wherein the Cas9 protein and
5 the guide RNA do not naturally occur together.

6 (*Id.* (emphasis added)) According to Broad, the term “fused” in claim 18 narrows
7 the generic term “guide RNA” in claim 15. (*See* Broad Motion 3, Paper 268, 22:2–
8 3.) As Broad argues, under the doctrine of claim differentiation, “the presence of a
9 dependent claim that adds a particular limitation gives rise to a presumption that
10 the limitation in question is not present in the independent claim.” (*Phillips v.*
11 *AWH Corp.*, 415 F.3d 1303, 1314–15 (Fed. Cir. 2005); *see* Broad Motion 3,
12 Paper 268, 22:3–7.)

13 Broad cites to other claims to argue that not all are drawn to a single-
14 molecule RNA configuration. Specifically, claim 3 of patent 8,993,233 (“the
15 ’233 patent”) recites an engineered CRISPR-Cas system that alters expression of at
16 least one gene product, with one or more vectors comprising:

17 a) a first regulatory element operable in a eukaryotic cell
18 operably linked to a guide sequence capable of hybridizing to a target
19 sequence in the eukaryotic cell, and at least one or more tracr mate
20 sequences, and

21 b) a second regulatory element operable in a eukaryotic cell
22 operably linked to a nucleotide sequence encoding a fusion of a Type-
23 II Cas9 protein and one or more protein domains, and

24 c) a third regulatory element operably linked to a tracr sequence,
25 wherein:

Interference 106,115

1 *components (a), (b) and (c) are located on same or different*
2 *vectors of the system, the Cas9 protein comprises one or more*
3 *mutations in a catalytic domain, the guide RNA comprises a tracr*
4 *sequence which is 30 or more nucleotides in length, the Cas9 protein*
5 *and the guide RNA do not naturally occur together,*

6 (Broad Clean Copy of Claims, Paper 14, 55–57 (emphasis added).) According to
7 Broad, a delivery system with the recited sequences on different vectors would
8 result in a complex with “guide RNA” in a dual-molecule configuration. (*See*
9 *Broad Motion 3, Paper 268, 22:10–15, citing Breaker Decl., Ex. 3403, ¶ 5.10.*)

10 CVC opposes these arguments, noting that claim differentiation is not a rigid
11 rule. (*See CVC Opp. 3, Paper 591, 20:20–23, citing Howmedica Osteonics Corp.*
12 *v. Zimmer, Inc.*, 822 F.3d 1312, 1323 (Fed. Cir. 2016) (“claim differentiation is a
13 rebuttable presumption that may be overcome by a contrary construction dictated
14 by the written description or prosecution history.”), and *GPNE Corp. v. Apple,*
15 *Inc.*, 830 F.3d 1365, 1371 (Fed. Cir. 2016) (“Claim differentiation is “not a hard
16 and fast rule,” but rather a presumption that will be overcome when the
17 specification or prosecution history dictates a contrary construction.”).)

18 CVC argues further that claim 3 of the '233 patent does not require the
19 “guide RNA” to have a dual-molecule configuration because element (a),
20 comprising the guide sequence and tracr mate sequence, and element (c),
21 comprising the tracr sequence, may be on one vector, whereas element (b), the
22 comprising the sequence encoding Cas9, is on a different vector in satisfaction of
23 the requirement that the elements (a), (b), and (c) be on different vectors. (*See*
24 *CVC Opp. 3, Paper 591, 20:23–21:8.*)

Interference 106,115

1 We agree with Broad that some of its claims, such as claims 15 and 18 of the
2 '359 patent tend to indicate that “guide RNA” is a generic term, which could be
3 limited to single-molecule RNA configuration by the term “fused” in a dependent
4 claim. We agree with CVC, though, that other instances, such as claim 3 of the
5 '233 patent could be interpreted differently than Broad asserts. Although we are
6 mindful of claim differentiation, we review the other evidence presented by the
7 parties to see if the presumptions it creates are rebutted.

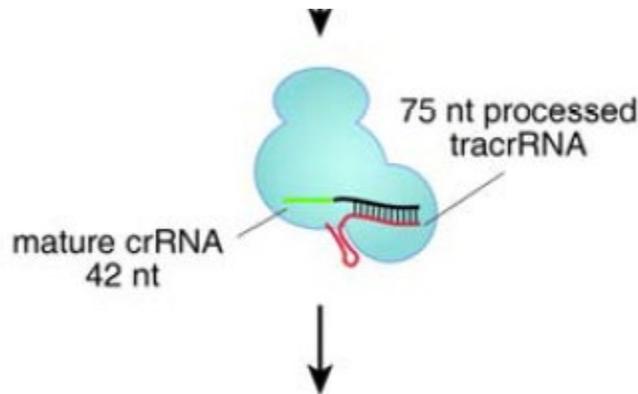
8 Broad argues further that the term “guide RNA” in Broad’s involved claims
9 must be interpreted broadly, to include both single- and dual-molecule RNA
10 configurations, because there is no clear disavowal of claim scope in the
11 specification. (*See* Broad Motion 3, Paper 268, 20:20–21:17, citing *Thorner v.*
12 *Sony Computer Entertainment America LLC*, 669 F.3d 1362, 1366–67 (Fed. Cir.
13 2012).) According to Broad, the term “guide RNA” had a plain meaning in the art,
14 which “indisputably” included both single- and dual-molecule RNA
15 configurations. (*See* Broad Motion 3, Paper 268, 21:9–15.)

16 Broad cites to Jinek 2012 (Ex. 3202), which was authored by CVC
17 inventors, in support of its argument of a plain meaning of the term “guide RNA”
18 in the art. (*See* Broad Motion 3, Paper 268, 21:10–14.) The caption of Figure S1
19 of Jinek 2012 provides a schematic diagram depicting the Type II RNA-mediated
20 CRISPR/Cas immune pathway. (Jinek 2012, Ex. 3202, 14.) The caption states:
21 “In this ternary complex, the dual tracrRNA:crRNA structure acts as *guide RNA*
22 that directs the endonuclease Cas9 to the cognate target DNA.” (*Id.* (emphasis
23 added).) Dr. Breaker testifies:

Interference 106,115

1 The “ternary complex” refers to the three part complex that consists of
2 (1) Cas9, (2) a mature crRNA molecule and (3) a tracrRNA molecule.
3 This is significant because “the dual tracrRNA:crRNA structure”
4 makes up two parts of the three part complex. Otherwise, Jinek 2012
5 would not have referred to the Cas9:RNA complex as a “ternary
6 complex,” but as a binary complex. Thus, the “guide RNA” in that
7 sentence references the dual-guide RNA consisting of separate strands
8 of tracrRNA and crRNA.

9 (Breaker Decl., Ex. 3403, ¶ 5.19.) Figure S1 of Jinek 2012, which is reproduced
10 below, is consistent with Dr. Breaker’s testimony.



11
12 The reproduced portion of Figure S1 depicts a Cas9 protein with two separate
13 RNAs: a “mature crRNA” and a “tracrRNA.” Thus, we agree that Jinek 2012
14 (Ex. 3202) uses the term “guide RNA” to indicate a dual molecule RNA
15 configuration.

16 Broad’s other evidence in support of a plain meaning for the term “guide
17 RNA” in the art is less persuasive. For example, Broad cites to Dr. Breaker’s
18 testimony about the specification of CVC’s 15/947,680 application (“the
19 ’680 application”). (See Broad Motion 3, Paper 268, 21:14–15, citing Breaker
20 Decl., Ex. 3403, ¶¶ 5.19–5.23.) Dr. Breaker testifies that the ’680 application

Interference 106,115

1 states: “The term ‘DNA-targeting RNA’ or ‘gRNA’ is inclusive, referring both to
2 double-molecule DNA-targeting RNAs and to single-molecule DNA-targeting
3 RNAs (i.e., sgRNAs).” (’680 appl., Ex. 3018, ¶ 136; *see* Breaker Decl., Ex. 3403,
4 ¶ 5.20.) Although the term “gRNA” likely refers to “guide RNA,” it is not exactly
5 the same term used in Broad’s claims.

6 Dr. Breaker testifies further to a publication co-authored by CVC inventors
7 in 2014, Sternberg¹⁰ (Ex. 3217). (*See* Breaker Decl., Ex. 3403, ¶ 5.21, citing
8 Sternberg 2014, Ex. 3217, 62.) According to Dr. Breaker, Sternberg uses the term
9 “guide RNA” to refer to all crRNA:tracrRNA complexes, whether present as a
10 single or a double-molecule. (*See* Breaker Decl., Ex. 3403, ¶ 5.21.) Dr. Breaker
11 does not cite to specific examples in Sternberg to support his testimony. We note
12 that in the abstract Sternberg states: “Cas9–guide RNA complexes are also
13 effective genome engineering agents in animals and plants” (Sternberg, Ex. 3217,
14 62), presumably referring to a single-molecule RNA configuration, and depicts a
15 dual-molecule configuration in Figure 1b, which may be referred to as a “λ2 guide
16 RNA” (*id.* at 63). But without an explanation of how these specific instances of
17 the terms would have been understood by those in the art at the time, we are not
18 certain they demonstrate uses of “guide RNA” as a generic term.

19 Dr. Breaker also cites to statements made by CVC’s witnesses in the prior
20 ’048 interference. (*See* Breaker Decl., Ex. 3403, ¶ 5.22, citing Grieder Decl.,
21 Ex. 3406, ¶ 374, and Carroll Decl., Ex. 3407, ¶ 365.) Drs. Grieder and Carroll

¹⁰ Sternberg, *et al.*, “DNA interrogation by the CRISPR RNA-guided endonuclease Cas9,” *Nature*, 507:62 (2014) (Ex. 3217).

Interference 106,115

1 stated: “the use of a composition that includes purified recombinant *S. pyogenes*
2 Cas9 protein and either a single-guide or dual-guide DNA targeting RNA, *i.e.*, the
3 complex of Count 1 and Proposed Count 2 (single-guide DNA-targeting RNA
4 complex).” (Grieder Decl., Ex. 3406, ¶ 374, and Carroll Decl., Ex. 3407, ¶ 365.)
5 Although the witnesses refer to “guide DNA targeting RNA,” they do not use the
6 specific term “guide RNA.” Thus, their testimony does not shed light on how that
7 specific term would have been used in the art at the time.

8 Dr. Breaker points further to representations made by CVC’s counsel in the
9 prior ’048 interference, using the term “guide RNA” to “cover both the dual guide
10 and single guide embodiments.” (*See* Breaker Decl., Ex. 3403, ¶ 5.23, citing
11 Paper 45, ’048 Interference, Ex. 3106, 19:8–11, 22:12–23:7.) CVC’s counsel may
12 have used this term in a generic way, but he is not one of skill in the art and we are
13 not persuaded that his use of technical terms indicates anything about how they
14 would have been understood by those in the art at the time.

15 Dr. Breaker cites to Bhaya¹¹, published in 2011 (“Bhaya”), which describes
16 naturally occurring CRISPR systems in bacteria and archaea. (*See* Bhaya,
17 Ex. 3218; *see* Breaker Decl., Ex. 3403, ¶¶ 5.24-5.25.) Bhaya defines “CRISPR
18 RNA (crRNA)” as “small noncoding RNA produced by cleavage of pre-crRNA
19 (also known as psiRNA or guide RNA).” (Bhaya, Ex. 3218, 276, side bar.) Bhaya
20 also states: “The crRNA serves as a guide (hence the term guide RNA has also

¹¹ Bhaya, *et al.*, “CRISPR-Cas Systems in Bacteria and Archaea: Versatile Small RNAs for Adaptive Defense and Regulation,” *Ann. Rev. Genet.*, 45:273–97 (2011) (Ex. 3218).

Interference 106,115

1 been used) to allow for specific base pairing between the exposed crRNA within
2 the ribonucleoprotein interference complex and the corresponding protospacer on
3 the foreign DNA [citations omitted].” (Bhaya, Ex. 3218, 286.) Although Bhaya
4 uses the term “guide RNA” to describe an unfused RNA component of a CRISPR
5 system, as CVC argues, the term refers only to the crRNA, not to both the crRNA
6 and tracrRNA as a complex. (See CVC Opp. 3, Paper 591, 22:2–6.) We agree
7 with CVC that the use of the term “guide RNA” in Bhaya is not relevant to the
8 term “guide RNA” in Broad’s claims.

9 Dr. Breaker cites to several other scientific articles published before 2012,
10 which use the term “guide RNA” to refer to RNA components of naturally
11 occurring CRISPR systems. (See Breaker Decl., Ex. 3403, ¶ 5.24, citing Carte¹²,
12 Ex. 3219, 3490; Hale¹³, Ex. 3220, 2577; Jore¹⁴, Ex. 3221, 529; and Brouns¹⁵, Ex.
13 3222, 960.) And Dr. Breaker cites to scientific articles published before 2012,
14 which use the term “guide RNA” to refer to RNA components of RNA interference
15 systems having protein/RNA complexes asserted to be similar to CRISPR systems.

¹² Carte, *et al.*, “Cas6 is an endoribonuclease that generates guide RNAs for invader defense in prokaryotes,” *Genes & Dev.*, 22:3489–96 (2008) (Ex. 3219).

¹³ Hale et al., Prokaryotic silencing (psi)RNAs in *Pyrococcus furiosus*, *RNA*, 14:2572–79 (2008) (Ex. 3220).

¹⁴ Jore *et al.*, “Structural basis for CRISPR RNA-guided DNA recognition by Cascade,” *Nature Structural & Molecular Biology*, 18:529–37 (2011) (Ex. 3221).

¹⁵ Brouns *et al.*, “Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes,” *Science*, 321:960–64 (2008) (Ex. 3222).

Interference 106,115

1 (See Breaker Decl., Ex. 3403, ¶ 5.25, citing Horvath¹⁶, Ex. 3223, 169; Rand¹⁷, Ex.
2 3224, 621; Tolia¹⁸, Ex. 3225, 36.) We do not agree with Broad or Dr. Breaker that
3 these uses of the term “guide RNA” in early publications are relevant to the issue
4 of whether the term “guide RNA” in Broad’s claims are limited to a single-
5 molecule RNA configuration. It is not clear from Dr. Breaker’s explanation that
6 the term “guide RNA” in these publications refers to a complex of RNAs
7 comparable to the RNA configurations of Broad’s claims. For example, Carte (Ex.
8 3219) states that “[t]he CRISPR loci are transcribed as long RNAs that must be
9 processed to smaller guide RNAs.” (Carte, Ex. 3219, abstract.) Thus, the term
10 “guide RNA” in Carte refers to any RNA produced from the CRISPR loci, not
11 specifically a complex of the crRNA and the tracrRNA. (See CVC Opp. 3, Paper
12 591, 22:2–6.)

13 We are not persuaded from the extrinsic evidence cited by Broad that the
14 term “guide RNA” was well known in the art to mean either a single or a dual
15 RNA molecule configuration. In some publications cited by Broad, such as
16 Jinek 2012, the term “guide RNA” is used to refer to a dual molecule RNA
17 configuration. But in other examples, such as CVC’s ’680 application and
18 Drs. Geider and Carroll’s declarations in the prior ’048 interference, the specific

¹⁶ Horvath and Barrangou, “CRISPR/Cas, the Immune System of Bacteria and Archaea,” *Science*, 327:167–70 (2010) (Ex. 3223).

¹⁷ Rand *et al.*, “Argonaute2 Cleaves the Anti-Guide Stand of siRNA during RISC Activation,” *Cell*, 123:621–29 (2005) (Ex. 3224).

¹⁸ Tolia and Joshua-Tor, “Slicer and the Argonautes,” *Nature Chemical Biology*, 3:36–43 (2007) (Ex. 3225).

Interference 106,115

1 term “guide RNA” was not actually used. In yet other references, such as Bhaya,
2 Horvath, Rand, and Tolia, the term is used, but not for a complex of the crRNA
3 and tracrRNA. This evidence does not persuade us that the term “guide RNA” had
4 a plain meaning in the art, which “indisputably” included both single- and dual-
5 molecule RNA configurations, as Broad argues. (*See* Broad Motion 3, Paper 268,
6 21:9–15.)

7 Because we are not persuaded there was a clear meaning of the term
8 “guide RNA” in the art at time of Broad’s filing, we are not persuaded by Broad’s
9 argument that the specification must provide a clear intent to exclude a dual-
10 molecule RNA configuration from the term. (*See* Broad Motion 3, Paper 268,
11 23:17–23 and 25:15–20.) *See Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d
12 1359, 1363 (Fed. Cir. 2016) (explaining that “*Phillips [v. AWH Corp.*, 415 F.3d
13 1303, 1320 (Fed. Cir. 2005 (en banc),] rejected an approach ‘in which the
14 specification should be consulted only after a determination is made, whether
15 based on a dictionary, treatise, or other source, as to the ordinary meaning or
16 meanings of the claim term in dispute.’”). Instead, we look to the language of the
17 specification to interpret the term.

18 Broad and CVC point to the portion of the Broad specification that reads:

19 In aspects of the invention the terms “chimeric RNA”, “chimeric
20 guide RNA”, “guide RNA”, “single guide RNA” and “synthetic guide
21 RNA” are used interchangeably and refer to the polynucleotide
22 sequence comprising the guide sequence, the tracr sequence and the
23 tracr mate sequence. The term “guide sequence” refers to the about
24 20 bp sequence within the guide RNA that specifies the target site and
25 may be used interchangeably with the terms “guide” or “spacer”. The

Interference 106,115

1 term “tracr mate sequence” may also be used interchangeably with the
2 term “direct repeat(s)”. An exemplary CRISPR-Cas system is
3 illustrated in FIG. 1.

4
5 (*E.g.*, ’359 patent, Ex. 3011, 12:6–16; *see* Broad Motion 3, Paper 268, 24:2–5; *see*
6 CVC Opp.3, Paper 591, 18:10–17.) The parties dispute whether this paragraph
7 defines the term “guide RNA.”

8 Broad argues that CVC incorrectly interprets the term “guide RNA” in the
9 first sentence of this paragraph to mean that “guide RNA” is always the equivalent
10 of “chimeric RNA” or “single guide RNA.” (*See* Broad Motion 3, Paper 268,
11 24:6–8.) Instead, Broad argues that the phrase “[i]n aspects of the invention”
12 refers to certain embodiments, some of which are single molecule, but not to the
13 invention as a whole. (*See id.* at 24:9–24.) Broad contrasts the reference to
14 “aspects of the invention” with terms that indicate a definition. For example,
15 Broad cites to the following sentence as defining a term: “As used herein the term
16 ‘wild type’ is a term of the art understood by skilled persons and means the typical
17 form of an organism, strain, gene or characteristic as it occurs in nature as
18 distinguished from mutant or variant forms.” (’359 patent, Ex. 3011, 12:17–20.)
19 Broad argues that this language is “definitional and universal,” in contrast to
20 discussion of “aspects of the invention.” (*See* Broad Motion 3, Paper 268, 24:16–
21 17.)

22 Broad argues further that the term “used interchangeably” does not mean the
23 listed terms have the same meaning. (*See id.* at 25:1–14.) Broad cites to other uses
24 of the phrase in its specification, for example: “The terms ‘polynucleotide’,

Interference 106,115

1 ‘nucleotide’, ‘nucleotide sequence’, ‘nucleic acid’ and ‘oligonucleotide’ are used
2 interchangeably.” (’359 patent, Ex. 3011, 11:50–52; *see* Broad Motion 3, Paper
3 268, 25:4–5.) Broad argues that one of ordinary skill in the art would not have
4 understood a polynucleotide to be the same thing as a nucleotide, but rather that
5 these terms could be substituted where appropriate. According to Broad, the same
6 is true about the phrase “used interchangeably” in regard to “guide RNA” and
7 “chimeric RNA,” wherein one of ordinary skill would not have understood the
8 terms to mean the same thing, rather that they could be substituted for each other,
9 where appropriate, in certain aspects of the invention. (*See* Broad Motion 3, Paper
10 268, 25:6–14.)

