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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*.

I. Introduction

The current interference is between The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier ("CVC") and The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College ("Broad") regarding CRISPR-Cas9 systems. A CRISPR-Cas9 system is a combination of protein and ribonucleic acid ("RNA") that can alter the genetic sequence of an organism. (*See* CVC involved application 15/947,680, Ex. 4018, at ¶ 4; Broad involved patent 8,697,359, Ex. 3011, at 1:45-46 and 2:13–20.) In their natural environment, CRISPR-Cas systems protect bacteria against infection by viruses. (*See* Declaration of Randall T. Peterson, Ph.D. ("Randall Decl.")[1], Ex. 4036, ¶ 37; *see* Declaration of Technical Expert 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.

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

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

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

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

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

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

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

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

a motion to change the designation of claims corresponding to the count (Broad Motion 3, Paper 268), which we deny; and

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

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

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

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

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

II. Broad Motion 1 - Estoppel

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CVC should have sought. (*See* Broad Reply 1, Paper 433, 10:23–11:7.) Nevertheless, the explanation quoted above could have been interpreted to mean that the Board would entertain future interferences on different, but related subject matter and that Rule 127(a)(1) estoppel would not apply to that subject matter.

Because we are not persuaded by Broad's arguments that CVC is estopped from participating in this interference, we DENY Broad Motion 1.[4]

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

III. Claim Construction

Some of the issues in Broad's motions, particularly Motions 2 and 3, are related to the scope of Broad's claims regarding the configuration of the CRISPR-Cas9 system. The CRISPR-Cas systems of the parties' claims comprise two RNA components and one protein component to achieve site specific cleavage of a double-stranded DNA. (*See* Seeger Decl., Ex. 3401, ¶ 2.10.) Figure 5A of Jinek 2012[5] depicts a schematic diagram of the components of a CRISPR-Cas9 system and is reproduced, in part, below.

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[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).

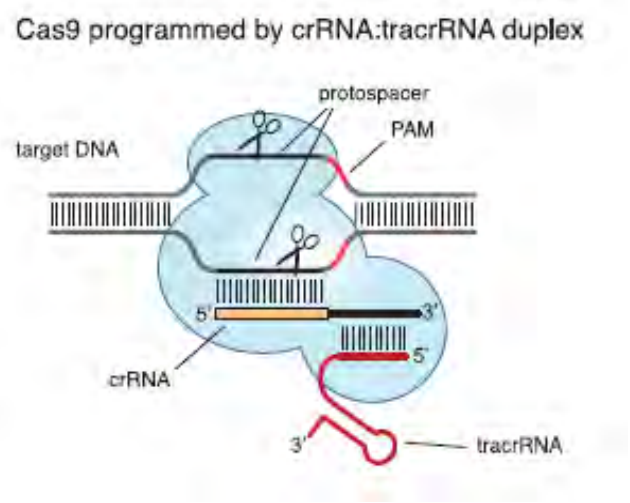

Figure 5A depicts a (1) a Cas9 protein shown as blue connected circular shapes in the background, (2) a "crRNA" [6] shown as bonded to a target DNA (vertical black lines indicating nucleic acid base pairing)[7], and (3) a "tracrRNA"[8] shown as a red curved line bonded to the crRNA. (*See* Jinek 2012,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

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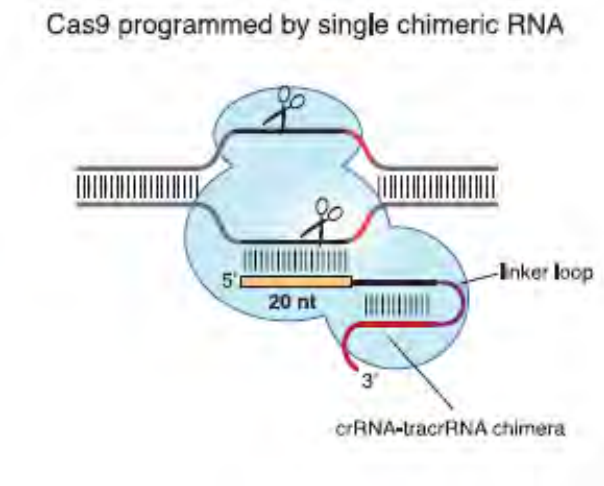
[6] CVC uses the term "targeted RNA" for this component in its involved claims. (*See, e.g.,* CVC Clean Copy of Claims, Paper 7, 3.)