11 CVC disputes Broad’s characterization of this portion of the Broad
12 specification. (*See* CVC Opp. 3, Paper 591, 18:10–19:12.) CVC argues that the
13 specification specifically states that the terms “guide RNA,” “chimeric RNA,”
14 “chimeric guide RNA,” and “single guide RNA” all “refer to the polynucleotide
15 sequence comprising the guide sequence, the tracr sequence and the tracr mate
16 sequence.” (*See id.* at 18:18–21, citing ’359 patent, Ex. 3011, 12:6–10, and citing
17 Third Peterson Decl., Ex. 4193, ¶¶ 84–85.) According to CVC, this portion of the
18 specification defines “guide RNA” as a singular polynucleotide sequence
19 comprising a guide sequence, a tracr sequence, and a tracr mate sequence and
20 corresponding to the fused crRNA and the tracrRNA. (*See* CVC Opp. 3,
21 Paper 591, 18:21–23.)

22 We are persuaded by CVC’s argument. Although the phrase “used
23 interchangeably” could be interpreted as Broad argues, the phrase “refer to”

Interference 106,115

1 indicates that each of the RNAs recited in this paragraph comprise three
2 components: a guide sequence, a tracr sequence, and a tracr mate sequence. Thus,
3 this paragraph of the Broad specification indicates that “chimeric RNA,” “chimeric
4 guide RNA,” single guide RNA,” as well as “guide RNA” include these three
5 components.

6 The parties disagree about the use of the term “guide RNA” in other parts of
7 the Broad specification. Broad cites to Example 6 of the ’356 patent specification,
8 which is entitled “Optimization of the Guide RNA for *Streptococcus pyogenes*
9 CAs 9 (Referred to as SpCas9).” (See Broad Motion 3, Paper 268, 22:16–23:4; see
10 ’356 patent, Ex. 3016, 105:3–4.) Relying on Dr. Breaker’s testimony, Broad
11 argues that the term “guide RNA” refers to both dual and single molecule RNA
12 configurations because the specification explains either “the tracrRNA and direct
13 repeat sequences” or “the chimeric guide RNA” was mutated to enhance the RNAs
14 in cells. (See ’356 patent, Ex. 3016, 105:3–8; see Breaker Decl., Ex. 3403, ¶ 5.14.)
15 CVC opposes this characterization of Example 6 of the ’356 patent, arguing that it
16 reports results from only single molecule configurations, as described in the text
17 and depicted in Figure 3. (See CVC Opp. 3, Paper 591, 20:4–13; see Third
18 Peterson Decl., Ex. 4193, ¶ 95.)

19 We agree with CVC that if only single molecule RNA configuration guide
20 RNAs are used in the experiments of Example 6, the term in the title does not refer
21 to both single- and dual-molecule configurations. We are not persuaded that the
22 language “mutated the tracrRNA and direct repeat sequences” necessarily means
23 that they are on different RNAs in a dual molecule configuration.

Interference 106,115

1 Broad cites further to its involved '308 patent (Ex. 3013), specifically the
2 reference to “chimeric guide RNA” and a “combination of tracr RNA and cr RNA”
3 collectively as “guide RNA.” (Broad Motion 3, paper 268, 22:23–23:3, citing
4 '308 patent, Ex. 3013, 38:33–43.) The portion cited by Broad recites, exactly:

5 Cas9 and its chimeric guide RNA, or combination of tracrRNA and
6 crRNA. can be delivered either as DNA or RNA. Delivery of Cas9
7 and guide RNA both as RNA (normal or containing base or backbone
8 modifications) molecules can be used to reduce the amount of time
9 that Cas9 protein persist in the cell. This may reduce the level of off-
10 target cleavage activity in the target cell. Since delivery of Cas9 as
11 mRNA takes time to be translated into protein, it might be
12 advantageous to deliver the guide RNA several hours following the
13 delivery of Cas9 mRNA, to maximize the level of guide RNA
14 available for interaction with Cas9 protein.

15

16 ('308 patent, Ex. 3013, 38:33–43.)

17 We disagree with Broad’s characterization of this passage because the first
18 lines of this portion clearly includes a typographical error. Specifically, the phrase
19 “Cas9 and its chimeric guide RNA, or combination of tracrRNA and crRNA” is
20 not a full sentence and, therefore, should not end with a period. Instead, the period
21 should be a comma, wherein the sentence would read: “Cas9 and its chimeric
22 guide RNA, or combination of tracrRNA and crRNA, can be delivered either as
23 DNA or RNA.” Written correctly, the combination of tracrRNA and crRNA
24 characterizes “chimeric guide RNA.” This portion of the '308 patent describes a
25 single molecule chimeric RNA only, not a dual molecule guide RNA. We agree
26 with CVC’s witness, Dr. Peterson, that the subsequent recitation of “guide RNA”

Interference 106,115

1 in this passage would not be understood to refer to a dual-molecule RNA
2 configuration of tracrRNA and crRNA. (See Third Peterson Decl., Ex. 4193,
3 ¶¶ 96–97; see CVC Opp. 3, Paper 591, 20:14–15.)

4 Broad also argues that the specification of the involved '359 patent identifies
5 preferred embodiments that have dual-molecule RNA configurations and should
6 not be read out of the '359 patent claims. (See Broad Motion 3, Paper 268, 23:5–
7 10, citing '359 patent, Ex. 3011, 44:5–8.) This argument fails to persuade us that
8 the claim term “guide RNA” is generic to the RNA configuration because the
9 portion cited by Broad fails to use the term “guide RNA.” Even if single- or
10 double-molecule RNA configurations are preferred embodiments, whether or not
11 Broad claims these embodiments depends on the language of the claims.

12 Our review of the parties' arguments leads us to the conclusion that Broad's
13 use of the term “guide RNA” in its involved claims is not a generic term, but is
14 limited to a single-molecule RNA configuration of the guide sequence and
15 tracrmate, which together make the crRNA, and the tracrRNA sequences.
16 Although some dependent claims, such as claim 18 of the '359 patent, might
17 indicate by claim differentiation that the term “guide RNA” is generic, that
18 presumption is overcome by Broad's specification. The specification of Broad's
19 involved patents, specifically the sentence providing that “guide RNA” and other
20 terms “refer to the polynucleotide sequence comprising the guide sequence, the
21 tracr sequence and the tracr mate sequence” ('359 patent, Ex. 3011, 12:6–10),
22 limits the interpretation of the term. Broad fails to direct us to other uses of the
23 term “guide RNA” in the specification that indicate a dual-molecule RNA

Interference 106,115

1 configuration and we are not persuaded that the term was so clearly understood in
2 the art to be a generic term that only a clear disavowal in the specification would
3 define it to mean a single-molecule RNA configuration. Thus, we are persuaded
4 that the broadest reasonable interpretation of Broad claim term “guide RNA”
5 encompasses only a single-molecule RNA configuration.

6 *IV. Broad Motion 2 – To Change the Count*

7 Broad requests in its Motion 2 that Count 1 be changed to proposed Count 2.
8 (*See* Broad Motion 2, Paper 271, 1:2–5.) Because Broad fails to provide a
9 sufficient reason why the count should be changed, we deny Broad’s request.

10 A count is “the Board's description of the interfering subject matter that sets
11 the scope of admissible proofs on priority.” 37 C.F.R. § 41.201. Thus, the count
12 in an interference determines which proofs will show priority. Count 1 was
13 provided upon Declaration of this interference. (*See* Declaration, Paper 1, 12–13.)

14 Although parties may request that a count be changed to a proposed count
15 with a different scope, in order to change the scope of the proofs necessary, we will
16 make such a change only if there is a compelling reason to do so. *See Louis v.*
17 *Okada*, 59 U.S.P.Q.2d 1073, 1076 (BPAI 2001). This is particularly true if the
18 scope of the proposed count is broader than the sum of what each party has
19 claimed. Arguments that a moving party's best or earliest proofs are outside the
20 scope of the existing count are ordinarily not compelling by themselves. (*See id.*)

21 Broad argues that each party has involved claims drawn to eukaryotic
22 CRISPR-Cas9 systems that are not limited to a single- or dual-molecule RNA
23 configuration and that this non-limited subject matter is the interfering subject

Interference 106,115

1 matter. (*See* Broad Motion 2, Paper 271, 13:13–14.) According to Broad, Count 1
2 is improper because it is limited to a single-molecule RNA configuration. (*See id.*
3 at 2:12–13.)

4 Broad’s proposed Count 2 recites:

5 A method, in a eukaryotic cell, of cleaving or editing a target
6 DNA molecule or modulating transcription of at least one gene
7 encoded by the target DNA molecule, the method comprising:

8 contacting, in a eukaryotic cell, a target DNA molecule having a
9 target sequence with an engineered and/or non-naturally-occurring
10 Type II Clustered Regularly Interspaced Short Palindromic Repeats
11 (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system
12 comprising:

13 a) a Cas9 protein, and

14 b) RNA comprising

15 i) a targeter-RNA that is capable of hybridizing with the target
16 sequence of the DNA molecule or a first RNA comprising (A) a first
17 sequence capable of hybridizing with the target sequence of the DNA
18 molecule and (B) a second sequence; and

19 ii) an activator-RNA that is capable of hybridizing to the
20 targeter-RNA to form an RNA duplex in the eukaryotic cell or a
21 second RNA comprising a tracr sequence that is capable of
22 hybridizing to the second sequence to form an RNA duplex in the
23 eukaryotic cell,

24 wherein, in the eukaryotic cell, the targeter-RNA or the first
25 sequence directs the Cas9 protein to the target sequence and the DNA
26 molecule is cleaved or edited or at least one product of the DNA
27 molecule is altered.

28

Interference 106,115

1 (Broad Motion 2, Paper 271, 1:16–2:10.) According to Broad, the “critical
2 distinction” between Count 1 and proposed Count 2 is that the latter is not limited
3 by a configuration of the RNA molecule and can encompass both a single- and a
4 dual-molecule configuration. (*See id.* at 1:9–13.)

5 We agree with CVC that there are other differences between Count 1 and
6 proposed Count 2. For example proposed Count 2 is directed to a method, whereas
7 Count 1 is directed to a system or a eukaryotic cell. (*See* Declaration, Paper 1, 12–
8 13; *see* CVC Opp. 2, Paper 575, 3:14–12:9.) Broad does not explain why these
9 other changes are necessary. (*See, e.g.*, Broad Reply 2, Paper 820, 9:3–11 (arguing
10 that the method of proposed Count 2 includes a system and takes place in a
11 eukaryotic cell and that CVC has argued in the past that the decision in the prior
12 ’048 interference extends to both method and system claims).) Because we decline
13 to make a change in the count “for change’s sake” (*Louis*, 59 U.S.P.Q.2d at 1076),
14 we deny Broad’s request on this basis alone.

15 Even if Broad had provided a sufficient reason for these other changes,
16 Broad’s argument for broadening the scope of the count to be generic as to RNA
17 configuration is unpersuasive. Broad argues:

18 Proceeding with Count 1 could preclude the Broad from relying
19 on its best and earliest proofs, generic molecule experiments. This [is]
20 plainly unfair to Broad, given the majority of Broad’s claims at issue
21 in this interference are generic molecule claims. Whether Broad can
22 keep its generic claims to the fundamental breakthrough – the
23 invention of use of CRISPR in eukaryotic cells – should not turn on
24 who invented the single molecule modification to the fundamental
25 invention first.

Interference 106,115

1
2 (Broad Motion 2, Paper 271, 3:17–22.) Broad’s argument has three main points.
3 First, Broad argues that Count 1 does not describe the full scope of the interfering
4 subject matter because both parties have claims that are not limited by the
5 configuration of the RNA, with the majority of Broad’s claims being generic. (*See*
6 *id.* at 14:17–15:6.) Second, Broad argues that the current Count precludes Broad
7 from relying on its best and earliest proofs, which are of experiments with generic
8 molecules. (*See id.* at 15:17–16:19.) Third, Broad argues that Count 1 will
9 determine which party is entitled to claims to generic or dual molecule systems in
10 eukaryotic cells, even though no priority determination will have been made to
11 those systems. (*See id.* at 16:20–17:20.)

12 CVC opposes the first part of Broad’s argument by asserting that all of
13 Broad’s claims are limited to a single-molecule RNA configuration because all
14 recite either “guide RNA” or “chimeric RNA.” (*See* CVC Opp. 2, Paper 575,
15 13:19–14:12.) Thus, according to CVC, a CRISPR-Cas9 system with a single-
16 molecule RNA is the only common subject matter between the parties and is
17 properly encompassed by the Count 1. (*See id.*)

18 As discussed above, after considering both parties’ arguments and evidence
19 regarding the proper interpretation of the claim term “guide RNA,” we are
20 persuaded that it means a single-molecule RNA configuration of the guide
21 sequence, tracr mate sequence, and tracr sequence. In addition, we agree with
22 CVC that Broad admits the term “chimeric RNA” means a single-molecule RNA
23 configuration. (*See* CVC Opp. 2, Paper 575, 14:6, citing Broad Motion 3,
24 Paper 268, 19:16–20 (“only 43 of Broad’s 387 involved claims require single-

Interference 106,115

1 molecule guide RNA by virtue of containing a limitation to “fused” RNA or
2 “chimeric” RNA.”.) Thus, Broad claims with the terms “guide RNA” or
3 “chimeric RNA” indicate a single-molecule RNA configuration.

4 Broad argues that the “the vast majority of [its] involved claims are directed
5 to non-limited RNA systems and methods,” but fails to provide an interpretation of
6 each claim, or even some of its claims, in support. (*See* Broad Motion 2,
7 Paper 271, 3:10–11.) Broad lists, in a footnote, claims it argues are limited to a
8 single-molecule RNA configuration. (*See* Broad Motion 2, Paper 271, 28, n. 5; *see*
9 Transcript, Paper 871, 13:19–25.) Specifically, Broad identifies only the following
10 claims as being limited to a single-molecule RNA:

- 11 ’359 patent - claims 4, 11, and 18;
- 12 ’965 patent - claims 1–30;
- 13 ’945 patent - claim 5;
- 14 ’616 claims - 2 and 5;
- 15 ’713 patent - claims 8, 9, 16, and 27
- 16 ’551 application - claims 2, 4,–8, and 12–18.

17 (*See* Broad Motion 2, Paper 271, 28, n. 5)

18 We are unpersuaded that these are the only Broad claims limited to a single-
19 molecule RNA configuration because many of Broad’s other claims recite the term
20 “guide RNA” or depend on claims that recite the term “guide RNA.” For example,
21 independent claims 1, 8, and 15 of the ’359 patent each recite CRISPR-Cas9
22 systems including a “guide RNA that hybridizes with a target sequence,” or similar
23 sequence. (*See* Broad Clean Copy of Claims, Paper 14, 3–5.) These independent

Interference 106,115

1 claims do not recite the RNA components of a CRISPR-Cas9 system individually
2 (*i.e.*, the guide sequence, the tracr mate sequence, and the tracr sequence) or any
3 specific arrangement for them. Thus, under our interpretation of the term “guide
4 RNA” from Broad’s specification, and contrary to Broad’s characterization (*see*
5 Broad Motion 2, Paper 271, 9:17–10:4), these independent claims are limited to a
6 single-molecule RNA configuration.

7 Although dependent claims 4, 11, and 18 require the guide RNA to be
8 comprised of a guide sequence “fused” to a tracr sequence, Broad has not
9 persuaded us that the presumption of claim differentiation in these claims
10 overcomes the interpretation of the term “guide RNA” dictated by Broad’s
11 specification. Broad fails to provide an analysis of the relationship of the terms of
12 dependent claims 4, 11, and 18 with the terms of the claims from which they
13 depend, relying instead only on the word “fused” in the dependent claims.

14 Similarly, independent claims 1, 11, 19, and 26 of the ’945 patent recite the
15 term “guide RNAs that hybridize with the target sequence(s),” or a similar phrase,
16 without specifying a relationship between the RNA components of a CRISPR-
17 Cas9 system. (*See* Broad Clean Copy of Claims, Paper 14, 7–11.) We are not
18 persuaded that dependent claim 5 is the only claim of the ’945 patent limited to a
19 single-molecule RNA configuration merely because it recites the phrase “guide
20 sequence fused to a tracr sequence.”

21 Furthermore, the independent claims of at least the ’406, ’445, ’356, ’308,
22 ’814, and ’839 patents have phrases similar to a “guide RNA that hybridizes with a
23 target sequence.” (*See* Broad Clean Copy of Claims, Paper 14, generally.) Broad

Interference 106,115

1 does not identify any claims of these patents that provide a relationship between
2 the RNA components of a CRISPR-Cas9 system. In the absence of a reason why
3 these claims should not be interpreted under the broadest reasonable interpretation
4 of “guide RNA,” we are not persuaded that all of the claims of these patents are not
5 limited to a single-molecule RNA configuration.

6 Broad fails to identify any claims that are directed to generic or dual-
7 molecule RNA configurations under our interpretation of “guide RNA” in its
8 Motion 2. We note that in its reply brief, Broad argues that claim 15 of the ’713
9 patent is directed to a “generic guide RNA.” (See Broad Reply 2, Paper 820, 3:12–
10 13.) Broad cites to footnote 5 on page 28 of its Motion 2, but this claim is not
11 listed in that footnote. Accordingly, CVC did not have notice of arguments
12 regarding claim 15 or of any other claim Broad asserts is directed to a generic
13 RNA configuration without using the term “guide RNA.” Because Broad did not
14 provide arguments about the interpretation of specific claims in its Motion 2 we are
15 not persuaded by its argument that the scope of the “vast majority” of its claims
16 requires a broader count. (Broad Motion 2, Paper 271, 3:10–11, 16:4–6.) See 37
17 C.F.R. § 41.122(b) (“All arguments for the relief requested in a motion must be
18 made in the motion. A reply may only respond to arguments raised in the
19 corresponding opposition.”); see 37 C.F.R. § 41.121(b) (“*Burden of proof.* The
20 party filing the motion has the burden of proof to establish that it is entitled to the
21 requested relief.”).

22 Because Broad fails to persuade us that a majority of its claims are generic
23 as to RNA configuration, we are not persuaded by the argument that the

Interference 106,115

1 interference is only about eukaryotic CRISPR-Cas9 systems. (*See* Broad
2 Motion 2, Paper 271, 15:1–4.) Instead, both parties present a significant number of
3 claims directed to CRISPR-Cas9 systems in eukaryotic cells using a single-
4 molecule RNA configuration. Similarly, we are not persuaded by Broad’s
5 arguments that Count 1 improperly limits Broad’s ability to rely on its best proofs.
6 (*See id.* at 15:17–16:19.) Although Broad characterizes its “best proofs” as
7 including the use of a dual-molecule guide RNA, Broad fails to persuade us in
8 Motion 2 that its claims, properly interpreted, encompass this subject matter.

9 Broad argues further that Count 1 will result in an award of priority to
10 claims not limited to an RNA configuration. (*See id.* at 16:20–17:20.) But Broad
11 fails, in Motion 2, to explain which of its claims are not limited. We note that this
12 issue is also addressed in Broad Motion 3 regarding correspondence to the count,
13 which is discussed below.

14 Broad argues Count 1 is unfair because Broad was denied the opportunity to
15 use these best proofs in the prior interference due to “CVC’s strategic decisions.”
16 (*See* Broad Motion 2, Paper 271, 14:2–9.) This argument is unpersuasive because
17 Broad’s motion for no interference-in-fact was granted in the prior interference,
18 achieving Broad’s desired remedy – ending the interference. Had Broad wished to
19 remain in a priority contest with CVC under the count in that interference, it could
20 have chosen not to file the motion for no interference-in-fact. We see no
21 unfairness in Broad not having had a chance to present its best proofs in a priority
22 contest with CVC in the ’048 interference under these circumstances.

Interference 106,115

1 We are also not persuaded by Broad’s arguments of unfairness because
2 given the potential for ambiguity in the language describing RNA components and
3 their configurations in Broad’s specification, Broad could have presented a “vast
4 majority” of claims that are clearly directed to dual-molecule RNA configurations
5 or are generic as to configuration. (*Contra* Broad Motion 2, Paper 271, 3:10–11.)

6 Broad requests, in one alternative, that if we decline to adopt proposed
7 Count 2 instead of Count 1, we redeclare the interference with two counts: Count 1
8 and proposed Count 2. (*See id.* at 18:1–17.) Broad refers to comments in a Final
9 Rulemaking that explain: “If a party with a generic claim that corresponds to a
10 species count is concerned about the designation, its remedy is to move to have the
11 generic claim designated as not corresponding to the species count.” (*See* 69 Fed.
12 Reg. 49960-01, Ex. 3305, 62.) Broad was authorized, and filed, Motion 3, which
13 argues that certain of its claims should be designated as not corresponding to
14 Count 1. We discuss the parties’ arguments in regard to this motion below. We
15 decline to redeclare the interference with two counts because Broad fails to explain
16 why this would be an appropriate remedy, given that we are not persuaded that a
17 majority, or even a significant number, of its claims are drawn to a generic RNA
18 configuration.

19 Because Broad fails to persuade us that the count should be changed, we
20 DENY Broad’s Motion 2.

21 *V. Broad Motion 3 – Claim Correspondence*

22 Broad argues that if we deny its Motion 2 to change the count, we should

Interference 106,115

1 designate many of its currently involved claims¹⁹ as not corresponding to Count 1.
2 (See Broad Motion 3, Paper 268, 1:2–19.) The claims that Broad highlights fall
3 into three categories: (1) claims that Broad argues are not limited to a single-
4 molecule RNA configuration, (2) claims that are limited to the *Staphylococcus*
5 *aureus* Cas9 protein (“SaCas9”), and (3) claims that are limited to including two
6 nuclear localization signals (“NLSs”). See *id.*

7 *A. RNA Configuration*

8 In regard to the first set of claims, those argued to be not limited to a single-
9 molecule RNA configuration, Broad states:

10 This motion assumes that, Broad Motions 1 and 2 have been denied
11 and the PTAB has determined to proceed with the Interference to
12 determine priority as to *single-molecule* RNA eukaryotic CRISPR
13 claims as a *separate* patentable invention from non-limited guide
14 RNA claims (*i.e.* claims that cover both dual- and single-molecule
15 guide RNA) using Count 1.

16

17 (See Broad Motion 3, Paper 268, 2:15–19.) Broad states further: “Motion 3 is in
18 relevant respect contingent on the PTAB finding that the genus and species claims

¹⁹ Specifically, Broad argues that the following claims should be designated as not corresponding to Count 1: ’406 patent, claims 1–30 (all); ’445 patent, claims 1–30 (all); ’356 patent, claims 1–30 (all); ’814 patent, claims 1–30 (all); ’839 patent, claims 1–28 (all); ’233 patent, claims 1–43 (all); ’641 patent, claims 1–28 (all); ’359 patent, claims 1–3, 5–10, 12–17, and 19–20; ’945 patent, claims 1–4 and 6–29; ’308 patent, claims 1–9 and 11–28; ’616 patent, claims 1, 3–4, and 6–30; ’713 patent, claims 1–7, 10–15, 17–26, and 28–41; and ’551 application (all). (See Broad Motion 3, Paper 268, 1:8–13 and Appendix 3.)

Interference 106,115

1 are separately patentable.” (Broad Reply 3, Paper 822, 2:13–14; *see also id.* at
2 7:14–16.)

3 At the outset of this analysis we clarify that our denials of Broad Motions 1
4 and 2 are not based on a determination that claims to a single-molecule RNA
5 CRISPR-Cas9 system are separately patentable from non-limited guide RNA
6 claims. Rather, our denials of Broad Motions 1 and 2 are based on a failure of
7 Broad to meet its burdens. For example, in Motion 2 Broad failed to meet its
8 burden of persuading us of its argument that the majority of its claims are properly
9 interpreted as encompassing a generic configuration of RNA molecules. We
10 review Broad’s arguments in Motion 3 on their own merits. We have made no
11 determination of the patentability of any RNA molecule configuration over any
12 other configuration.

13 “A claim corresponds to a count if the subject matter of the count, treated as
14 prior art to the claim, would have anticipated or rendered obvious the subject
15 matter of the claim.” 37 C.F.R. § 41.207(b)(2). Thus, for Broad to prevail on its
16 Motion 3, its burden is to show that the claims it identifies would not be
17 anticipated or rendered obvious by the subject matter of Count 1.

18 Broad argues that its “non-limited guide RNA claims should be designated
19 as not corresponding to Count 1 if single-molecule RNA constructs are considered
20 a separate patentable invention.” (Broad Motion 3, Paper 268, 2:19–3:1.) Many of
21 Broad’s supporting reasons are similar to those put forth in Motion 2. For
22 example, Broad argues that the “vast majority” of Broad’s claims encompass a
23 generic RNA configuration. (*See id.* at 19:14–25:23.) Broad argues that awarding

Interference 106,115

1 priority to generic RNA claims based on priority to the single-molecule RNA
2 configuration of Count 1 would violate the purpose of determining priority of the
3 common invention claimed by the parties. (*See id.* at 3:20–5:4.)

4 Broad argues that its

5 involved claims that do not recite “fused” or “chimeric” limitations
6 are not limited to single molecule RNA and so should be designated
7 as not corresponding to Count 1. These are the vast majority of
8 Broad’s Involved Claims; only 43 of Broad’s 387 involved claims
9 require single-molecule guide RNA by virtue of containing a
10 limitation to “fused” RNA or “chimeric” RNA. MF 13; Paper 14;
11 Ex. 3403, Breaker ¶ 5.10. The remaining claims are not limited and so
12 cover both systems with single molecule and ones with dual molecule
13 RNA. MF 13, 20; Paper 14; Ex. 3403, Breaker Dec. ¶¶ 5.1-5.25.

14 (Broad Motion 3, Paper 268, 19:16–22.) Because, as discussed above, we interpret
15 the claim term “guide RNA” to be limited to a single-molecule RNA configuration,
16 we disagree with Broad that only claims with the terms “fused” or “chimeric” are
17 drawn to single-molecule RNA CRISPR-CAs9 systems. Thus, we disagree that all
18 but 43 of Broad’s currently involved claims should be designated as not
19 corresponding to Count 1 because only those claims use the terms “fused” or
20 “chimeric.” Broad fails in Motion 3 to point to any reason other than use of the
21 claim term “guide RNA” to argue that almost all of the claims it cites are not
22 limited to an RNA configuration and should be designated as not corresponding to
23 Count 1. Accordingly, we deny Broad’s Motion 3 for such claims, for the same
24 reasons that we denied Motion 2.

Interference 106,115

1 In Motion 3 Broad argues that two claims, independent claims 15 and 26 of
2 the '713 patent, are generic as to RNA configuration but not because they require a
3 “guide RNA.” (See Broad Motion 3, Paper 268, 20:3–14.) Claim 15 of the
4 '713 patent recites:

5 A CRISPR-Cas complex-mediated method for the production
6 of a multicellular genetically modified non-human animal or
7 multicellular genetically modified plant, the method comprising
8 delivery to one or more target sequences in a cell of the multicellular
9 non-human animal or plant of:

10 a Cas9 protein;

11 a guide sequence linked to a tracr mate sequence; and

12 a tracr sequence;

13 wherein the guide sequence directs sequence-specific binding
14 of a *CRISPR* complex to the target sequence in the cell, whereby the
15 multicellular genetically modified non-human animal or multicellular
16 genetically modified plant is produced, and displays a phenotype or
17 carries DNA to display a phenotype of the genetic modification.

18 (Broad Clean Copy of Claims, Paper 14, 70:13–71:2.) Claim 15 recites linkage
19 between the guide sequence and the tracr mate sequence, but does not expressly
20 recite other linking, fusing, or similar language to describe a relationship between
21 the guide sequence/tracr mate sequence and the tracr sequence.

22 Claim 26 of the '713 patent recites:

23 A CRISPR-Cas complex-mediated method for the production
24 of a multicellular genetically modified non-human animal or
25 multicellular genetically modified plant, the method comprising
26 delivery to a cell of the multicellular non-human animal or plant

Interference 106,115

1 having one or more target sequences of a Cas9 protein, or a nucleic
2 acid molecule encoding the Cas9 protein; and a guide sequence linked
3 to a tracr mate sequence; and a tracr sequence, or one or more nucleic
4 acid molecules encoding the guide sequence linked to the tracr mate
5 sequence and the tracr sequence,

6 wherein the guide sequence directs sequence-specific binding
7 of a CRISPR complex to the target sequence in the cell, whereby the
8 multicellular genetically modified non-human animal or multicellular
9 genetically modified plant is produced, and displays a phenotype or
10 carries DNA to display a phenotype of the genetic modification.

11 (Broad Clean Copy of Claims, Paper 14, 72:5–15.) Claim 26 provides a method of
12 delivering either nucleic acids individually encoding a Cas9 protein, a “guide
13 sequence linked to a tracr mate sequence,” and a “tracr sequence” or, in the
14 alternative, nucleic acids “encoding the guide sequence linked to the tracr mate
15 sequence and the tracr sequence.”

16 CVC argues that claim 15 is limited to a single-molecule RNA configuration
17 because of the language of independent claim 26. (*See* CVC Opp. 3, Paper 591,
18 22:13–23:4.) According to CVC, because claim 26 requires, in the alternative, that
19 the “guide sequence” is linked to both the “tracr mate sequence” and the “tracr
20 sequence,” independent claim 15 must require the same configuration. CVC
21 argues:

22 In view of the parallel structure between the Cas9 and RNA
23 components in claim 26 and for consistency, the phrase in claims 15
24 and 26 with a semicolon should in fact be interpreted to mean “the
25 guide sequence linked to the tracr mate sequence and the tracr
26 sequence.” Accordingly, claims 15 and 26 require that these three
27 sequences are all linked together and present on a single RNA.

Interference 106,115

1 (CVC Opp. 3, Paper 591, 22:19–23:3.) According to CVC, the language of
2 claim 26 limits the language of claim 15.

3 We are not persuaded by CVC’s argument. We are not persuaded that the
4 language of one independent claims necessarily informs the interpretation of the
5 other. Claim 15 does not recite a physical relationship between the guide
6 sequence/tracr mate sequence and the tracr sequence. Accordingly, the broadest
7 reasonable interpretation of claim 15 is that it encompasses any physical
8 relationship between the two – linked, fused, or separate. Claim 26 even
9 contemplates that these two RNAs could be on different nucleic acid molecules.
10 Thus, we find no reason to limit the scope of claim 15 to a single-molecule RNA
11 configuration because of claim 26.

12 Having determined that claims 15 and 26 of the ’713 patent are not limited
13 to a single-molecule RNA configuration, we turn to Broad’s arguments that these
14 claims should not be designated as corresponding to Count 1. To prevail, Broad
15 must show that the subject matter of claims 15 and 26 would not be anticipated or
16 rendered obvious by the subject matter of Count 1, if Count 1 were prior art, in
17 light of 37 C.F.R. § 41.207(b)(2).

18 Broad acknowledges that “[a] count directed to a species, if prior in time,
19 would typically anticipate a generic claim,” but argues that Rule 41.2017(b)(2) is a
20 “presumption,” which apparently does not apply to Broad in this case. (See Broad
21 Motion 3, Paper 286, 13:18–22.) Broad argues that the Rule is not a *per se* rule of
22 unpatentability for generic claims. (See Broad Motion 3, Paper 286, 13:22–24,
23 citing 69 Fed. Reg. 49960-01, *49994, Ex. 3305, 62.) In support, Broad cites to

Interference 106,115

1 comment 186 of the Final Rulemaking, which states that the case law “did not
2 create a per se rule of unpatentability for generic claims, but neither does
3 § 41.207(b). It simply creates a presumption that must be addressed.” (See 69
4 Fed. Reg. 49960-01, *49994, Ex. 3305, 62.)

5 We are not persuaded that the comment relates specifically to 37 C.F.R.
6 § 41.207(b)(2) or indicates that this rule presents a presumption allowing the
7 framework for determining claims correspondence to be changed. Rather, it relates
8 to 37 C.F.R. § 41.207(b)(1), which provides the rebuttable presumption that all
9 claims designated as corresponding to a count stand or fall together. In contrast,
10 Rule 207(b)(2) explains when a claim corresponds to a count. (See CVC Opp. 3,
11 Paper 591, 3:13–7:2.) The plain reading of Rule 207(b)(2) does not indicate any
12 presumption and we are not persuaded that the determination of claim
13 correspondence involves a presumption merely because the title of the section in
14 which this rule is found is “Presumptions.”²⁰ (Contra Broad Reply 3, Paper 822,
15 3:6–8.)

16 Broad appears to argue that the “primary purpose” of interference
17 proceedings and “fairness” can be used as a metric for determining claim

²⁰ We note that 37 C.F.R. § 41.207(a)(2), which provides the evidentiary standard for proving priority, does not present a presumption either. The standard is a preponderance of the evidence except that an applicant with a later date of constructive reduction to practice must prove priority by clear and convincing evidence. See *Brown v. Barbacid*, 276 F.3d 1327, 1332 (Fed. Cir. 2002).

Interference 106,115

1 correspondence. (See Broad Motion 3, Paper 268, 14:15–19:13.) Broad argues
2 that

3 the major advance was successful engineering of CRISPR-Cas9
4 systems for use in eukaryotic cells. This enormous breakthrough was
5 not tied to the mere use of single-molecule guide RNA—Dr. Zhang
6 succeeded with both dual and single molecule RNA systems. Thus, it
7 would be entirely inappropriate to award priority to the broad
8 invention of eukaryotic CRISPR systems to a party who made a
9 species invention long after the breakthrough.

10

11 (Broad Motion 3, Paper 268, 16:5–9.) Broad cites to no authority that holds
12 unfairness or any other condition, such as facts beyond the relationship of the
13 subject matter of the claims and the count, can be used to determine claim
14 correspondence differently.

15 We note that Broad’s reliance on the result in *Eli Lilly & Co. v. Bd. of*
16 *Regents of Univ. of Washington*, 334 F.3d 1264 (Fed. Cir. 2003), is also misplaced.
17 (See Broad Motion 3, Paper 268, 17:16–18:4; see CVC Opp. 3, Paper 591, 15:18–
18 16:1.) That case does not discuss or hold issues of claim correspondence, as
19 determined by a one-way test, but instead is about determination of interference-in-
20 fact by a two-way test. The *Lilly* court did not state that a genus invented before a
21 species is separately patentable, as Broad asserts. (See Broad Motion 3, Paper 268,
22 17:21–23.) Instead, the court stated: “If the interference proceeding, however,
23 leads to a conclusion that the genus claim was invented first, it is possible that both
24 the genus and the species are separate patentable inventions.” *Lilly*, 334 F.3d at

Interference 106,115

1 1268. The “possibility” that they are separate patentable inventions is what Broad
2 must prove in this proceeding.

3 Similarly, neither *Godtfredsen v. Banner*, 598 F.2d 589, 590 (CCPA 1979),
4 *Theeuwes v. Bogentoft*, 2 U.S.P.Q.2d 1378 (B.P.A.I. 1987), nor *Ex Parte*
5 *Hardman*, 142 U.S.P.Q. 329 (CCPA 1964), holds that claim correspondence is
6 determined by anything other than the test provided in 37 C.F.R. § 41.207(b)(2).
7 (See Broad Motion 3, Paper 268, 15:4–16:4.) These cases discuss determination of
8 priority when patentably distinct species are included in one count, but neither of
9 them discuss the standard for claim correspondence to a count or the current
10 interference rules.

11 In contrast to the presumption argued by Broad, the comment to the Final
12 Rulemaking cited by Broad provides that correspondence to a count is a
13 determination of estoppel. The comment states:

14 [37 C.F.R. § 41.207(b)] simply formalizes the effect of estoppel
15 arising out of cases like *In re Deckler*, 977 F.2d 1449, 1452, 24
16 USPQ2d 1448, 1449 (Fed. Cir. 1992), in which a party could not
17 subsequently seek claims that were patentably indistinct from the
18 subject matter of the count lost in the interference. As discussed
19 earlier, no one “wins” a count because surviving a priority contest for
20 one count does not mean that one is thereby entitled to a claim.
21 *Kyrides* [159 F.2d 1019, 1022 (CCPA 1947)].

22

23 (69 Fed. Reg. 49960-01, *49994, Ex. 3305, 62.) Broad’s arguments about the
24 unfairness of an award of priority to CVC on Count 1 do not explain why such a
25 result is improper under the principles put forth in *Deckler*. In *Deckler*, the Board

Interference 106,115

1 properly rejected claims under principles of res judicata and collateral estoppel
2 where the applicant was not entitled to claims that were patentably
3 indistinguishable from the claim on which he lost an interference. *See Deckler*,
4 977 F.2d at 1453. If Broad’s generic claims are anticipated or rendered obvious by
5 CRISPR-Cas9 with a single-molecule RNA configuration, Broad is not entitled to
6 the claims under the principles of estoppel if it loses on priority to Count 1.
7 Broad’s burden is to show that its claims are not anticipated or rendered obvious
8 by Count 1.

9 Furthermore, although comment 186 of the Final Rulemaking provides
10 instruction to a party with a generic claim designated as corresponding to a species
11 count to move to have the generic claim designated as not corresponding, it does
12 not provide any guidance on the outcome of such a motion. Instead, the burden is
13 on the movant to prove that the claim should be designated as not corresponding to
14 the count. *See* 37 C.F.R. § 41.208(b) and § 41.121(b). (*See* CVC Opp. 3,
15 Paper 591, 16:12–17:2.) Broad fails to meet the burden of persuading us that
16 either its claims do not correspond to Count 1 or that we should add a separate
17 count.

18 The only part of Broad’s Motion 3 that seems to be an argument regarding
19 anticipation or obviousness of Broad’s claims over Count 1 is a general reference
20 to CVC’s arguments that claims to CRISPR/Cas9 systems with single-molecule
21 RNA configurations are separately patentable from claims to systems with generic
22 RNA configurations. (*See* Broad Motion 3, Paper 268, 12:3–13:7.) Broad states
23 that “CVC has argued the very point that requires that Broad’s non-limited claims

Interference 106,115

1 be designated as not corresponding to Count 1 if single-molecule RNA systems are
2 considered to be a separate patentable invention.” (*Id.* at 13:5–7; *see also* Broad
3 Reply 3, Paper 822, 11:22–23 (“CVC thus concedes that in a two-count
4 interference, generic RNA claims would not correspond to a single-molecule RNA
5 count.”).)

6 Broad’s reference to CVC’s statement, though, is confusing because
7 elsewhere Broad states: “As set forth in its Motion 2, Broad disagrees that mere
8 addition of the single-molecule RNA in CVC’s claims at issue in this interference
9 imparts patentability over Proposed Count 2 to eukaryotic CRISPR-Cas9 systems
10 with non-limited RNA.” (Broad Motion 3, Paper 268, 2, n.2.) Thus, it is Broad’s
11 position that CVC’s single-molecule RNA claims are not patentable over a generic
12 count, such as proposed Count 2. (*See* CVC Opp. 3, Paper 591, 16:16–18.) Given
13 that Broad appears to consider the single molecule RNA configuration to be the
14 same patentable invention as a generic configuration, it is not clear that Broad
15 could argue that a count reciting a single-molecule RNA configuration CRISPR-
16 Cas9 system would not at least render obvious a claim reciting a generic RNA
17 configuration.

18 Because Broad does not set forth a clear argument that the subject matter of
19 its generic claims, claims 15 and 26 of its ’713 patent, would not be anticipated or
20 rendered obvious by the single-molecule RNA configuration CRISPR-Cas9 system
21 recited in Count 1, Broad has failed to meet its burden of showing that these claims
22 were not properly designated as corresponding to Count 1. Broad’s references to
23 CVC’s positions do not meet Broad’s burden.