[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.)

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

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



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

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

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

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

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

> The CRISPR-Cas system of claim 15**,** wherein the *guide RNAs* comprise a guide sequence fused to a tracr sequence.

(Broad Clean Copy of Claims, Paper 14, 5 (emphasis added).) Claim 15, from which claim 18 depends, recites:

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

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[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.

> 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 molecules, 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.

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

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

> a) a first regulatory element operable in a eukaryotic cell operably linked to a guide sequence capable of hybridizing to a target sequence in the eukaryotic cell, and at least one or more tracr mate sequences, and
>
> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a fusion of a Type-II Cas9 protein and one or more protein domains, and
>
> c) a third regulatory element operably linked to a tracr sequence,
>
> wherein:

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

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

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

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

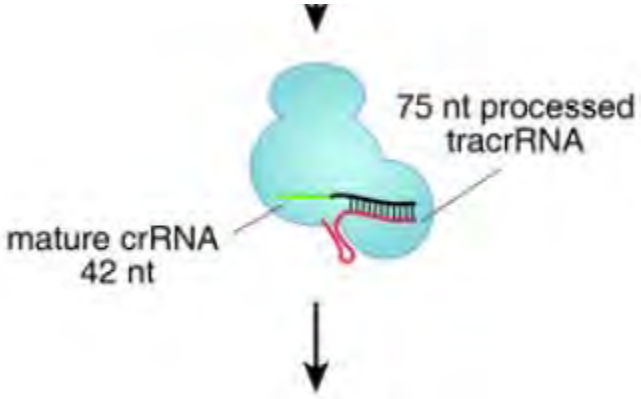
We agree with Broad that some of its claims, such as claims 15 and 18 of the '359 patent tend to indicate that "guide RNA" is a generic term, which could be limited to single-molecule RNA configuration by the term "fused" in a dependent claim. We agree with CVC, though, that other instances, such as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

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

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

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

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



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

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

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

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

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

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

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

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

Dr. Breaker cites to Bhaya[11], published in 2011 ("Bhaya"), which describes naturally occurring CRISPR systems in bacteria and archaea. (*See* Bhaya, Ex. 3218; *see* Breaker Decl., Ex. 3403, ¶¶ 5.24-5.25.) Bhaya defines "CRISPR RNA (crRNA)" as "small noncoding RNA produced by cleavage of pre-crRNA (also known as psiRNA or guide RNA)." (Bhaya, Ex. 3218, 276, side bar.) Bhaya 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).

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

Dr. Breaker cites to several other scientific articles published before 2012, which use the term "guide RNA" to refer to RNA components of naturally occurring CRISPR systems. (*See* Breaker Decl., Ex. 3403, ¶ 5.24, citing Carte[12], Ex. 3219, 3490; Hale[13], Ex. 3220, 2577; Jore[14], Ex. 3221, 529; and Brouns[15], Ex. 3222, 960.) And Dr. Breaker cites to scientific articles published before 2012, which use the term "guide RNA" to refer to RNA components of RNA interference systems having protein/RNA complexes asserted to be similar to CRISPR systems.

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[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 *Pyrococcoccus 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).