Interference 106,115

1 Accordingly, we are not persuaded that any of Broad’s claims were
2 improperly designated as corresponding to Count 1, either because Broad’s claims
3 are not properly interpreted to encompass generic subject matter or because Broad
4 has failed to show that generic claims do not correspond under 37 C.F.R.
5 § 41.207(b)(2).

6 *B. SaCas9*

7 Broad argues that all of the claims of its involved ’406 and ’308 patents
8 should be designated as not corresponding to Count 1 because they recite methods
9 or systems comprising SaCas9 protein or nucleic acid sequences²¹ and, therefore,
10 are not anticipated or rendered obvious by Count 1. (*See* Broad Motion 3,
11 Paper 268, 26:1–30:8.)

12 Broad argues that because Count 1 recites Cas9 generically, not SaCas9, it
13 does not anticipate Broad’s SaCas9 claims. (*See* Broad Motion 3, Paper 268,
14 26:8–9, citing Seeger Decl., Ex. 3401, ¶¶ 6.3–6.4.) Broad argues further that
15 Count 1 does not render claims reciting SaCas9 obvious because there was no
16 teaching or suggestion in Count 1 or in the prior art to use SaCas9 in a CRISPR-

²¹ For example, claim 24 of the ’406 patent recites: “An engineered, programmable, non-naturally occurring Type II CRISPR-Cas system comprising a *Staphylococcus aureus* Cas9 protein and at least one guide RNA that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell, wherein the DNA molecule encodes and the eukaryotic cell expresses at least one gene product and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.” (Broad Clean Copy of Claims, Paper 14, 20:12–18.)

Interference 106,115

1 Cas9 system in eukaryotes, relying on Dr. Seeger’s testimony. (*See* Broad
2 Motion 3, Paper 268, 26:10–30:8, citing Seeger Decl., Ex. 3401, ¶¶ 6.3–6.13.)

3 Dr. Seeger states:

4 A person of skill in the art reading Count 1 in December 2012 would
5 have known that the most common Cas9 being studied was that for *S.*
6 *pyogenes* (“SpCas9”) followed by *S. thermophilus* Cas9 (“StCas9”).
7 In fact, this was even true when Broad filed its non-provisional
8 applications seeking to claim SaCas9 specifically a year later. To my
9 knowledge, the use of SaCas9 had not been published or reported
10 prior to the work of the Broad inventors and I am not aware of anyone
11 else in the art suggesting the use of SaCas9 in a CRISPR-Cas system
12 in 2012 or even in 2013.

13

14 (Seeger Decl., Ex. 3401, ¶ 6.4.) Dr. Seeger testifies further:

15 It certainly could not have been predicted until the work of the
16 Broad inventors that out of over 600 Cas9 orthologues, SaCas9 would
17 have efficiencies in eukaryotic cells comparable to those of SpCas9.
18 *See* Ex 3226, Ran *et al.*, (2015), at 1. There would have been no
19 reason to single out SaCas9 based on Count 1 or any other prior art I
20 am aware of, particularly given the significant structural differences
21 between SaCas9 and SpCas9.

22 (Seeger Decl., Ex. 3401, ¶ 6.5.)

23 Broad argues that SaCas9 systems had surprisingly high efficacy in
24 eukaryotes compared to Cas9 from *Staphylococcus pyogenes* (“SpCas9”), given its
25 small size and lack of homology to SpCas9, the more commonly used Cas9 protein
26 at the time. (*See* Broad Motion 3, Paper 268, 26:11–16, citing Seeger Decl.,
27 Ex. 3401, ¶¶ 6.7–6.9.) Dr. Seeger testifies that the coding sequence for SaCas9 is

Interference 106,115

1 about 1 kb shorter than the coding sequence for SpCas9. (See Seeger Decl.,
2 Ex. 3401, ¶ 6.5.)

3 According to Dr. Seeger, there would not have been a reason for one of
4 ordinary skill in the art to use a smaller Cas9 at the time. (See Seeger Decl.,
5 Ex. 3401, ¶ 6.9; see Broad Motion 3, Paper 268, 27:19–28:11 and 29:13–21.)
6 Dr. Seeger testifies that although larger Cas9 proteins, such as SpCas9, were
7 known to have high efficiencies, smaller Cas9 proteins, such as StCas9,
8 demonstrated lower efficiencies. (See Seeger Decl., Ex. 3401, ¶ 6.9; see Broad
9 Motion 3, Paper 268, 27:19–28:11 and 29:13–21.)

10 CVC opposes Broad’s argument, asserting that SaCas9 and its DNA
11 sequence were known in the art as of 2012 and that even though one of ordinary
12 skill in the art would have known SaCas9 is smaller than SpCas9, SaCas9 was also
13 known to have domains that characterize a functional Cas9 protein. (See CVC
14 Opp. 3, Paper 591, 24:1–21, citing Third Peterson Decl., Ex. 4193, ¶¶ 120–123.)
15 CVC argues further that SaCas9 had been designated as one of the models for
16 studying CRISPR systems before December 2012, which would have motivated
17 one of ordinary skill in the art to use SaCas9 in the CRISPR-Cas9 system of
18 Count 1. (See CVC Opp. 3, Paper 268, 24:4–5, citing Third Peterson Decl.,
19 Ex. 4193, ¶ 120.) Specifically, Dr. Peterson refers to a 2011 publication that states:
20 “A few model systems have been established in the study of CRISPR/Cas
21 functionality, notably in *Escherichia coli* . . . , *Staphylococcus aureus* . . . ,

Interference 106,115

1 *Pyrococcus furiosus* . . . and *Streptococcus thermophilus*” (Sapranaukas,²²
2 Exs. 3215/4048, 9276 (citations omitted); see Third Peterson Decl., Ex. 4193,
3 ¶ 120.)

4 Broad counters that Sapranaukas would have discouraged a person of
5 ordinary skill in the art to use SaCas9 in eukaryotic cells because it reports that
6 StCas9, not SaCas9, was successful. (See Broad Reply 3, Paper 822, 17:1–6.)
7 Broad argues further that Sapranaukas cites to the work of other scientists, who
8 had been unsuccessful in using *S. aureus* CRISPR-Cas9 in eukaryotes for several
9 years prior. (See *id.* at 17:6–9.)

10 We are persuaded that Sapranaukas indicates what systems those of
11 ordinary skill in the art were using as model systems because of its plain language.
12 (See Sapranaukas, Exs. 3215/4048, 9276.) Whether or not others had successfully
13 used SaCas9 in a eukaryotic system years before does not negate the teaching in
14 Sapranaukas that *S. aureus* was considered to be a model CRISPR/Cas system in
15 2011.

16 Broad also argues that SaCas9 shares only 17% sequence with SpCas9,
17 whereas other Cas9 orthologs known at the time had about 60% sequence
18 homology with SpCas9. (See Broad Motion 3, Paper 268, 28:15–29:3, citing
19 Seeger Decl., Ex. 3401, ¶ 6.13.) In addition, Broad cites to the differences in the
20 domain regions between SpCas9 and SaCas9 as a reason why those of ordinary

²² Sapranaukas et al., “The *Streptococcus thermophilus* CRISPR/Cas system provides immunity in *Escherichia coli*,” *Nucleic Acids Research*, 39:9275–82 (2011) (Exs. 3215, 4048).

Interference 106,115

1 skill would not have looked to SaCas9 for CRISPR-Cas9 systems. (*See* Broad
2 Motion 3, Paper 268, 29:4–29:12, citing Seeger Decl., Ex. 3401, ¶ 6.13.)
3 According to Dr. Seeger, these differences would have “taught away” from
4 selecting SaCas9. (*See* Seeger Decl., Ex. 3401, ¶ 6.13.)

5 Again, in light of the express teaching in Sapranaukas that SaCas9 was
6 known to be a model system, we are not persuaded that its sequence homology or
7 any other differences would have indicated it would not be a potential protein for
8 the system of Count 1. Broad does not direct us to a teaching that specifically
9 indicates Sa Cas9 should not be chosen. Thus, we are not persuaded that anything
10 taught away from it. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738
11 (Fed. Cir. 2013) (“A reference does not teach away, [] if it merely expresses a
12 general preference for an alternative invention but does not criticize, discredit, or
13 otherwise discourage investigation into the invention claimed.”).

14 In opposition to Broad’s arguments regarding how those of ordinary skill in
15 the art would have viewed SaCas9, CVC argues that because AAV vectors were
16 known to work better with less DNA to maximize efficiency, there would have
17 been a reason to try the smaller SaCas9 protein. (*See* CVC Opp. 3, Paper 268,
18 24:22–25:15, citing Third Peterson Decl., Ex. 4193, ¶¶ 124–126.) CVC argues
19 further that those of ordinary skill in the art would have considered the smaller size
20 of Sa Cas9 an advantage to add additional regulatory elements to the vector, such
21 as for tissue specific expression, or to be able to include all of the CRISPR-Cas9
22 components on one vector. (*See* CVC Opp. 3, Paper 591, 25:15–26:2, citing Third
23 Peterson Decl., Ex. 4193, ¶ 127.)

Interference 106,115

1 Broad’s witness, Dr. Seeger, echoes CVC’s argument by stating: “This
2 combination of efficient indel^[23] production and small size is key for many basic
3 research and therapeutic applications that employ the highly versatile adeno-
4 associated virus (AAV) as the delivery vehicle.” (Seeger Decl., Ex. 3401, ¶¶ 6.8
5 and 6.15, citing ’406 patent, Ex. 3017, 83:25 – 84:23 (discussing size limitations
6 on DNA inserted into AAV vectors).) Dr. Seeger’s statements tend to support
7 CVC’s argument that those of ordinary skill in the art would have been motivated
8 to use a smaller sized Cas9 protein to be able to fit desired elements into an AAV
9 delivery vehicle. Thus, we are not persuaded by Broad’s argument that one of
10 ordinary skill would not have been motivated to at least try the smaller SaCas9.

11 CVC argues further that because *S. aureus* was known to have a complete
12 CRISPR locus, and SaCas9 had been identified as a Cas9 protein with
13 characteristic domains, a person of ordinary skill in the art would have reasonably
14 expected it to be successful in a CRISPR-Cas9 editing system, as provided in
15 Count 1. (See CVC Opp. 3, Paper 591, 29:5–18, citing Third Peterson Decl.,
16 Ex. 4193, ¶ 136.)

17 Broad also argues that the results obtained with SaCas9 were unexpected.
18 (See Broad Motion 3, Paper 268, 29:13–30:6.) According to Dr. Seeger,

19 [t]he use of a CRISPR-SaCas9 system in eukaryotic cells has
20 unexpected attributes and its high efficacy and small size make it
21 particularly advantageous. The Broad scientists demonstrated that

²³ The term “indel” refers to insertions and deletions of nucleotide bases during genetic editing activity. (See Seeger Decl., Ex. 3401, ¶ 5.44

Interference 106,115

1 CRISPR-Cas9 systems using the SaCas9 orthologue produced indels
2 *in vivo* with efficiencies comparable to those of the larger SpCas9
3 orthologue and with lower off-target double strand breaks, in stark
4 contrast to the poor performance of other orthologues in comparison
5 to SpCas9 such as StCas9.

6 (Seeger Decl., Ex. 3401, ¶ 6.15.) Dr. Seeger characterized the results as
7 unexpected because they were expected to be worse with SaCas9, not because they
8 are better than the results with other Cas proteins.

9 We are not persuaded by Dr. Seeger's testimony because we are not
10 persuaded that one of ordinary skill in the art would have considered the activity of
11 SaCas9 to be inferior to that of SpCas9 solely because of its size. Dr. Seeger
12 testifies that those of ordinary skill would have considered the comparable
13 efficiency of SaCas9 to be unexpected because of the poor performance of another
14 Cas9 protein, StCa9, which happens to also be small. But Dr. Seeger does not
15 direct us to evidence that StCa9 is inefficient because of its small size or that those
16 of ordinary skill would have considered all small Cas9 proteins to be similarly
17 inefficient. Accordingly, we are not persuaded by Broad's argument that the
18 activity comparable to that of SpCas9 would have indicated to those of ordinary
19 skill that SaCas9 produced results unexpected over a generic Cas9 as recited in
20 Count 1.

21 Furthermore, we are persuaded by CVC that the results reported by
22 Dr. Seeger would not have been unexpected because the evidence does not show
23 that StCas9 was less efficient than SpCas9. (See CVC Opp. 3, Paper 591, 29:19–

Interference 106,115

1 31:17.) Dr. Peterson testifies in support of CVC’s argument that Ran²⁴ (Ex. 3226)
2 reports slightly *more* efficient cleavage for StCas9 than for SpCas9. (See Third
3 Peterson Decl., Ex. 4193, ¶ 140.) Extended Data Figure 3a of Ran report “Indel
4 (%)” for *S. aureus* as 6.7%, for *S. pyogenes* of 3.0% and for *S. thermophiles*, which
5 Dr. Peterson characterizes as “comparable activity.” (See Ran. Ex. 3226, 11; see
6 Third Peterson Decl., Ex. 4193, ¶ 141.) We agree that these results contradict
7 Dr. Seeger’s conclusion that because StCas9 had a lower efficiency, the results
8 obtained with SaCas9 would have been unexpected.

9 Dr. Peterson testifies further that Dr. Seeger misinterprets the results
10 reported in Table S1 of Cong 2013²⁵ (Ex. 3201). (See Third Peterson Decl.,
11 Ex. 4192, ¶¶ 144–150.) Dr. Seeger stated: “SpCas9 was more efficient
12 experimentally than StCas9 (1121 amino acids) in early *in vivo* experiments.
13 Ex. 3201, Cong *et al.*, (2013) Supplement Table S1 and Fig. S8 (showing SpCas9
14 routinely provides indel percentages as high as 25% whereas StCas9 showed 14%
15 at most).” (Seeger Decl., 3401, ¶ 6.9) Dr. Peterson testifies that, contrary to
16 Dr. Seeger’s characterization of the data, only one data point for SpCas9 was as
17 high as 25% and one of ordinary skill in the art would not have considered this one
18 point to be a routine result. (See Third Peterson Decl., Ex. 4193, ¶¶ 144–150.)
19 Dr. Peterson provides a different analysis of all of the data in Table S1,

²⁴ Ran et al., “In vivo genome editing using *Staphylococcus aureus* Cas9,” *Nature*, 520:186–92 (2015) (Ex. 3226).

²⁵ Cong et al., “Multiplex Genome Engineering Using CRISPR/Cas Systems,” *Science* 339:819–23 (2013) (Ex. 3201).

Interference 106,115

1 determining that the results do not show that StCas9 is less efficient than SpCa9.
2 (*See id.*)

3 Broad does not dispute Dr. Seeger’s analysis of the data, but argues that it
4 ignores the full context of the surprising result because StCas9 had a lower cutting
5 efficiency. (*See* Broad Reply 3, Paper 822, 18:1–8.) Broad does not point to any
6 flaws in Dr. Seeger’s analysis of either Ran or Cong 2013. Because we are
7 persuaded that Ran provides data on its face that disputes Broad’s assertion and
8 that one of ordinary skill in the art would not merely look to the highest efficiency
9 reported for SpCas9 to compare to StCas9, we are not persuaded by Broad’s
10 argument that StCas9 would have been considered to be less efficient.

11 Accordingly, we are not persuaded by Broad’s argument that the lower efficiency
12 of StCas9 would have created an expectation of lower efficiency in SaCas9, and
13 that when this lower efficiency did not result, those of ordinary skill would have
14 considered it unexpected. That is, we are not persuaded that SaCas9 produces
15 results that would have been unexpected, given the results of a generic CRISPR-
16 Ca9 system as recited in Count 1.

17 In summary, Broad fails to persuaded us that a CRISPR-Cas9 system using
18 SaCas9 would not have been obvious over Count 1. As the Supreme Court
19 explained:

20 When there is a design need or market pressure to solve a problem
21 and there are a finite number of identified, predictable solutions, a
22 person of ordinary skill has good reason to pursue the known options
23 within his or her technical grasp. If this leads to the anticipated
24 success, it is likely the product not of innovation but of ordinary skill

Interference 106,115

1 and common sense. In that instance the fact that a combination was
2 obvious to try might show that it was obvious under § 103.

3
4 *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Accordingly, we are not
5 persuaded that Broad's claims limited to SaCas9 should be designated as not
6 corresponding to Count 1 under 37 C.F.R. § 41.2017(b)(2).

7 *C. Multiple Nuclear Localization Signal Sequences*

8 Broad argues that its claims²⁶ requiring two or more nuclear localization
9 signals ("NLSs") should be designated as not corresponding to Count 1. (*See*
10 *Broad Motion 3, Paper 268, 30:9–32:5.*)

11 First, Broad argues that Count 1 does not recite a CRISPR-Cas9 system with
12 two or more NLSs and, therefore does not anticipate Broad's claims. (*See Broad*
13 *Motion 3, Paper 268, 30:16–17.*) Broad argues further that including two or more
14 NLSs would not have been obvious to those of ordinary skill in the art because the
15 prior art does not suggest doing so and there would have been no reasonable
16 expectation that doing so would be operable as a CRISPR-Cas9 system. (*See*
17 *Broad Motion 3, Paper 268, 30:17–32:5, citing Seeger Decl., Ex. 3401, ¶¶ 6.16–*
18 *6.32.*) Broad explains that an NLS acts to localize the Cas9 protein, which is
19 normally found in a prokaryotic cell, which has no nucleus, to the nucleus of

²⁶ Specifically, Broad argues that the following claims require two or more NLSs: '445 patent – all claims, '814 – patent all claims; '233 patent – claim 7; and '551 application - claims 9-11. (*Broad Motion 3, Paper 268, 30:11–15.*)

Interference 106,115

1 eukaryotic cells, allowing it to act on the DNA in the nucleus. (Broad Motion 3,
2 Paper 286, 30:19–31:2, citing Seeger Decl., Ex. 3401, ¶¶ 6.17–6.21.)

3 Broad relies on Dr. Seeger’s testimony to argue that using NLSs, especially
4 with a prokaryotic protein, would have been highly unpredictable to those of
5 ordinary skill in the art because such a sequence could alter a protein’s structure
6 and impair its function. (See Broad Motion 3, Paper 268, 31:9–22, citing Seeger
7 Decl., Ex. 3401, ¶¶ 6.22–6.27; see Seeger Decl., Ex. 3401, ¶ 6.22.) Dr. Seeger
8 cites to Fieck²⁷ (Ex. 3258), which reports the results of adding NLS sequences to
9 the “lac repressor” protein in order to use this inducible prokaryotic protein in the
10 nucleus of a eukaryotic cell. (See Seeger Decl., Ex. 3401, ¶ 6.23.) Dr. Seeger
11 reports that the results of experiments adding an NLS to different places on the lac
12 repressor showed that some NLS-repressor fusion proteins failed to bind the lack
13 operon at all, whereas other NLS-repressor fusion proteins bound the lac operator,
14 but did not function properly. (See Seeger Decl., ex. 3401, ¶ 6.25.) Dr. Seeger
15 concludes:

16 whether a particular prokaryotic protein will work at all or in the same
17 way after the addition of an NLS is dependent on a host of factors that
18 are specific to the structure of the protein, the way the protein carries
19 out its activity, and the specific location used for placement of the
20 NLS.

21 (Seeger Decl., Ex. 3401, ¶ 6.27.)

²⁷ Fieck, et al., “Modifications of the *E. coli* Lac repressor for expression in eukaryotic cells: effects of nuclear signal sequences on protein activity and nuclear accumulation,” *Nucl. Acids. Res.* 20:1785–91 (1992) (Ex. 3258).

Interference 106,115

1 We are not persuaded by Dr. Seeger’s testimony or Broad’s argument there
2 would have been no reasonable expectation of success because Fieck teaches that
3 one NLS position produced “efficient nuclear accumulation, strong repressor
4 activity and greater sensitivity to IPTG induction.” (*See* Fieck, Ex. 3258, abstract.)
5 Thus, even if one of ordinary skill would know that all NLS positions will not
6 work as expected, Fieck teaches that with routine experimentation, one of ordinary
7 skill in the art would have reasonably expected to be able to attach one or more
8 NLSs to a protein and still maintain its function. (*See* Third Peterson Decl.,
9 Ex. 4193, ¶¶ 181, 183; *see* CVC Opp3, Paper 591, 33:18–34:5.) Broad does not
10 direct us to a teaching in the art that for some proteins, there is no position of the
11 NLS that will successfully locate a functional protein into the nucleus.

12 Broad argues further that one of ordinary skill would not have had a
13 reasonable expectation of success in changing Cas9 protein by adding NLSs
14 because doing so was known to possibly affect protein activity. (*See* Broad
15 Motion 3, Paper 268, 31:9–22.) Broad relies on Dr. Seeger’s testimony that when
16 a protein is expressed as a fusion with added amino acids, such as NLSs or
17 chimeric tags, the results can be unpredictable, further confirming there was no
18 reasonable expectation of success as to a eukaryotic CRISPR-Cas9 system wherein
19 the Cas9 includes one or two or more NLSs. (*See id.*; *see* Seeger Decl., Ex. 3401,
20 ¶¶ 6.30, citing Turner (Ex. 3264), Brothers (3263).)

21 We are not persuaded by Broad’s argument because, as CVC asserts, it was
22 already known in the art that Cas9 could be expressed as a functional protein with
23 amino acids added to make a chimeric protein. (*See* CVC Opp. 3, Paper 591,

Interference 106,115

1 33:14-16, citing Jinek 2012 (Ex. 3202) and Third Peterson Decl., Ex. 4193,
2 ¶¶ 175–178.) Dr. Peterson explains that Jinek 2012 reports that adding a four
3 amino acid tag to a Cas9 protein did not destroy its function. (See Peterson Decl.,
4 Ex. 4193, ¶¶175–178.) Dr. Peterson reports that NLS sequences can be as short as
5 five amino acids long. (See *id.* at ¶¶ 175 and 177.) Thus, according to
6 Dr. Peterson, Jinek 2012 show that it would have been expected that the addition
7 of a similarly short two or more NLSs to Cas9 would have allowed it to retain its
8 function. (See *id.* at ¶ 177.)

9 CVC argues further that contrary to Broad’s position, before
10 December 2012, those of ordinary skill in the art has routinely used two or more
11 NLSs to successfully increase nuclear localization of prokaryotic proteins. (See
12 CVC Opp. 3, Paper 591, 32:5–12.) Relying on Dr. Peterson’s testimony, CVC
13 cites publications that use NLS sequences on proteins of Type I and III CRISPR
14 systems, Zinc finger nucleases, TALENS, Rec A, LacZ, and HaloTag reporter
15 proteins. (See *id.*, citing Third Peterson Decl., Ex. 4193, ¶¶ 157–162.) For
16 example, Sontheimer²⁸ (Ex. 3054) teaches appending NLS sequences to Cas
17 constructs for subcellular localization to the nucleus (see ¶¶ 54 and 58). CVC
18 argues further that it was known that more than one NLS could increase nuclear
19 localization, citing to several publications and Dr. Peterson’s testimony. (See CVC

²⁸ Sontheimer and Marraffini, U.S. Patent Application Publication, 2010/0076057, published 25 March 2010. (Ex. 3054.)

Interference 106,115

1 Opp. 3, Paper 591, 32:13–33:7, citing Third Peterson Decl., Ex. 4193, ¶¶ 164–
2 170.)

3 Broad refutes CVC’s evidence, arguing that none of the publications it cites
4 show success in eukaryotic cells, which we held in the prior ’048 interference was
5 necessary for a reasonable expectation of success. (*See* Broad Reply 3, Paper 822,
6 19:9–23.) We are not persuaded by Broad’s argument because the issue in the
7 prior interference was whether a CRISPR-Cas9 system would have been expected
8 to work in a eukaryotic cell. That issue is assumed under the framework of 37
9 C.F.R. § 41.207(b)(2), wherein Count 1 is presumed to be prior art to the Broad
10 claims. The issue for Broad’s request is whether adding two or more NLSs to the
11 functional eukaryotic system of Count 1 would have been obvious. Broad does not
12 direct us to evidence it would not have been obvious.

13 In addition, Broad argues that adding two NLS sequences to Cas9
14 significantly improved localization and unexpectedly improved efficiency. (*See*
15 Broad Motion 3, Paper 268, 31:3–8.) Broad does not direct us to evidence that
16 these improvements would have been unexpected given the teachings in the art
17 about the effect of NLSs on localization of proteins to the nucleus where they are
18 intended to act. Accordingly, we are not persuaded of any secondary
19 considerations that would have rendered Broad’s claims requiring two or more
20 NLSs to be obvious over Count 1.

21 We are not persuaded that any of Broad’s claims reciting NLS sequences
22 would not have been obvious over the subject matter of Count 1. Accordingly, we

Interference 106,115

1 are not persuaded that these claims should be designated as not corresponding to
2 Count 1.

3 In summary, Broad fails to persuade us that any of its claims should be
4 designated as not corresponding to Count 1 and we DENY Broad Motion 3.

5 *VI. Broad Motion 4 – Benefit*

6 Broad argues that it should be accorded benefit of the filing date,
7 12 December 2012, of its provisional application 61/736,527 (“Zhang B1”)
8 (Ex. 3001). (*See* Broad Motion 4, Paper 269.)

9 To be accorded benefit of its filing date, an application must provide a
10 proper constructive reduction to practice under 35 U.S.C. 102(g)(1). (*See*
11 37 C.F.R. § 41.201.) A constructive reduction to practice is a described and
12 enabled anticipation, in a patent application, of the subject matter of a count.
13 Written description and enablement are required under 35 U.S.C. § 112, first
14 paragraph, wherein

15 [t]he specification shall contain a written description of the invention,
16 and of the manner and process of making and using it, in such full,
17 clear, concise, and exact terms as to enable any person skilled in the
18 art to which it pertains, or with which it is most nearly connected, to
19 make and use the same

20
21 A patent application need only meet these requirements for one embodiment within
22 the count because the determination of a constructive reduction to practice of a
23 count is a vehicle for contesting priority, not a determination of patentability. *See*
24 *Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (CCPA 1975).

Interference 106,115

1 To determine if subject matter is sufficiently described, we look to the
2 factual issue of “whether the disclosure of the application relied upon reasonably
3 conveys to those skilled in the art that the inventor had possession of the claimed
4 subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d
5 1336, 1351 (Fed. Cir. 2010) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555,
6 1562–63 (Fed.Cir.1991).).

7 To determine if subject matter is enabled, we ask whether it would have
8 required undue experimentation to make and use it, a legal question support by
9 factual determinations. *See In re Wands*, 858 F.2d 731, 736–37 (Fed.Cir.1988);
10 *see also Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360
11 (Fed.Cir.1998). Factors to be considered in determining whether a disclosure
12 would require undue experimentation include:

13 (1) the quantity of experimentation necessary, (2) the amount of direction or
14 guidance presented, (3) the presence or absence of working examples,
15 (4) the nature of the invention, (5) the state of the prior art, (6) the relative
16 skill of those in the art, (7) the predictability or unpredictability of the art,
17 and (8) the breadth of the claims.

18

19 *Wands*, 858 F.2d at 737. A specification may be enabling if the amount of
20 experimentation required by one of ordinary skill is sufficiently routine as to be
21 reasonably expected to carry it out. *See id.*

22 We turn to the issue of written description first. Broad focuses on
23 Example 1, including what Broad refers to as Embodiment 17, of Zhang B1 as a
24 constructive reduction to practice of Count 1. (Broad Motion 4, Paper 269, 5:13–
25 25:19.) Broad argues that Example 1 provides a single-molecule CRISPR-Cas

Interference 106,115

1 system as recited in Count 1, wherein “[t]o further simplify the three-component
2 system, a chimeric crRNA-tracrRNA hybrid design was adapted, where a mature
3 crRNA (comprising a guide sequence) is fused to a partial tracrRNA via a stem-
4 loop to mimic the natural crRNA:tracrRNA duplex (Figure 2A).” (Zhang B1,
5 Ex. 3001, ¶ 176; *see* Broad Motion 4, Paper 269, 8:16–9:22, citing Seeger Decl.,
6 Ex. 3401, ¶ 5.7.)

7 Broad argues further that Zhang B1 describes this CRISPR-Cas system in a
8 eukaryotic cell, stating: “The mature crRNA detected from transfected 293FT total
9 RNA is ~33bp and is shorter than the 39-42bp mature crRNA from *S. pyogenes*.
10 These results demonstrate that a CRISPR system can be transplanted into
11 eukaryotic cells and reprogrammed to facilitate cleavage of endogenous
12 mammalian target polynucleotides.” (Zhang B1, Ex. 3001, ¶ 174; *see* Broad
13 Motion 4, Paper 169, 9:23–10:10, citing Seeger Decl., Ex. 3401, ¶ 5.11.)

14 Broad cites to results of transfecting different combinations of CRISPR-Cas
15 components (Cas9, SpRNase III, tracrRNA, and pre-crRNA array carrying the
16 *EXM1*-target spacer, including a satisfactory PAM sequence) in eukaryotic, HEK
17 293FT cells.²⁹ (*See* Zhang B1, Ex. 3001, ¶¶ 173, 175, citing Figure 1D.) Co-
18 transfection with all four CRISPR-Cas components is reported to induce up to
19 5.0% insertions and deletions in the protospacer and transfecting with all CRISPR
20 components minus SpRNase III is reported to induce up to 4.7% insertions and

²⁹ Dr. Seeger testifies that it was commonly known in the field as of 2012 that HEK293 cells, used as reported in Zhang B1, express genes such as EXM1, that were targeted in Example 1. (*See* Seeger Decl., Ex. 3401, ¶ 5.38.)

Interference 106,115

1 this portion of Zhang B1 would have concluded that the element of Count 1
2 requiring the Cas9 protein to cleave DNA molecules and alter the expression of at
3 least one gene product was described in Zhang B1. (See Seeger Decl., Ex. 3401,
4 ¶¶ 5.40–5.49.)

5 Similarly, in regard to the fused crRNA-tracrRNA design, Zhang B1 states:
6 “The efficiency of chimeric RNA-mediated cleavage was tested by targeting the

Zhang B1. (Seeger Decl., Ex. 3401, ¶ 5.43.) According to CVC, Dr. Seeger inappropriately testifies that Broad’s experiments were “successful,” asserting that an expert may not function as a “conduit” for the substantive admission of inadmissible hearsay. (See CVC Motion to Exclude, Paper 844, 7:21–22, 8:6–9:8.) We are not persuaded that this statement is in admissible hearsay because it is not a statement made outside of the proceeding and is not used to prove the truth of the matter asserted. (See Fed. R. Evid. 802.) Rather, Dr. Seeger provides his opinion about how one of ordinary skill in the art would understand the disclosure in Zhang B1 of Figure 1D and related statements, such as “we confirmed that the chimeric RNA design facilitates cleavage of human EMX1 locus with approximately a 4.7% modification rate.” (See Zhang B1, Ex. 3001, ¶ 176; see Seeger Decl., Ex. 3401, ¶ 5.40.) Dr. Seeger testifies that those of ordinary skill would understand that the experiments were successful from the data presented. CVC cites cases such as *U.S. v. Ramos-Gonzales*, 664 F.3d 1 (1st Circ. 2011), in which the Court held an expert’s testimony about the report of a colleague to be hearsay, but these cases are not relevant because we rely on Dr. Seeger’s testimony for his own opinions. (See CVC Misc. Motion 2, Paper 844, 8:7–20.) CVC could have directed us to evidence, including cross-examination testimony of Dr. Seeger, to show that one of ordinary skill would have understood the disclosure of Zhang B1 differently. CVC fails to explain why Dr. Seeger’s testimony is unreliable based on the disclosures of Zhang B1 or any other evidence. (See CVC Misc. Motion 2, Paper 844, 8:25–26.) Accordingly, we are not persuaded that the testimony we cite should be excluded and deny CVC Miscellaneous Motion 2 to exclude evidence to the extent it asks us to exclude it.

Interference 106,115

1 same *EMXI* locus described above. Using both Surveyor assay and Sanger
2 sequencing of amplicons, we confirmed that the chimeric RNA design facilitates
3 cleavage of human *EMXI* locus with approximately a 4.7% modification rate
4 (Figures 2B).” (Zhang B1, Ex. 3001, ¶ 176; see Broad Motion 4, Paper 269,
5 11:11–12:22 and 19:18–21:2.) When cleavage of other gene products were
6 targeted, Zhang B1 reports:

7 A modification rate of 6.3% and 0.75% was achieved for the human
8 *PVALB* and mouse *Th* loci respectively, demonstrating the broad
9 applicability of the CRISPR system in modifying different loci across
10 multiple organisms (Figures 2B and 5). While, cleavage was only
11 detected with one out of three spacers for each locus using the
12 chimeric constructs, all target sequences were cleaved with efficiency
13 of indel production reaching 27% when using the co-expressed pre-
14 crRNA arrangement (Figure 5).”

15 (Zhang B1, Ex. 3001, ¶ 177.) (See Broad Motion 4, Paper 279, 12:17–22, see also
16 Seeger Decl., Ex. 3401, ¶ 5.45.)

17 Broad argues that these results demonstrate that Zhang B1 describes and
18 enables a bicistronic expression vector co-expressing chimeric guide RNA and
19 Cas9, because it provides the sequences that one would need to make each vector
20 and provides the means of engineering these vectors for use in eukaryotic cells to
21 cleave target DNA. (Broad Motion 4, Paper 269, 22:6–25:2.) Dr. Seeger testifies:

22 Zhang B1 provides a method for adapting the CRISPR-Cas9 system
23 for function in a eukaryotic cell and, among other things, using guide
24 RNAs comprising a guide sequence fused to a tracr sequence
25 (Count 1) The Zhang B1 disclosure and teachings include
26 working examples, which are carried through all of the Involved

Interference 106,115

1 Broad Patents. For the reasons discussed above, it is my opinion that
2 Zhang B1 describes and enables multiple embodiments, that fall
3 within the scope of Count 1 . . . of the Interference.

4 (See Seeger Decl., Ex. 3401, ¶ 5.146.)

5 In light of the methods and results in Zhang B1 and Dr. Seeger’s testimony,
6 we are persuaded that Example 1 demonstrates a eukaryotic cell comprising a
7 target DNA molecule and an engineered, single-molecule CRISPR-Cas system that
8 achieves cleavage of the target DNA molecule to modulate transcription of the
9 DNA, as required in Count 1.

10 CVC argues a person of ordinary skill in the art could not have made and
11 used a cell as recited in Count 1 without undue experimentation according to
12 Broad’s characterization of Zhang B1 because Broad relies exclusively on the
13 chimeric guide RNA depicted in Figure 2A of that application. (See CVC Opp. 4,
14 Paper 576, 1:2–17.) CVC argues that Figure 2A shows a guide RNA with “T”
15 residues, which could not be expressed by an RNA polymerase. (See *id.* at 1:18–
16 22.)

17 The relevant part of Figure 2A of Zhang B1 is reproduced below from CVC
18 Opposition 4, page 1.

Interference 106,115

1 abbreviated G, C, A, and U. Naturally occurring RNA polymerases do not
2 incorporate T residues into growing RNA strands under normal cell conditions.
3 (*See id.*) Dr. Peterson testifies that those of those of ordinary skill in the art would
4 have known that there would be no way to control the incorporation of a T base at
5 a desired location. (*See id.*)

6 CVC argues that because embodiment E17 of Zhang B1 makes use of the
7 chimeric guide RNA depicted in Figure 2A, which includes T bases, and Broad
8 relies on embodiment E17 for a written description and enablement of Count 1,
9 Broad has not shown that Count 1 is enabled by Zhang B1. (*See CVC Opp.* 4,
10 Paper 576, 6:9–10:27.)

11 CVC argues further that Broad cannot argue that the nucleic acid of Figure
12 2A could be made by post-transcriptional modifications of the nucleic acid of
13 Figure 2A to convert the T bases to U bases or by chemical *ex vivo* synthesis,
14 because Broad relied exclusively on producing the RNA in a cell. (*See id.* at 11:1–
15 13:21.) CVC also argues that Broad also cannot argue that the T bases in Figure
16 2A are merely typographical errors because Broad reproduced the Figure in its
17 motion three times and Dr. Seeger reproduced it 21 times, without noting any
18 error. (*See id.* at 13:22–14:15.)

19 CVC relies on Dr. Peterson’s testimony that one of ordinary skill in the art
20 would have reasonably taken Broad’s disclosed sequence at face value, given the
21 broad definition of polynucleotides in Zhang B1. (*See id.* at 15:7–16:2, citing
22 Third Peterson Decl., Ex. 4193, ¶¶ 203–204.) CVC points to the guidance for
23 methylation processes that could convert U bases to T bases in RNA polymers as a

Interference 106,115

1 reason why Figure 2A would have been accepted with T bases and not considered
2 to be a typographical error. (*See* CVC Opp. 4, Paper 576, 15:15–16:2, citing Third
3 Peterson Decl., Ex. 4193, ¶¶ 203–204.)

4 In addition, CVC points to the prosecution history of the involved Broad
5 patents as evidence that the sequence of Figure 2A was not an error because the
6 same sequence was listed in the applications that became many of the involved
7 patents, described as being a “combined DNA/RNA molecule,” and because even
8 though errors in the figures were identified by the Examiner, Broad did not correct
9 Figure 2A. (*See* CVC Opp. 4, Paper 576, 16:3–18:2.) We note that in the
10 Examiner’s requirement for correction CVC highlights, the Examiner only
11 required Broad to include sequence identification numbers, not correction of the
12 actual sequence. (*See* File History of Appl. 14/704,551, Ex. 4204, Part 52, 13072.)
13 CVC does not direct us to any comment by the Examiner regarding the sequence in
14 Figure 2A or to any rejection based on lack of enablement because of it.

15 Broad opposes CVC’s allegations of non-enablement. (*See* Broad Reply 4,
16 Paper 821, 4:4–12:6.) Broad argues that those of ordinary skill would have known
17 that the Ts in Figure 2A and would not have been confused that it was an RNA,
18 citing CVC’s own witness testimony as evidence. (*See* Broad Reply 4, Paper 821,
19 4:6–5:14, citing Declaration of Dana Carroll, Ph.D., in Application 13/842,859
20 (“Carroll Decl.”), Ex. 3634, ¶¶ 125, 126.) Dr. Carroll, CVC’s witness in the ’048
21 interference, reviewed paragraph 176 of Zhang B1, which describes the E17
22 embodiment and Figure 2A, although he omitted reference to Figure 2A. (*See*
23 Carroll Decl., Ex. 3642, ¶ 125.) Dr. Carroll concluded:

Interference 106,115

1 This design of a chimeric crRNA-tracrRNA hybrid, where the mature
2 crRNA is fused to a partial tracrRNA via a stem-loop linker, is the
3 same as what is described in the First Provisional and in the Jinek
4 2012 SCIENCE paper. *See, e.g., First Provisional at ¶¶ [0077],*
5 *[0079], and Figure 1B; Exhibit 22* at Figure 5.

6
7 (Carroll Decl., Ex. 3634, ¶ 126.)³¹ We understand from Dr. Carroll’s testimony
8 that he considered the chimeric, fused crRNA-tracrRNA hybrid depicted in Figure
9 2A of Zhang B1 to be the same as the RNA taught in Jinek 2012, which was
10 authored by the CVC inventors. Figure 5 of Jinek 2012 (Ex. 3202) recites the
11 same sequence as Figure 2A of Zhang B1, but with U bases instead of T bases.
12 (See Jinek 2012, Ex. 3202, 6, Fig. 5.) Thus, Dr. Carroll’s testimony tends to
13 indicate that one of ordinary skill in the art would have understood the sequence of
14 Figure 2A of Zhang B1 to be an RNA sequence with U bases, despite the inclusion
15 of two T bases and contrary to CVC’s current argument and Dr. Peterson’s
16 testimony.