(*See* Breaker Decl., Ex. 3403, ¶ 5.25, citing Horvath[16], Ex. 3223, 169; Rand[17], Ex. 3224, 621; Tolia[18], Ex. 3225, 36.) We do not agree with Broad or Dr. Breaker that these uses of the term "guide RNA" in early publications are relevant to the issue of whether the term "guide RNA" in Broad's claims are limited to a single-molecule RNA configuration. It is not clear from Dr. Breaker's explanation that the term "guide RNA" in these publications refers to a complex of RNAs comparable to the RNA configurations of Broad's claims. For example, Carte (Ex. 3219) states that "[t]he CRISPR loci are transcribed as long RNAs that must be processed to smaller guide RNAs." (Carte, Ex. 3219, abstract.) Thus, the term "guide RNA" in Carte refers to any RNA produced from the CRISPR loci, not specifically a complex of the crRNA and the tracrRNA. (*See* CVC Opp. 3, Paper 591, 22:2–6.)

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

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[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 Activitation," *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).

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

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

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

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

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

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

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

Broad argues further that the term "used interchangeably" does not mean the listed terms have the same meaning. (*See id.* at 25:1–14.) Broad cites to other uses of the phrase in it specification, for example: "The terms 'polynucleotide',

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

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

We are persuaded by CVC's argument. Although the phrase "used interchangeably" could be interpreted as Broad argues, the phrase "refer to"

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

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

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

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

> Cas9 and its chimeric guide RNA, or combination of tracrRNA and crRNA. can be delivered either as DNA or RNA. Delivery of Cas9 and guide RNA both as RNA (normal or containing base or backbone modifications) molecules can be used to reduce the amount of time that Cas9 protein persist in the cell. This may reduce the level of off-target cleavage activity in the target cell. Since delivery of Cas9 as mRNA takes time to be translated into protein, it might be advantageous to deliver the guide RNA several hours following the delivery ofCas9 mRNA, to maximize the level of guide RNA available for interaction with Cas9 protein.

('308 patent, Ex. 3013, 38:33–43.)

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

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

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

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

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

IV. Broad Motion 2 – To Change the Count

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

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

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

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

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

Broad's proposed Count 2 recites:

> A method, in a eukaryotic cell, of cleaving or editing a target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule, the method comprising:
>
> contacting, in a eukaryotic cell, a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system comprising:
>
> a) a Cas9 protein, and
>
> b) RNA comprising
>
> i) a targeter-RNA that is capable of hybridizing with the target sequence of the DNA molecule or a first RNA comprising (A) a first sequence capable of hybridizing with the target sequence of the DNA molecule and (B) a second sequence; and
>
> ii) an activator-RNA that is capable of hybridizing to the targeter-RNA to form an RNA duplex in the eukaryotic cell or a second RNA comprising a tracr sequence that is capable of hybridizing to the second sequence to form an RNA duplex in the eukaryotic cell,
>
> wherein, in the eukaryotic cell, the targeter-RNA or the first sequence directs the Cas9 protein to the target sequence and the DNA molecule is cleaved or edited or at least one product of the DNA molecule is altered.

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

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

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

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

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

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

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

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

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

'359 patent - claims 4, 11, and 18;

'965 patent - claims 1–30;

'945 patent - claim 5;

'616 claims - 2 and 5;

'713 patent - claims 8, 9, 16, and 27

'551 application - claims 2, 4,–8, and 12–18.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

V. Broad Motion 3 – Claim Correspondence

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

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

A. RNA Configuration

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

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

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

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[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.)

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

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

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

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

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

Broad argues that its

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

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

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

> A CRISPR-Cas complex-mediated method for the production of a multicellular genetically modified non-human animal or multicellular genetically modified plant, the method comprising delivery to one or more target sequences in a cell of the multicellular non-human animal or plant of:
>
> a Cas9 protein;
>
> a guide sequence linked to a tracr mate sequence; and
>
> a tracr sequence;
>
> wherein the guide sequence directs sequence-specific binding of a *CRISPR* complex to the target sequence in the cell, whereby the multicellular genetically modified non-human animal or multicellular genetically modified plant is produced, and displays a phenotype or carries DNA to display a phenotype of the genetic modification.

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

Claim 26 of the '713 patent recites:

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

> having one or more target sequences of a Cas9 protein, or a nucleic acid molecule encoding the Cas9 protein; and a guide sequence linked to a tracr mate sequence; and a tracr sequence, or one or more nucleic acid molecules encoding the guide sequence linked to the tracr mate sequence and the tracr sequence,
>
> wherein the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence in the cell, whereby the multicellular genetically modified non-human animal or multicellular genetically modified plant is produced, and displays a phenotype or carries DNA to display a phenotype of the genetic modification.

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

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

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

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

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

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

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

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

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

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

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[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).

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

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

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

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

1268. The "possibility" that they are separate patentable inventions is what Broad must prove in this proceeding.

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

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

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

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

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

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

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

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

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

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

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

B. SaCas9

Broad argues that all of the claims of its involved '406 and '308 patents should be designated as not corresponding to Count 1 because they recite methods or systems comprising SaCas9 protein or nucleic acid sequences[21] and, therefore, are not anticipated or rendered obvious by Count 1. (*See* Broad Motion 3, Paper 268, 26:1–30:8.)

Broad argues that because Count 1 recites Cas9 generically, not SaCas9, it does not anticipate Broad's SaCas9 claims. (*See* Broad Motion 3, Paper 268, 26:8–9, citing Seeger Decl., Ex. 3401, ¶¶ 6.3–6.4.) Broad argues further that Count 1 does not render claims reciting SaCas9 obvious because there was no 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 gent 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.)

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

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

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

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

(Seeger Decl., Ex. 3401, ¶ 6.5.)

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

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

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

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

Pyrococcus furiosus . . . and *Streptococcus thermophilus* . . . ." (Sapranauskas,[22] Exs. 3215/4048, 9276 (citations omitted); *see* Third Peterson Decl., Ex. 4193, ¶ 120.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

31:17.) Dr. Peterson testifies in support of CVC's argument that Ran[24] (Ex. 3226) reports slightly *more* efficient cleavage for StCas9 than for SpCas9. (*See* Third Peterson Decl., Ex. 4193, ¶ 140.) Extended Data Figure 3a of Ran report "Indel (%)" for *S. aureas* as 6.7%, for *S. pyogenes* of 3.0% and for *S. thermophiles*, which Dr. Peterson characterizes as "comparable activity." (*See* Ran. Ex. 3226, 11; *see* Third Peterson Decl., Ex. 4193, ¶ 141.) We agree that these results contradict Dr. Seeger's conclusion that because StCas9 had a lower efficiency, the results obtained with SaCas9 would have been unexpected.

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

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[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).

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

Broad does not dispute Dr. Seeger's analysis of the data, but argues that it ignores the full context of the surprising result because StCas9 had a lower cutting efficiency. (*See* Broad Reply 3, Paper 822, 18:1–8.) Broad does not point to any flaws in Dr. Seeger's analysis of either Ran or Cong 2013. Because we are persuaded that Ran provides data on its face that disputes Broad's assertion and that one of ordinary skill in the art would not merely look to the highest efficiency reported for SpCas9 to compare to StCas9, we are not persuaded by Broad's argument that StCas9 would have been considered to be less efficient. Accordingly, we are not persuaded by Broad's argument that the lower efficiency of StCas9 would have created an expectation of lower efficiency in SaCas9, and that when this lower efficiency did not result, those of ordinary skill would have considered it unexpected. That is, we are not persuaded that SaCas9 produces results that would have been unexpected, given the results of a generic CRISPR-Ca9 system as recited in Count 1.

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

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

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

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

C. Multiple Nuclear Localization Signal Sequences

Broad argues that its claims[26] requiring two or more nuclear localization signals ("NLSs") should be designated as not corresponding to Count 1. (*See* Broad Motion 3, Paper 268, 30:9–32:5.)