17 Similarly, Broad relies on the cross-examination testimony of Dr. Peterson
18 as evidence of how the T bases were interpreted by those in the art at the time.
19 (See Broad Reply 4, Paper 821, 10:13–11:8.) Broad points to Figure 2B of Cong
20 2013 (Ex. 3201), which depicts “pre-crRNA + tracrRNA processing” involving a
21 nucleic acid with a T base. (See Cong 2013, Ex. 3201, 821, Fig. 2B.) Broad
22 argues that when Dr. Peterson was asked about his recognition of this figure on

³¹ We note that the term “First Provisional” in Dr. Carroll’s declaration refers to CVC’s provisional application 60/652,086. (See Carroll Decl., Ex. 3634, ¶ 21.)

Interference 106,115

1 cross-examination, he admitted that he did not notice the T base. (*See* Peterson
2 Dep., Ex. 3626, 163:14–18 (“Q. Okay. Okay. And when you read Cong 2013
3 before you were retained in this case, do you recall noticing there was a T in Figure
4 2B of Cong 2013? A. I don't recall noticing that in 2013.”); *see* Broad Reply 4,
5 Paper 821, 11:3–8.) Like Dr. Carroll’s, testimony, Dr. Peterson’s testimony tends
6 to indicate that one of ordinary skill in the art would have understood the sequence
7 of Figure 2A of Zhang B1 to an RNA without any confusion or need for
8 extraordinary processing, despite the inclusion of two T bases and contrary to
9 CVC’s current argument.

10 Broad argues further that even though Cong 2013 is one of the most highly
11 cited publications regarding CRISPR, no researchers or institution indicated a
12 problem understanding the Figure 2B of that publication, despite the inclusion of a
13 T base. (*See* Broad Reply 4, Paper 821, 10:15–11:2.) Broad’s assertion is difficult
14 to confirm, but we note that CVC does not direct us to a published correction of
15 Cong 2013, which might have been necessary if there had been confusion.

16 Given the testimony of two of CVC’s witnesses and the apparent
17 understanding of others ordinarily skilled in the art³², as discussed above, we agree

³² We note that although CVC denies Broad’s characterization of the level of skill of an ordinarily skilled artisan (*see* CVC Opp. 4, Paper 576, 35:5–10, response to Broad Material Fact 60, citing, *inter alia*, Seeger Decl., Ex. 3401, ¶ 4.1 (“Denied”)), elsewhere CVC agrees that the level of skill in the art was high (*see* CVC Motion 1, Paper 212, 3:17–20, citing Peterson Decl., Ex. 4036, ¶ 33). Based on the specifications and references cited by the parties, we find that the level of skill in the art was high, at least at the level of a practicing Ph.D. research scientist.

Interference 106,115

1 with Broad that the Ts in Figure 2B of Zhang B1 would not have been understood
2 as anything other an RNA sequence and would not have created any confusion.
3 CVC fails to persuade us that there is a reason one would have had to resort to
4 undue experimentation to carry out Count 1 when provided with Example 1 of
5 Zhang B1. Instead, we are persuaded by Broad’s argument that Example 1 of
6 Zhang B1 describes and enables Count 1 because those of ordinary skill would
7 have understood it shows successful use of a CRISPR-Cas system as recited and
8 provides the necessary guidance. (*See* Broad Motion 4, Paper 269, 5:23–7:9.)

9 In addition to presenting persuasive evidence that Example 1 of Zhang B1
10 provides a sufficient written and enabling description of at least an embodiment of
11 Count 1, Broad also argues that this disclosure was made continuously through the
12 chain of patent applications including in the involved application or patent. (*See*
13 37 C.F.R. § 41.201 (“Earliest constructive reduction to practice means the first
14 constructive reduction to practice that has been continuously disclosed through a
15 chain of patent applications including in the involved application or patent. For the
16 chain to be continuous, each subsequent application must comply with the
17 requirements of 35 U.S.C. 119-121, 365, or 386.”).) Broad argues, and CVC does
18 not cite evidence to the contrary, that Zhang B1 was continuously disclosed or
19 incorporated by reference in its entirety through each Broad patent or application
20 involved in the current interference or cited by these patents and applications. (*See*
21 Broad Motion 4, Paper 269, 3:2–4.) Broad also argues, and CVC does cite
22 evidence to the contrary, that each of Broad’s involved patents and application and
23 their respective intervening applications all contain an explicit disclosure of

Interference 106,115

1 Example 1 of Zhang B1. (*See* Broad Motion 4, Paper 269, 4:2–8.) Broad argues
2 further, and CVC does cite evidence to the contrary, that all of the requirements of
3 35 U.S.C. § 120 of common inventorship and timing of filing are met by Broad’s
4 involved patents and application and their respective intervening applications. (*See*
5 *id.* 4:21–5:7.)

6 Because Broad has persuaded us that Zhang B1 provides a constructive
7 reduction to practice of an embodiment of Count 1, we are persuaded that Broad
8 should be accorded its filing date. Accordingly, we GRANT Broad Motion 4.

9 *VII. CVC Motion 1 – Benefit*

10 CVC argues that it should be accorded benefit of the filing date of its
11 provisional application 61/652,086 (“P1”; Ex. 3002), 25 May 2012. (*See* CVC
12 Motion 1, Paper 212, 2:22–24.) In the alternative, CVC argues that it should be
13 accorded benefit of the filing date of its later provisional and non-provisional
14 applications. (*See id.* at 2:24-3: 4.)

15 CVC argues, and Broad does not direct us to evidence to the contrary, that at
16 least Example 1 of CVC’s P1 provisional application describes and enables a
17 single-molecule CRISPR-Cas system that is capable of cleaving, editing, or
18 modulating transcription of a target DNA molecule *in vitro*, that is, outside of a
19 cell. (*See id.* at 7:10–11:7, citing P1, Ex. 3002, ¶¶ 248–252, Figs. 3, 5, 9; *see*
20 Peterson Decl., Ex. 4036, ¶¶ 88–101.)

21 CVC argues that Example 1 of P1 would have also conveyed to a person of
22 ordinary skill in the art that the inventors were in possession of a eukaryotic cell,
23 specifically a fish cell, comprising a target DNA and a Type II CRISPR-Cas

Interference 106,115

1 system with an *S. pyrogenes* Cas9 and a “chimera A” sgRNA. (See CVC
2 Motion 1, Paper 212, 6:13–16, citing P1, Ex. 3002, ¶¶ 165, 248–251. Figs. 2, 3,
3 Peterson Decl., Ex. 4036, ¶¶ 87–106.) Specifically, CVC argues that P1 discloses
4 a “fish cell embodiment” that would have conveyed possession of a fish cell that
5 satisfies the elements of Count 1 because P1 discloses expression and purification
6 Cas9 protein and its use, along with an sgRNA comprising targeter-RNA and
7 activator-RNA covalently linked, to achieve DNA cleavage. (See, e.g., CVC
8 Motion 1, Paper 212, 7:12–8:4, 10:6–11, 10:26–11:3.) CVC cites to paragraph 165
9 of P1, which states that the disclosed methods of the specification may include a
10 cell from any organism, including fish. (See CVC Motion 1, Paper 212, 6:13–16.)
11 In addition to a fish cell, CVC argues that P1 describes and enables a “human cell
12 embodiment” and a “fruit fly cell embodiment” within the scope of Count 1, again
13 citing paragraph 165. (See CVC Motion 1, Paper 212, 22:15–30:11, citing P1,
14 Ex. 3002, ¶ 165.)

15 CVC does not direct us to a disclosure in P1 of results from a CRISPR-Cas
16 system in any of these eukaryotic cells.

17 Broad opposes CVC’s argument, arguing that the findings in the prior
18 ’048 interference bind our findings in this case. (See Broad Opp. 1, Paper 596,
19 11:2–22:8.) According to Broad, issue preclusion binds us in this case and the
20 decision in the ’048 interference is the law of the case. (See Broad Opp. 1,
21 Paper 596, 11:14–13:1.)

22 We are not persuaded by Broad’s argument that we are bound to come to
23 any decision on CVC’s benefit arguments because the issue in the prior

Interference 106,115

1 interference was interference-in-fact involving the obviousness of CVC’s *claims*
2 over Broad’s *claims*. The issue we address in CVC’s Motion 1 is the sufficiency
3 of the *disclosure* of an embodiment of Count 1 in CVC’s prior specifications.
4 Although the relevant facts considered in the prior interference may be similar to
5 and overlapping with the relevant facts raised by CVC Motion 1, we are not
6 persuaded that the prior determinations necessarily reveal anything about either
7 party’s disclosure. Broad does not cite to any determination in the prior decision
8 about the disclosures or CVC’s provisional or non-provisional applications and we
9 are not aware of any such determinations. Issue preclusion precludes relitigation
10 of issues actually litigated and determined in the prior suit. *See Lawlor v. National*
11 *Screen Serv. Corp.*, 349 U.S. 322, 326 (1955). The issue of obviousness or
12 interference-in-fact is not the same issue as the sufficiency of the disclosure in the
13 specification. We review Broad’s arguments regarding the substantive merits of
14 CVC’s claims to benefit.

15 Broad asserts that the fish cell, human cell, and fruit fly cell embodiments
16 CVC cites are “post-hoc creations of CVC’s expert, manufactured by stitching
17 together disparate disclosures in P1 and P2, using the Count as a roadmap.”
18 (Broad Opp. 1, Paper 596, 3:9–12.) Broad argues further that one of ordinary skill
19 in the art would not have concluded that the P1 applicants had possession of a
20 eukaryotic CRISPR-Cas system without disclosure of eukaryotic experiments
21 because of the unpredictable nature, well-known obstacles, and prior failures and
22 difficulties in adapting prior art prokaryotic systems to eukaryotic cells. (*See id.* at
23 34:7–38:2.) According to Broad, the embodiments on which CVC relies “suffer

Interference 106,115

1 from the fundamental flaw that they rely on an *in vitro* experiment only.” (*See id.*
2 at 34:9–10.) In support of its argument, Broad cites to the testimony of Dr. Mirkin.
3 (*See id.* at 34:18–35:18, citing Mirkin Decl., Ex. 3417, ¶¶ 124–147.)

4 CVC asserts that Dr. Mirkin’s testimony should be given no weight, and
5 even excluded, because he is unqualified to provide expert testimony on gene-
6 editing systems from the viewpoint of one of ordinary skill in the art in 2012. (*See*
7 CVC Reply 1, Paper 812, 5:1–18; *see also* CVC Misc. Motion 2, Paper 844,
8 10:10–14:13.) According to CVC, Dr. Mirkin’s field of expertise is nanoparticles,
9 not gene-editing or CRISPR systems. (*See* CVC Reply 1, Paper 812, 5:2–4; *see*
10 *also* CVC Misc. Motion 2, Paper 844, 10:12–15.) CVC cites to the lack of
11 Dr. Mirkin’s publications on gene editing before 2012, the fact that he has never
12 personally performed any CRISPR laboratory research and has no scientific
13 publications concerning CRISPR, and that his laboratory did not conduct any
14 research on CRISPR until 2015 or 2016, entering into the field only after a first
15 year graduate student suggested it. (*See* CVC Reply 1, Paper 812, 5:4–9, citing
16 Mirkin Depo, Ex. 4232, 28:22–29:1, 21:1–4, 27:5–29; *see also* CVC Misc.
17 Motion 2, Paper 844, 12:3–16.)

18 Contrary to CVC’s characterization of Dr. Mirkin, Broad argues that he is
19 one of the world’s foremost experts in the use of nanostructures for delivery of
20 proteins and nucleic acids to eukaryotic cells, having discovered RNA delivery
21 systems and published over 740 manuscripts, been awarded over 330 patents, and
22 received over 100 awards in this area. (*See* Broad Opp. to CVC Misc. Motion 2,

Interference 106,115

1 Paper 864, 8:23–9:7, citing Mirkin Decl., Ex. 3417, ¶¶ 5–6 and Mirkin *Curriculum*
2 *Vitae*, Ex. 3413.)

3 “Unlike an ordinary witness . . . an expert is permitted wide latitude to offer
4 opinions, including those that are not based on first hand knowledge or
5 observation.” *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 592 (1993). To
6 accept testimony of a witness as expert testimony, we must determine whether the
7 expert is proposing to testify to scientific knowledge that will assist us to
8 understand or determine a fact in issue. We look to “whether the reasoning or
9 methodology underlying the testimony is scientifically valid and of whether that
10 reasoning or methodology properly can be applied to the facts in issue.” *Id.* at
11 592–93.

12 CVC’s argument that Dr. Mirkin is unqualified to provide expert testimony
13 does not address whether Dr. Mirkin’s background is relevant to the facts of CVCs
14 Motion 1. Even if Dr. Mirkin did not do research on gene editing *per se* at the time
15 P1 and P2 were filed, his work is directly relevant to delivery of proteins and
16 nucleic acids to act in eukaryotic cells. For example, Dr. Mirkin’s *curriculum*
17 *vitae* lists the presentation “ACS Fall 2012 Plenary Symposium, Philadelphia, PA;
18 ‘Spherical Nucleic Acid (SNA) Nanostructures: A New Platform for Intracellular
19 Gene Regulation,’ (2012).” (See Mirkin *Curriculum Vitae*, Ex. 3413, 11.)
20 Furthermore, Dr. Mirkin testified: “I think ultimately the basis of my expertise is
21 the work that I do generally in the development of nucleic acid and protein-based
22 medicines and an understanding, perhaps a unique understanding, of the challenges
23 associated with taking those types of constructs into cells and getting them to

Interference 106,115

1 function appropriately.” (Mirkin Depo. Ex. 4232, 25:7–13; *see* Broad Opp. to
2 CVC Misc. Motion 2, Paper 864, 10:1–7.) We are persuaded that delivery of
3 nucleic acids for the purposes of gene regulation is sufficiently relevant to the
4 issues of CVC Motion 1 for Dr. Mirkin to be qualified to provide expert opinions
5 on RNA/protein CRISPR-Cas systems in eukaryotic cells.

6 Dr. Mirkin’s responses to CVC’s questions about what is currently known
7 about CRISPR-Cas systems do not persuade us otherwise because his testimony is
8 needed to know what one of ordinary skill would have thought in 2012. (*See* CVC
9 Reply to Misc. Motion 2, Paper 868, 5:1–11, citing Mirkin Depo., Ex. 4232,
10 84:11–17, 63:11–75:5 (*e.g.* 63:19–24, “Q. My question was do you have an
11 opinion as to whether RNA degradation precludes CRISPR-Cas9 from functioning
12 in a eukaryotic cell? A. Yeah. Yeah. So back in 2012, I think any POSA looking
13 at this would have realized and thought that that would be a major hurdle to
14 overcome.”).) *See Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d
15 1115, 1122 (Fed. Cir. 2008) (“Whether the written description requirement is
16 satisfied is a fact-based inquiry that will depend on the nature of the claimed
17 invention, . . . and the knowledge of one skilled in the art at the time an invention
18 is made and a patent application is filed. Such knowledge may change as time
19 progresses.”).

20 In addition, we evaluate Dr. Mirkin’s testimony, as we evaluate any
21 witness’s testimony, in light of the evidence provided in support. In accordance
22 with the instructions in *Daubert*, we look to whether an expert witness’s reasoning
23 is scientifically valid by reviewing the scientific literature. When his opinions

Interference 106,115

1 concur with the literature, they are not merely conclusory or speculative, as CVC
2 argues. (See CVC Reply 1, Paper 812, 5:9–12.) *Daubert* imposes no requirement
3 that an expert witness base his or her opinions only on his or her own work. See
4 *Monsanto Co., v. David*, 516 F.3d 1009, 1015 (Fed. Cir. 2008) (“David’s challenge
5 fails, however, because the Federal Rules of Evidence establish that an expert need
6 not have obtained the basis for his opinion from personal perception.”). We accord
7 weight to Dr. Mirkin’s opinions based on the support, not merely on his
8 background qualifications.

9 Because CVC fails to persuade us that either Dr. Mirkin is unqualified to
10 provide opinion testimony on issues relevant to CVC Motion 1 or that his
11 testimony is entirely unsupported, we decline to give his testimony no weight, in
12 general, or to exclude his testimony as whole, as CVC requests.

13 Turning to Broad’s substantive opposition to CVC Motion 1, Broad argues
14 that those of ordinary skill in the art would have been aware of reasons why
15 CRISPR-Cas9 systems might not work in eukaryotic cells and, therefore, would
16 have required more disclosure than the *in vitro* experiments provided in P1. (See
17 Broad Opp. 1, Paper 596, 34:18–35:18, citing Mirkin Decl, Ex. 3417, ¶¶124–147.)
18 The reasons Broad cites several reasons, including RNA degradation in eukaryotic
19 cells, differences in the environment of eukaryotic and prokaryotic cells, and toxic
20 effects of prokaryotic RNAs on eukaryotic cells. (See *id.*)

Interference 106,115

1 Dr. Mirkin cites to Karpala³³ (Ex. 3282), which relates to the effects of
2 degradation by eukaryotic proteins on RNA silencing, a technique for knockdown
3 or silencing of specific gene activity. (See Mirkin Decl., Ex. 3417, ¶ 130.)
4 Table 1 of Karpala includes proteins that cause RNA degradation as typical
5 eukaryotic proteins that interact with double-stranded RNA. (See Karpala 2005,
6 Ex. 3282, 214, Table 1.) Dr. Mirkin testifies that such anti-viral responses to
7 double-stranded RNA in eukaryotic cells would have been understood by those in
8 the art at the time P1 was filed to present barriers to the stability of CRISPR RNA
9 components. (See Mirkin Decl., Ex. 3417, ¶ 130.)

10 According to CVC, because Dr. Mirkin does not know whether degradation
11 is actually a problem with CRISPR-Cas systems in eukaryotic cells, his testimony
12 in support of Broad's argument is merely speculation. (See CVC Reply 1,
13 Paper 812, 12:24–13:1, 13:10–12, citing Mirkin Depo., Ex. 4232, 64:24-65:5.) As
14 explained above, we are not persuaded that questions about the ultimate
15 requirements for CRISPR-Cas function in eukaryotes are relevant to the issue of
16 written description because whether a disclosure indicates possession is viewed
17 from what one of ordinary skill in the art would have considered at the time of
18 filing. CVC does not present evidence to contradict Dr. Mikin's testimony about
19 the concerns one would have had, given the lack of discussion of RNA degradation
20 in P1, nor does CVC cite to a discussion of RNA degradation in P1 that would

³³ Karpala et al., "Immune response to ds RNA: Implications for gene silencing technologies," *Immuology and Cell Biol.*, 83:211–216 (2005) (Ex. 3282).

Interference 106,115

1 have indicated the applicants knew at the time of filing that RNA degradation
2 would not occur.

3 Broad relies further on Dr. Mirkin's testimony that those of ordinary skill in
4 the art would have known that temperature, pH, and concentration of ions in a
5 eukaryote could have unpredictable effects on CRISPR-Cas9 RNA expression,
6 protein folding, and function. (*See* Broad Opp. 1, Paper 596, 35:9–13, citing
7 Mirkin Decl., Ex. 3417, ¶ 132.) Dr. Mirkin testifies that those of ordinary skill
8 would have known that the natural function of CRISPR systems, as bacterial
9 adaptive immune systems, could have caused off-target reactions and toxicity in
10 eukaryotic cells. (*See* Mirkin Decl., Ex. 3417, ¶ 134.)

11 In addition to the possible difficulties one of ordinary skill would have
12 known could hamper a CRISPR-Cas system in eukaryotic cells, Broad argues that
13 the failures of adapting other prokaryotic systems to eukaryotic cells would have
14 also been known. (*See* Broad Opp. 1, Paper 596, 35:19–36:15.) Broad relies on
15 the testimony of Dr. Mirkin regarding Group II introns, T7 RNA polymerase,
16 hammerhead ribozymes, and designer riboswitches to show how one of ordinary
17 skill would have viewed the need for specific instructions and conditions in order
18 to conclude the inventors were in possession of a CRISPR-Cas system in
19 eukaryotic cells. (*See* Broad Opp. 1, Paper 596, 36:3–15, citing Mirkin Decl.,
20 Ex. 3417 ¶¶ 149–165.)