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

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

Broad relies on Dr. Seeger's testimony to argue that using NLSs, especially with a prokaryotic protein, would have been highly unpredictable to those of ordinary skill in the art because such a sequence could alter a protein's structure and impair its function. (*See* Broad Motion 3, Paper 268, 31:9–22, citing Seeger Decl., Ex. 3401, ¶¶ 6.22–6.27; *see* Seeger Decl., Ex. 3401, ¶ 6.22.) Dr. Seeger cites to Fieck[27] (Ex. 3258), which reports the results of adding NLS sequences to the "lac repressor" protein in order to use this inducible prokaryotic protein in the nucleus of a eukaryotic cell. (*See* Seeger Decl., Ex. 3401, ¶ 6.23.) Dr. Seeger reports that the results of experiments adding an NLS to different places on the lac repressor showed that some NLS-repressor fusion proteins failed to bind the lack operon at all, whereas other NLS-repressor fusion proteins bound the lac operator, but did not function properly. (*See* Seeger Decl., ex. 3401, ¶ 6.25.) Dr. Seeger concludes:

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

(Seeger Decl., Ex. 3401, ¶ 6.27.)

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[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).

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

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

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

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

CVC argues further that contrary to Broad's position, before December 2012, those of ordinary skill in the art has routinely used two or more NLSs to successfully increase nuclear localization of prokaryotic proteins. (*See* CVC Opp. 3, Paper 591, 32:5–12.) Relying on Dr. Peterson's testimony, CVC cites publications that use NLS sequences on proteins of Type I and III CRISPR systems, Zinc finger nucleases, TALENS, Rec A, LacZ, and HaloTag reporter proteins. (*See id.*, citing Third Peterson Decl., Ex. 4193, ¶¶ 157–162.) For example, Sontheimer[28] (Ex. 3054) teaches appending NLS sequences to Cas constructs for subcellular localization to the nucleus (*see* ¶¶ 54 and 58). CVC argues further that it was known that more than one NLS could increase nuclear 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.)

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

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

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

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

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

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

VI. Broad Motion 4 – Benefit

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

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

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

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

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

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

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

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

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

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

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

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

deletions in the protospacer (*see id.*), whereas removing any of the other three components abolished activity. (*See id.*) Figure 1D, which is cited for these results, is reproduced below.

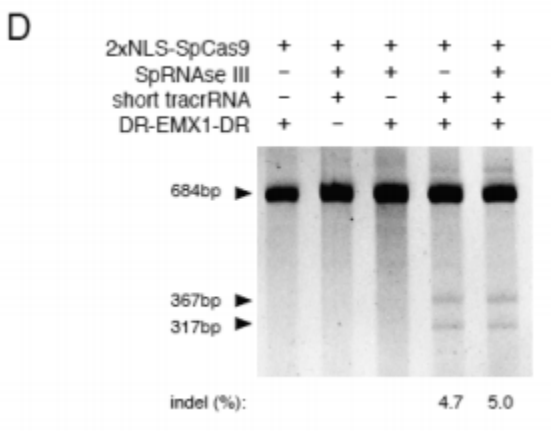

Figure 1D depicts a nuclease assay for SpCas9 mediated insertions and deletions wherein different combinations of four components of a CRISPR-Cas system are tested in each lane. Bands indicating a 367 bp and a 317 bp product are present in the lanes that include Cas9, tracrRNA, and *EXM1*-target spacer, but not in the lanes that are missing either tracrRNA or *EXM1*-target spacer. Zhang B1 provides the conclusion: "These results define a three-component system for efficient CRISPR-mediated genome modification in mammalian cells." (Zhang B1. Ex. 3001, ¶ 173.) Similarly, Dr. Seeger testifies[30] that one of ordinary skill reading

[30] CVC argues paragraphs 5.5 through 5.145 of Dr. Seeger's declaration are inadmissible hearsay and should be excluded. (*See* CVC Misc. Motion 2, Paper 844, 1:13–14, 7:21–22.) We rely on some of these paragraphs, for example Dr. Seeger's statement that "[t]he skilled artisan having read the Zhang B1 specification and considered the successful experiments and Figures therein would therefore conclude that this element is satisfied," in reference to Figure 1D of

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

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

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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 persuade 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.