21 Dr. Mirkin explains that Group II introns are a prokaryotic complex of an
22 RNA and protein that have been proposed for gene targeting in eukaryotic cells.
23 (*See* Mirkin Decl., Ex. 3417, ¶ 150.) Dr. Mirkin cites to publications and other

Interference 106,115

1 references to show that Group II introns are very inefficient, even unusable in
2 eukaryotes. (See Mirkin Decl., Ex. 3417, ¶ 152.) For example, in 2008,
3 Mastroianni³⁴ (Ex. 4068) states that after injecting fish cells with the components
4 of Group II introns and supplying additional Mg²⁺ ions, “efficient group II intron-
5 based gene targeting reactions have not been demonstrated in eukaryotes.” (See
6 Mastroianni, Ex. 4068, abstract.) Dr. Mirkin testifies that the technical issues
7 encountered with Group II introns, particularly the need for very high levels of
8 Mg²⁺ ions, would have indicated to one of ordinary skill in the art that CRISPR-
9 Cas systems would not work in eukaryotic cells without a description of specific
10 conditions for adaptation. (See Mirkin Decl., Ex. 3417, ¶ 154.)

11 CVC disputes Dr. Mirkin’s testimony about Mastroianni, arguing that it says
12 nothing about deleterious effects of Mg²⁺ ion levels on eukaryotic cells. (See CVC
13 Reply 1, Paper 812, 15:6–12.) CVC argues that in contrast, Mastroianni discloses
14 that any reduced efficiency related to Mg²⁺ ions “can be overcome by injecting
15 additional Mg²⁺ or Mg²⁺ in combination with polyamines” (Mastroianni, Ex. 4068,
16 9), which CVC interprets as simply optimization that one of ordinary skill in the art
17 would have considered in 2012. (See *id.*) In general, CVC argues:

18 Contrary to Broad’s assertions, no legal authority requires CVC to
19 describe and rule out all theoretical “unique conditions” that are
20 *unnecessary* for practicing the invention. Notably, Broad has not
21 identified *any* “adaptations,” “unique conditions,” or “specific
22 instructions” beyond P1’s disclosure that a POSA purportedly needed

³⁴ Mastroianni et al., “Group II Intron-Based Gene Targeting Reactions in Eukaryotes,” *PLOS One*, 3:e3121 (2008) (Ex. 4068).

Interference 106,115

1 for CRISPR-Cas9 to function in a eukaryotic cell. And when asked on
2 cross-exam what “adaptations” would be necessary, Dr. Mirkin
3 conceded he had *no opinion*. Ex. 4232, 34:14-21, 35:2-36:5.

4
5 (CVC Reply 1, Paper 812, 12:16–22.)

6 CVC’s arguments fail to persuade us that those of ordinary skill in the art
7 would not have considered specific instructions or conditions for a CRISPR-Cas9
8 activity in a eukaryotic cell to be necessary. Possession of an innovation is not
9 indicated by the need for optimization to obtain it because “[t]he question is not
10 whether a claimed invention is an obvious variant of that which is disclosed in the
11 specification. Rather, a prior application itself must describe an invention, and do
12 so in sufficient detail that one skilled in the art can clearly conclude that the
13 inventor invented the claimed invention as of the filing date sought.” *Lockwood v.*
14 *Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). As the Federal Circuit
15 and Supreme Court have explained:

16 Patents are not awarded for academic theories, no matter how
17 groundbreaking or necessary to the later patentable inventions of
18 others. “[A] patent is not a hunting license. It is not a reward for the
19 search, but compensation for its successful conclusion.” [*University of*
20 *Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 930, n. 10
21 (Fed.Cir.2004) (quoting *Brenner*, 383 U.S. 519, 536 (1966)].
22 Requiring a written description of the invention limits patent
23 protection to those who actually perform the difficult work of
24 “invention”—that is, conceive of the complete and final invention
25 with all its claimed limitations—and disclose the fruits of that effort to
26 the public.

Interference 106,115

1 *Ariad*, 598 F.3d at 1353. If the P1 applicants did not disclose specific instructions
2 or conditions necessary for CRISPR-Cas9 activity in a eukaryotic cell, or indicate
3 that no specific instructions or conditions were necessary, we are not persuaded
4 that one of ordinary skill would have considered there to be possession, given the
5 experiences in the art with the similarly complex Group II intron RNA/protein
6 system.

7 Dr. Mirkin testifies further to the problems encountered with T7 polymerase
8 would have indicated to those of ordinary skill in the art that unique circumstances
9 and specific instructions would likely have been needed to show possession of a
10 eukaryotic cell with a CRISPR-Cas system capable of cleaving or editing a target
11 DNA or of modulating transcription, as required in Count 1. (*See* Mirkin Decl.,
12 Ex. 3417, ¶¶ 158–161.) Dr. Mirkin explains that T7 polymerase is a prokaryotic
13 protein that transcribes any DNA linked to a T7 promoter, but not when the DNA
14 is present in the chromatin of higher eukaryotes because “of intrinsic differences in
15 chromatin structure between differently evolved eukaryotes or of an integration
16 site that is exceptionally permissive for T7 transcription due to a local accessible
17 chromatin conformation.” (Wirtz³⁵, Ex. 3284, 4626; *see* Mirkin Decl., Ex. 3417,
18 ¶ 160.)

19 Dr. Mirkin testifies further to reports about ribozymes and riboswitches that
20 would have led one of ordinary skill in the art to doubt the *in vitro* studies reported

³⁵ Wirtz, et al., “Regulated processive transcription of chromatin by T7 RNA polymerase in *Trypanosoma brucei*,” *Nucl. Acids Res.*, 26:4626–34 (1998) (Ex. 3284).

Interference 106,115

1 in P1 were sufficient to demonstrate possession of an embodiment of Count 1.
2 (See Mirkin Decl., Ex. 3417, ¶¶ 162–165.) Dr. Mirkin cites to Koseki³⁶ (Ex. 3294)
3 for its teachings of the problems RNA enzymes, such as ribozymes, can encounter
4 *in vivo*, including colocalization with a target, inhibition of binding to the target by
5 cellular factors (polysomes), and degradation before reaching the target. (See
6 Mirkin Decl., Ex. 3417, ¶ 163, citing Koseki, Ex. 3294, 1875–76.) Koseki
7 concludes that “For this reason, colocalization of a ribozyme and its target does
8 not, by itself, guarantee the efficacy of ribozymes *in vivo*.” (Koseki, Ex. 3294,
9 1876.) Similarly, Link³⁷ (Ex. 3295) reports that *in vitro* experiments do not predict
10 *in vivo* activity of riboswitches – RNAs that are engineered to control gene
11 activity. (See Link, Ex. 3295, 1190 (“Unfortunately, a number of factors intervene
12 to prevent many engineered RNA switches from becoming useful genetic switches.
13 For example, the functions of most aptamers have not been validated in cells, the
14 folding of RNA constructs might differ between test tube and cell, or the ribozyme
15 chosen for RNA switch construction might not be appropriate for controlling gene
16 expression.”); see Mirkin Decl., Ex. 3417, ¶ 165.)

17 CVC argues that Dr. Mirkin provides no evidence that any of the purported
18 hurdles he associates with T7 RNA polymerase, hammerhead ribozymes, and
19 designer riboswitches would have precluded a POSA from using CRISPR-Cas9 in

³⁶ Koseki et al., “Factors Governing the Activity In Vivo of Ribozymes Transcribed by RNA Polymerase III,” *J. Virol.*, 73:1868–77 (1999) (Ex. 3294).

³⁷ Link and Breaker, “Engineering ligand-responsive gene-control elements: lessons learned from natural riboswitches,” *Gene Therapy*, 16:1189–1201 (2009) (Ex. 3295).

Interference 106,115

1 a eukaryotic cell. (CVC Reply 1, Paper 812, 15:12–17.) We disagree because
2 Dr. Mirkin cites to Koseki and Link. CVC fails to direct us to evidence that
3 contradicts Dr. Mirkin’s interpretation of these reports.

4 Broad argues there were structural characteristics of CRISPR-Cas systems
5 that those of ordinary skill in the art would have known about as of the filing date
6 of CVC’s P1 application and would have expected should be described to show
7 possession of a CRISPR-Cas9 system in a eukaryotic cell. (*See* Broad Opp. 1,
8 Paper 596, 36:16–38:2.) Broad includes proto-spacer adjacent motifs (PAM)
9 sequences, NLSs, codon-optimization, and chromatin access as characteristics that
10 might have been expected to play a role in activity in eukaryotes. (*See id.*)

11 Broad agrees with CVC that PAM sequences were known to play a role in
12 DNA targeting in natural CRISPR systems before the filing of P1, but Broad
13 argues that it was not known whether these sequences played a role in cleaving
14 non-natural targets and that P1 fails to provide any discussion of the sequences
15 with eukaryotic targets. (*See* Broad Opp. 1, Paper 596, 36:22–37:7.) Broad relies
16 on Dr. Mirkin’s testimony that the lack of discussion in P1 would have indicated to
17 those in the art that the CVC inventors had not yet begun to consider the type of
18 information required for possession of a CRISPR-Cas9 system applied to non-
19 natural targets. (*See id.*, citing Mirkin Decl., Ex. 3417, ¶ 145.)

20 CVC attempts to refute Broad’s argument about the role of PAM sequences
21 by citing to Dr. Peterson’s testimony regarding what was known in the art about
22 them before P1 was filed. (*See* CVC Motion 1, Paper 212, 31:17–33:23; *see*
23 Reply 1, Paper 812, 14:13–21, citing Peterson Decl., Ex. 4036, ¶¶ 47–57, 190–

Interference 106,115

1 194.) Broad does not disagree that much was known about their role with natural
2 targets. But Broad’s argument is that their role in targeting non-natural or
3 eukaryotic DNA was not known. According to Dr. Peterson, because the
4 experiments disclosed in P1 took place in a cell-free environment, the results “only
5 solidifies that the CVC inventors had identified the necessary and sufficient
6 components for a functional Type II CRISPR-Cas9 DNA cleavage complex.” (*See*
7 *Peterson Decl., Ex. 4036, ¶ 193.*) This statement does not fully address Broad’s
8 argument because Dr. Peterson does not state that the CVC inventors identified the
9 necessary and sufficient components in *any* environment or in a eukaryotic
10 environment.

11 Dr. Peterson testifies further that “the origin(s) of the target DNA sequences
12 in Example 1 (i.e., prokaryotic or otherwise) would not have mattered to a POSA
13 because the target DNA sequences are made up of the same four nucleotides—A’s,
14 C’s, G’s, and T’s—that make up eukaryotic DNA.” (*Peterson Decl., Ex. 4036,*
15 *¶ 193.*) Thus, Dr. Peterson’s opinion is that those of ordinary skill would not have
16 considered there to be any difference in the role of the PAM sequences in
17 eukaryotic gene targeting versus prokaryotic or *in vitro* gene-targeting.

18 Whether or not this is true (Dr. Peterson does not cite to evidence in support
19 of this opinion), we agree with Broad that P1 fails to disclose how PAM sequences
20 should be used with non-natural targets in a eukaryotic CRISPR-Cas9 system.
21 (*See Broad Opp. 1, Paper 596, 36:24–37:3* (“Thus, a POSA would have expected
22 that if P1 described a eukaryotic CRISPR-Cas9 embodiment, it would address
23 whether or not PAM played a role with respect to non-natural targets in

Interference 106,115

1 eukaryotes.”); *see also* Mirkin Decl., Ex. 3417, ¶ 145.) That is, even if PAM
2 sequences play the same role as in prokaryotic settings, we agree that one of
3 ordinary skill in the art would have expected P1 to discuss the inclusion of these
4 sequences in DNA targets that allow for successful cleavage.

5 CVC’s argument that a PAM sequence is not a limitation of Count 1 also
6 fails. (*See* CVC Motion 1, Paper 212, 32:3–8.) Count 1 requires a system that is
7 capable of cleaving or editing target DNA molecules and modulating transcription
8 of at least one gene or altering the expression of at least one gene product. (*See*
9 Declaration, Paper 1, 13.) Thus, if a PAM sequence is necessary to achieve this
10 result, it must be sufficiently described in P1 for it to be a constructive reduction to
11 practice of Count 1.

12 Because CVC fails to direct us to a disclosure or discussion of P1 in DNA
13 targets that are specifically designed for use in eukaryotic CRISPR systems, we are
14 not persuaded the disclosure demonstrates possession of activity in eukaryotic
15 cells.

16 Broad’s arguments about the disclosure of the role of localization of the
17 CRISPR-Cas system to target DNA in a eukaryotic cell and the optimization of
18 codons are similar to its arguments about PAM sequences – that the P1 application
19 should have explained their role to show possession in eukaryotic cells. (*See*
20 Broad Opp. 1, Paper 596, 37:8–15, citing Mirkin Decl., Ex. 3417, ¶ 146; *see also*
21 Mirkin Decl., Ex. 3417, ¶¶ 136–140.) CVC argues that Dr. Mirkin’s testimony on
22 these topics are merely speculation and we agree that he does not cite to evidence
23 in support of his contentions that the role of these features were unknown for

Interference 106,115

1 CRISPR systems in eukaryotic cells. (*See* CVC Reply, Paper 812, 14:4–13.)
2 Nevertheless, we are not persuaded by Dr. Peterson’s testimony that neither NLSes
3 nor codon-optimization were required for CRISPR-Cas systems to work in
4 eukaryotic cells or that they were known techniques in the art in 2012. (*See*
5 Peterson Decl., Ex. 4036, ¶¶ 76–80 and 136–139.) The ultimate determination that
6 a feature is not required for a CRISPR-Cas9 system as recited in Count 1 is not
7 relevant to whether those of ordinary skill in the art would have considered a
8 disclosure to show possession at the time of filing. Broad fails to persuade us that
9 these particular features would have been considered by those of ordinary skill, but
10 we consider all the evidence cited by the parties in determining whether Broad has
11 shown that P1 provides a sufficient written description, indicating possession of an
12 embodiment of Count 1

13 Broad argues further that one of ordinary skill in the art would have
14 expected the P1 applicants to address the role of chromatin when adapting the
15 prokaryotic CRISPR-Cas9 system to eukaryotic cells because at the time it was
16 uncertain if Cas9 could access chromatinized DNA. (*See* Broad Opp. 1, Paper 596,
17 37:16–22.) Dr. Mirkin supports Broad’s argument, testifying that it was not
18 predictable whether Cas9 could access chromatinized DNA and citing to
19 discussions in publications about the difficulties researchers encountered when
20 using T7 polymerase and the bacteriophage protein, cre, on chromatinized DNA.
21 (*See* Mirkin Decl., Ex. 3417, ¶ 141, citing Ex. 3284, 3285.)

22 CVC contradicts Dr. Mirkin’s testimony and Broad’s argument by
23 presenting the testimony of Dr. Peterson that those of ordinary skill in the art at the

Interference 106,115

1 time would not have considered chromatin to be a barrier. (*See* CVC Reply 1,
2 Paper 812, 13:1–16, citing Peterson Decl., Ex. 4036, ¶ 189.) Dr. Peterson supports
3 CVC’s argument, citing to publications that report success with other prokaryotic
4 proteins and systems, including TALENS, RecA recombinase, Cre recombinase,
5 ϕ C31 integrase, Group II introns, restriction nucleases, and chimeric
6 prokaryotic/eukaryotic ZFN nucleases cleave or modify targeted DNA with
7 chromatin structure in a eukaryotic cells. (*See* Peterson Decl., Ex. 4036, ¶ 189,
8 citing Exs. 4039, 4054, 4056, 4057, 4059, 4163, 4119, 4068, 4130, 4134, 4132,
9 4136, 4109, 4135, 4131, 4133.) Dr. Peterson explains chromatin structures were
10 known to be dynamic and variable, having both open and closed conformations,
11 and it was also known that prokaryotic genomes possess chromatin in the genome,
12 even without a nucleus. (*See* Peterson Decl., Ex. 4036, ¶ 189, citing Exs. 4165,
13 4168, 4166, 4167.)

14 Dr. Mirkin and Dr. Peterson present conflicting testimony about how
15 chromatin structure was perceived by those of ordinary skill in the art when
16 designing prokaryotic systems for use in eukaryotic cells. For example, Both Dr.
17 Mirkin and Dr. Peterson cite Sauer³⁸, published in 1988 (Ex. 3285/4109), which
18 reports site-specific DNA recombination by the bacteriophage Cre recombinase on
19 an artificial circular plasmid introduced into mammalian cells. Sauer demonstrates
20 recombination of a non-chromosome target in a mammalian cell, but asks:

³⁸ Sauer and Henderson, “Site-specific DNA recombination in mammalian cells by the Cre recombinase of bacteriophage P1,” *Proc. Nat’l Acad. Sci.*, 85:5166–70 (1988) (Ex. 3285/4109)

Interference 106,115

1 Can Cre also cause recombination at *lox* sites located within the
2 genome of a mammalian cell? Such recombination events would
3 allow the precise integration and excision of DNA at a predetermined
4 chromosomal locus, thus facilitating the analysis of gene regulation in
5 a particular chromosomal context. However, the ability of the Cre
6 protein to access a *lox* site placed on a chromosome and then to
7 perform site specific synapsis of DNA and reciprocal recombination
8 may be highly dependent on surrounding chromatin structure and on
9 the particular location within the genome of the *lox* site. Some regions
10 of the genome may be inaccessible to a bacterial recombinase, for
11 example. If so, the *Cre-lox* system may provide important information
12 on chromosomal structure and its response to regulatory mechanisms
13 in the cell.

14

15 (Sauer, Ex. 3285/4109, 5170.) Thus, although Sauer demonstrates an artificial
16 system, which does not include modulating or altering transcription of a eukaryotic
17 target DNA, it also questions whether the Cre protein will work on a chromatin
18 structure.

19 Similarly, Dr. Mirkin cites Wirtz³⁹ (Ex. 3284), which reports that a
20 bacteriophage polymerase that naturally transcribes DNA into RNA in
21 prokaryotes, T7 RNA polymerase, is unable to fully transcribe higher eukaryotic
22 chromatin because “of intrinsic differences in chromatin structure between
23 differently evolved eukaryotes or of an integration site that is exceptionally

³⁹ Wirtz, et al., “Regulated processive transcription of chromatin by T7 RNA polymerase in *Trypanosoma brucei*,” *Nucl. Acids Res.*, 26:4626–34 (1998) (Ex. 3284).

Interference 106,115

1 permissive for T7 transcription due to a local accessible chromatin conformation.”
2 (Wirtz, Ex. 3284, 4626; *see* Mirkin Decl., Ex. 3417, ¶ 141.)

3 In contrast, Dr. Peterson cites to publications regarding prokaryotic
4 restriction enzyme activity in eukaryotic cells. (*See* Peterson Decl., 4036, ¶ 189,
5 citing Carney⁴⁰, Ex. 4130, and Morgan⁴¹, Ex. 4133.) CVC also cites Mastroianni
6 (Ex. 4068), which was discussed above in regard to specific Mg²⁺ conditions
7 needed to use a prokaryotic system in eukaryotic cells, but also states that
8 “interference from chromatin with group II intron gene targeting is expected to be
9 mitigated in systems undergoing active transcription or DNA replication.”
10 (Mastroianni, Ex. 4068, 11; *see* CVC Reply 1, Paper 812, 13:7–10.)

11 Thus, we are presented with different evidence, and even different
12 interpretations of the same evidence, in support of each party’s position about what
13 was necessary regarding access to eukaryotic chromatin for one of ordinary skill to
14 have considered the P1 applicants had possession of an embodiment of Count 1 at
15 the time P1 was filed. Neither witness presents a full discussion of the systems
16 they use as comparisons to CRISPR-Cas systems, often presenting only listing
17 exhibit numbers or quotations with little context.

⁴⁰ Carney and Morgan, “Induction of DNA Double-Strand Breaks by Electroporation of Restriction Enzymes into Mammalian Cells,” in *DNA Repair Protocols*, Humana Press, 465–71 (1999) (Ex. 4130).

⁴¹ Morgan et al., “Inducible Expression and Cytogenetic Effects of the *Eco RI* Restriction Endonuclease in Chinese Hamster Ovary Cells,” *Mol. Cell Biol.*, 8:4204–11 (1988) (Ex. 4133).

Interference 106,115

1 Nevertheless, Dr. Mirkin presents evidence of the specific concerns those
2 of ordinary skill would have had about a CRISPR-Cas9 system in a eukaryotic cell
3 at the relevant time by citing statements made by Dr. Dana Carroll, whose
4 technical opinions CVC put forth in the prior '048 interference. (See Mirkin Decl.,
5 Ex. 3417, ¶ 141, citing Carroll⁴², Ex. 3286, 1660; see Broad Opp. 1, Paper 596,
6 37:19–20.) In a September 2012 review of the CVC inventors' results showing
7 DNA cleavage *in vitro* with a CRISPR-Cas9 system, Dr. Carroll stated:

8 What about activity of the system in eukaryotic cells? Both zinc
9 fingers and TALE modules come from natural transcription factors
10 that bind their targets in a chromatin context. This is not true of the
11 CRISPR components. There is no guarantee that Cas9 will work
12 effectively on a chromatin target or that the required DNA–RNA
13 hybrid can be stabilized in that context. This structure may be a
14 substrate for RNA hydrolysis by ribonuclease H and/or *FEN1*, both of
15 which function in the removal of RNA primers during DNA
16 replication. Only attempts to apply the system in eukaryotes will
17 address these concerns.

18
19 (Carroll 2012, Ex. 3286, 1660.) Thus, even after P1 was filed, Dr. Carroll stated
20 that actual experiments were necessary to address concerns about chromatin
21 structure and RNA stability and to determine if CRISPR-Cas9 systems would work
22 in eukaryotic cells. CVC argues that “[s]tatements from one of CVC’s inventors or
23 one past expert – made in other contexts that did not reference P1 – do not negate

⁴² Carroll, “A CRISPR Approach to Gene Targeting,” *Mol. Therapy* 20:1658–60 (2012) (Ex. 3286.)

Interference 106,115

1 the disclosures of P1.” (CVC Motion 1, Paper 212, 31:1–2.) But CVC fails to
2 direct us to disclosure in P1 that addresses the concerns those of ordinary skill
3 would have had, as highlighted by Dr. Carroll. Thus, his statements shift the
4 preponderance of the evidence towards Broad’s argument that without at least a
5 discussion of the role of chromatic access in P1, those of ordinary skill in the art
6 would not have considered the P1 applicants to have had possession of an
7 embodiment of Count 1.

8 Broad cites to other similar statements by the inventors named on P1,
9 indicating doubt that a CRISPR-Cas9 system would work in eukaryotic cells until
10 the actual experiment had been done. (*See* Broad Opp. 1, Paper 596, 7:4–9.) For
11 example, in a publication dated 2013, CVC inventors Jinek and Doudna wrote that

12 [t]hese findings [that Cas9 would be programmed to cleave double-
13 stranded DNA at any site defined by a guide RNA sequence including
14 a PAM sequence] suggested the exciting possibility that Cas9:sgRNA
15 complexes might constitute a simple and versatile RNA-directed
16 system for generating DSBs that could facilitate site-specific genome
17 editing. However, it was not known whether such a bacterial system
18 would function in eukaryotic cells.

19 (Jinek 2013⁴³, Ex. 4137, 1–2.) Similarly, CVC inventor Doudna was credited as
20 saying:

21 Our 2012 paper [showing that the Cas9 endonuclease family can be
22 programmed with single RNA molecules to cleave specific DNA
23 sites,] was a big success, but there was a problem. We weren’t sure if

⁴³ Jinek et al., “RNA-programmed genome editing in human cells,” *eLife* DOI: 10.7554/elife.00471 (2013) (Ex. 4137).

Interference 106,115

1 CRISPR/Cas9 would work in eukaryotes—plant and animal cells.
2 Unlike bacteria, plant and animal cells have a cell nucleus, and inside,
3 DNA is stored in a tightly wound form, bound in a structure called
4 chromatin.”

5 (Catalyst⁴⁴, Ex. 3287, 3.) Thus, even the CVC inventors, who could be considered
6 to have had more skill than the ordinary artisans, were not sure if the eukaryotic
7 chromatin would allow for a functional CRISPR-Cas9 system in a eukaryotic cell.
8 The CVC inventors’ comments tend to indicate that they did not have possession
9 of a functional CRISPR-Cas9 system in eukaryotic cells until such experiments
10 had been done. “A ‘mere wish or plan’ for obtaining the claimed invention is not
11 adequate written description.” *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636
12 F.3d 1341, 1348 (Fed. Cir. 2011).

13 After taking all of the evidence regarding how those of ordinary skill in the
14 art would have viewed whether P1 demonstrates the applicants were in possession
15 of an embodiment of Count 1, we determine that a preponderance of the evidence
16 indicates possession would not have been understood. Broad has persuaded us that
17 absent results of a successful working example, the lack of discussion of PAM
18 sequences, or sample target DNA sequences, the lack of special instructions or
19 conditions necessary to accommodate the eukaryotic cellular environment, and the
20 lack of a discussion of whether access to chromatin could hinder CRISPR-Cas

⁴⁴ “The CRISPR Revolution,” *Catalyst Magazine* (2014),
<http://catalyst.berkeley.edu/slideshow/the-crispr-revolution/>[19/12/2014
12:40:53] (Ex. 3287).

Interference 106,115

1 activity would have indicated to those of ordinary skill in the art that the P1
2 applicants were not in possession of an embodiment of Count 1.

3 We are not persuaded by CVC that denying its request to accord benefit to
4 P1 is improperly based on a requirement for working examples or an improper
5 requirement to show there would have been a reasonable expectation of success in
6 an embodiment of Count 1. (*See* CVC Reply 1, Paper 812, 1:11–13, 2:6–13.)
7 Instead, we base our opinion on whether one of ordinary skill in the art would have
8 considered the CVC inventors to have had possession of an embodiment of
9 Count 1 at the time P1 was filed based on the disclosure of the P1 application. The
10 answer may hinge on the lack of a working example or on whether there was an
11 expectation of success, but would reflect the nature of the subject matter and the art
12 – highly unpredictable – not a general requirement for such things. *See Ariad*, 598
13 F.3d at 1357–58 (holding claims invalid for lack of a written description where the
14 patent disclosed no working or even prophetic examples of the claimed method
15 and no completed syntheses of any of the molecules prophesized to be capable of
16 the claimed method and the state of the art at the time of filing was “primitive and
17 uncertain” with an insufficient supply of prior art knowledge to fill the gaping
18 holes in its disclosure); *see Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed.Cir.2005)
19 (what is required to meet the written description requirement “varies with the
20 nature and scope of the invention at issue, and with the scientific and technologic
21 knowledge already in existence.”).

22 Similarly, we are not persuaded that we require CVC to “describe and rule
23 out all theoretical ‘unique conditions’ that are *unnecessary* for practicing the

Interference 106,115

1 invention.” (CVC Reply 1, Paper 812, 12:16–18.) Although the inquiry we must
2 make is difficult – asking what description was necessary when it is now known
3 what is or is not required for a eukaryotic cell with a functional CRSIPR-Cas9
4 system –to satisfy the written description requirement, “the applicant must ‘convey
5 with reasonable clarity to those skilled in the art that, *as of the filing date sought*,
6 he or she was in possession of the invention,’ and demonstrate that by disclosure in
7 the specification of the patent.” *Carnegie Mellon*, 541 F.3d at 1122 (emphasis
8 added) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64
9 (Fed.Cir.1991)). Thus, we consider the evidence the parties present of what one of
10 ordinary skill in the art would have considered at the time P1 was filed, not what
11 was later determined to be needed for CRISPR-Cas9 function.

12 In the absence of a disclosure that would have indicated to those of ordinary
13 skill in the art at the time of filing that the P1 applicants had possession of an
14 embodiment of Count 1, we are not persuaded that P1 satisfies the written
15 description requirement of 35 U.S.C. § 112, first paragraph, and therefore are not
16 persuaded that P1 is a constructive reduction to practice of Count 1, as defined in
17 37 C.F.R. § 41.201.

18 CVC argues further that P1 enables making and using an embodiment of
19 Count 1 because it provides multiple methods of obtaining a CRISPR-Cas9 system
20 and introducing it into a fish cell, none of which would have required undue
21 experimentation. (*See* CVC Motion 1, Paper 212, 12:18–19:4.) We need not
22 determine whether the P1 disclosure would have enabled an embodiment of
23 Count 1 because we have determined that the P1 disclosure does not sufficiently

Interference 106,115

1 describe an embodiment of Count 1. *See Ariad*, 598 F.3d at 1344 (“We agree with
2 Lilly and read the statute to give effect to its language that the specification “shall
3 contain a written description of the invention” and hold that § 112, first paragraph,
4 contains two separate description requirements: a “written description [i] of the
5 invention, *and* [ii] of the manner and process of making and using [the invention”].
6 35 U.S.C. § 112, ¶ 1 (emphasis added).”) Accordingly, even without considering
7 enablement, we are persuaded that P1 is insufficient as a constructive reduction to
8 practice of Count 1 for benefit of its filing date to be accorded.

9 CVC argues in the alternative that it should be accorded benefit of the filing
10 date of its provisional application 61/716,256 (“P2”) (Ex. 3003), filed
11 19 October 2012, or of its provisional application 61/757,640 (“P3”) (Ex. 3004),
12 filed 28 January 2013), because both include the same disclosures as P1 and, thus,
13 are constructive reductions to practice of an embodiment of Count 1. (*See CVC*
14 *Motion 1, Paper 212, 33:16–22.*) CVC argues that P2 provides supplemental
15 disclosures about expressing Cas9 protein in *E. coli* and information about what
16 was known in the art about PAM sequences. (*See CVC Motion 1, Paper 212,*
17 *33:23–34:6.*) Broad’s opposition included arguments that the disclosures of P2
18 were insufficient for the same reasons as P1. We are unpersuaded that expression
19 of Cas9 protein in the prokaryote *E. coli* or general information about PAM
20 sequences cures the deficiencies discussed above in regard to P1. Accordingly, we
21 are not persuaded that P2 provides a constructive reduction to practice of an
22 embodiment of Count 1.

Interference 106,115

1 CVC argues, though, that P3 includes Example 2, which provides an actual
2 reduction to practice of a human cell embodiment. (See CVC Motion 1, Paper 212,
3 34:7–20, citing P3, Ex. 3004, ¶¶ 416–423.) Relying on Dr. Peterson’s testimony,
4 CVC argues that P3 discloses transfecting nucleic acids encoding a *S. pyogenes*
5 Cas9 protein and a chimera A RNA targeting the human CLTA locus into an
6 established mammalian cell line culture (HEK293T 11 cells), and describes
7 cleavage of a target DNA sequence. (See CVC Motion 1, Paper 212, 34:9–13,
8 citing P3, Ex. 3004, ¶¶ 408–423, Figs. 36-12; Peterson Decl., Ex. 4036, ¶¶ 200-
9 201.) Broad agrees that P3 discloses eukaryotic experiments in P3. (See Broad
10 Opp. 1, Paper 596, 8:18–19.)

11 Because Example 2 provides the protocols necessary and results of a
12 CRISPR-Cas9 system in eukaryotic, human cells, we are persuaded that P3
13 presents a sufficient written and enabled description of an embodiment of Count 1.
14 Accordingly, P3 is a constructive reduction to practice of Count 1.

15 CVC argues further that benefit of the parent non-provisional application of
16 its involved applications should also be accorded because they all share a common
17 specification. (See CVC Motion 1, Paper 212, 35:4–9.) Because, according to
18 CVC and as unopposed by Broad, benefit of the earlier P3 application has been
19 continuously disclosed through the chain of continuing applications including
20 CVC’s currently involved applications, the issue of whether benefit should be
21 accorded to CVC’s non-provisional applications is moot.

Interference 106,115

1 Accordingly, we grant in-part CVC Motion 1 and accord benefit of the filing
2 date of the P3 application to CVC on redeclaration of the interference, entered
3 separately.

4 *VIII. CVC Miscellaneous Motion 2 to Exclude Evidence*

5 CVC argues that several of Broad’s exhibits should be excluded because
6 they are inadmissible hearsay. (*See* CVC Misc. Motion 2, Paper 844, 4:5–10:9.)
7 Specifically, CVC argues that the declarations of Neville Sanjana (Ex. 3410), Feng
8 Zhang (Ex. 3629), and Alan Lambowitz (Ex. 3416), as well as portions of the
9 declaration of Christoph Seeger (Ex. 3401), should be excluded because they are
10 out of court statements, submitted for the truth of the matters asserted, but Broad
11 has failed to make the declarants available for cross-examination. (*See* CVC Misc.
12 Motion 2, paper 844, 4:16–5:5.) We do not cite or rely on any declarations by
13 Drs. Sanjana, Zhang, or Lambowitz in our opinion and, therefore, the issue of
14 whether they are inadmissible is moot.

15 CVC argues that paragraphs 5.5–5.145, 6.6, 6.8, 6.15, 6.19–6.21, and 7.2–
16 7.13 of Dr. Seeger’s declaration (Ex. 3401) should be excluded because they recite
17 hearsay for improper purposes. (*See* CVC Misc. Motion 2, paper 844, 7:21–24.)
18 We rely on paragraphs 6.6 and 6.8, 6.19–6.21 of Dr. Seeger’s declaration in our
19 analysis of Broad Motion 3, which we deny. Thus, whether or not paragraph 6.6
20 and 6.8, 6.19–6.21 are inadmissible is moot because even when we consider them,
21 Broad does not prevail.

22 We rely on paragraphs within the range of paragraphs 5.5–5.145 in our
23 analysis of Broad Motion 4 and, as discussed above, conclude that CVC fails to

Interference 106,115

1 provide a reason to exclude them. (*See*, n. 30 *supra*.) We do not cite or rely on the
2 other paragraphs of Dr. Seeger’s declaration that CVC argues should be excluded.
3 Accordingly, whether or they should be excluded is a moot issue.

4 CVC argues that paragraphs 4.15, 5.10, and 5.18 of Dr. Breaker’s
5 declaration (Ex. 3403) should be excluded because they offer articles for the truth
6 of the matters asserted within them. (*See* CVC Misc. Motion 2, Paper 844, 7:24–
7 26.) We rely on these paragraphs of Dr. Breaker’s declaration, if at all, in our
8 analysis of claim construction, which is relevant to Broad Motions 2 and 3.
9 Because we deny Broad Motions 2 and 3 even when we consider Dr. Breaker’s
10 testimony, the issue of whether it is admissible is moot.

11 CVC argues that paragraphs 150-153 of Dr. Mirkin’s declaration should be
12 excluded because it recites inadmissible hearsay for improper reasons, apparently
13 the Lambowitz Declaration. (*See* CVC Misc. Motion 2, Paper 844, 7:27–8:2.)
14 Because we do not rely on these paragraphs or the Lambowitz Declaration the
15 issue of their admissibility is moot.

16 CVC argues that all of Dr. Mirkin’s declaration (Ex. 3417) should be
17 excluded because he is not an expert in a relevant field. (*See* CVC Misc. Motion 2,
18 Paper 844, 10:10–14:13.) As explained above in our analysis of CVC Motion 1,
19 we are not persuaded by CVC’s arguments.

20 CVC also argues that Exhibits 3055, 3256, 3297, 3513, 3514, and 3638
21 should be excluded because neither party cites to them. (*See* CVC Misc. Motion 2,
22 Paper 844, 14:16–19.) Broad does not dispute CVC’s assertion. Accordingly, we
23 grant CVC’s motion regarding these exhibits only. We note that CVC argues that

Interference 106,115

1 “portions” of Exhibit 3411 were not cited by Broad. (*See* CVC Misc. Motion 2,
2 paper 844, 14:16.) Because we understand this to mean that portions of Exhibit
3 3411 were cited by Broad, we deny CVC’s request regarding Exhibit 3411.

4 Accordingly, we grant in-part CVC Miscellaneous Motion 2 and exclude
5 Exhibits 3055, 3256, 3297, 3513, 3514, and 3638 only.

6 *IX. Conclusion*

7 In summary, we make the following decisions on the parties’ motions:

8 Broad Motion 1 – denied,

9 Broad Motion 2 – denied,

10 Broad Motion 3 – denied,

11 Broad Motion 4 – granted,

12 CVC Motion 1 – granted in part,

13 CVC Motion 2 – dismissed, and

14 CVC Miscellaneous Motion 2 – granted in part.

15 As result of the parties’ motions to be accorded the benefit of earlier filing
16 dates, CVC remains the junior party, having been accorded benefit of the filing
17 date of 28 January 2013 when its provisional application 61/757,640 was filed.

18 Broad remains the senior party, having been accorded benefit of the filing date of
19 12 December 2012, when its provisional application 61/736,527 was filed.

20 In its priority statement⁴⁵, CVC asserts that it earliest conception and
21 initiation of diligence was 16 March 2011, with an actual reduction to practice by

⁴⁵ CVC requested and received authorization to file a protective order sealing its priority statement until a priority phase of the interference is scheduled. (*See*

Interference 106,115

1 August 9, 2012. (CVC Priority Statement, Paper 453.) Broad asserts that it earliest
2 conception and initiation of diligence was 4 February 2011, with an earliest actual
3 reduction to practice by 6 March 2011. (Broad Priority Statement, Paper 455.)
4 Because CVC could prevail on priority in light of its asserted dates and Broad's
5 accorded benefit date, the interference proceeds to a second, priority phase.

cc (via e-mail):

Attorney for Junior Party

Eldora L. Ellison
Eric K. Steffe
David H. Holman
Ralph Wilson Powers III
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
ellison-PTAB@sternekessler.com
esteffe-PTAB@sternekessler.com
dholman-PTAB@sternekessler.com
tpowers-PTAB@sternekessler.com

Li-Hsien Rin-Laures
RINLAURES LLC
lily@rinlauresip.com

Sandip H. Patel
Greta E. Noland
MARSHALL GERSTEIN & BORUN LLP

Order, Paper 432; Order, Paper 451). Because a schedule for the priority phase of this interference is entered concurrently with this Decision on Motions, the parties' priority statements and the dates asserted in them are no longer under seal.

Interference 106,115

spatel@marshallip.com
gnoland@marshallip.com

Attorney for Senior Party

Raymond N. Nimrod
Matthew D. Robson
QUINN EMANUEL URQUHART & SULLIVAN, LLP
raynimrod@quinnemanuel.com
matthewrobson@quinnemanuel.com

Steven R. Trybus
LOCKE LORD LLP
Steven.Trybus@lockelord.com
patent@lockelord.com

APPENDIX

Involved Applications and Patents

CVC

Application Number	Filing Date
15/947,680	6 April 2018
15/947,700	6 April 2018
15/947,718	6 April 2018
15/981,807	16 May 2018
15/981,808	16 May 2018
15/981,809	16 May 2018
16/136,159	19 September 2018
16/136,165	19 September 2018
16/136,168	19 September 2018
16/136,175	19 September 2018
16/276,361	14 February 2019
16/276,365	14 February 2019
16/276,368	14 February 2019
16/276,374	14 February 2019

Interference 106,115

Broad

Patent Number	Application Number	Filing Date
8,697,359	14/054,414	15 October 2013
8,771,945	14/183,429	18 February 2014
8,795,965	14/183,486	18 February 2014
8,865,406	14/222,930	24 March 2014
8,871,445	14/259,420	23 April 2014
8,889,356	14/183,471	18 February 2014
8,895,308	14/293,498	2 June 2014
8,906,616	14/290,575	29 May 2014
8,932,814	14/258,458	22 April 2014
8,945,839	14/256,912	18 April 2014
8,993,233	14/105,017	12 December 2013
8,999,641	14/226,274	26 March 2014
9,840,713	14/523,799	24 October 2014
	14/704,551	5 May 2015