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

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

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

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

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

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

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

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

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

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

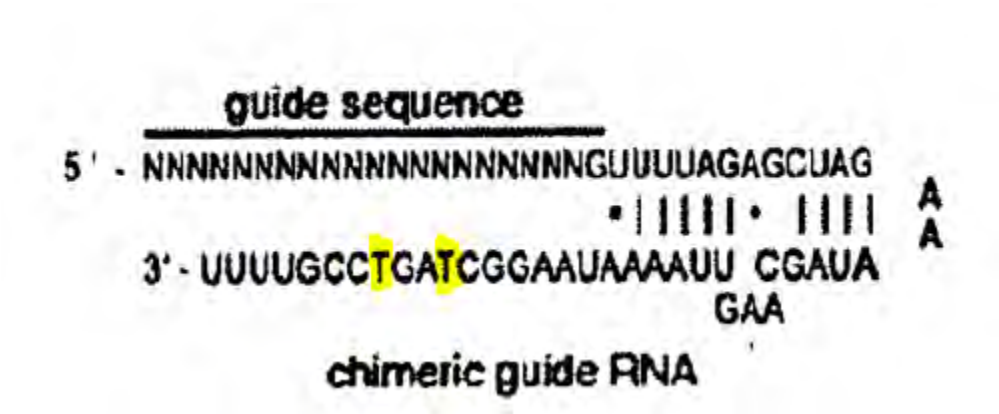

Figure 2A depicts a nucleic acid structure referred to as a "chimeric guide RNA." As highlighted by CVC, the chimeric RNA is depicted with two "T" residues. According to CVC,

> [a]lthough Broad's Motion relies on expression of the chimeric guide RNA *inside* a cell by an RNA polymerase, Broad has not shown how an RNA polymerase within a cell can incorporate "T" residues into an RNA strand, much less only at two *specific positions* in an RNA strand. Unlike DNA polymerases, RNA polymerases do not incorporate "T" residues. And neither Zhang B1 nor Broad's Motion offers any explanation as to how, as of December 12, 2012, a POSA could have used an RNA polymerase, which incorporates "U" rather than "T" residues, to make and use the chimeric guide RNA of Embodiment E17 in a cell without undue experimentation. Thus, Broad's Motion fails to show that Embodiment E17 in Zhang B1 is enabled as of December 12, 2012.

(CVC Opp. 4, Paper 576, 1:18–2:5.)

As CVC's witness, Dr. Peterson, explains, naturally occurring DNA includes four bases, abbreviated as G, C, A, and T. (Third Peterson Decl., Ex. 4193, ¶ 197. In contrast, RNA includes three of these bases and one different base, also

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

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

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

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

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

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

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

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

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

Similarly, Broad relies on the cross-examination testimony of Dr. Peterson as evidence of how the T bases were interpreted by those in the art at the time. (*See* Broad Reply 4, Paper 821, 10:13–11:8.) Broad points to Figure 2B of Cong 2013 (Ex. 3201), which depicts "pre-crRNA + tracrRNA processing" involving a nucleic acid with a T base. (*See* Cong 2013, Ex. 3201, 821, Fig. 2B.) Broad 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.)

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

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

Given the testimony of two of CVC's witnesses and the apparent understanding of others ordinarily skilled in the art[32], as discussed above, we agree

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[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.

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

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

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

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

VII. CVC Motion 1 – Benefit

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Mirkin cites to Karpala[33] (Ex. 3282), which relates to the effects of degradation by eukaryotic proteins on RNA silencing, a technique for knockdown or silencing of specific gene activity. (*See* Mirkin Decl., Ex. 3417, ¶ 130.) Table 1 of Karpala includes proteins that cause RNA degradation as typical eukaryotic proteins that interact with double-stranded RNA. (*See* Karpala 2005, Ex. 3282, 214, Table 1.) Dr. Mirkin testifies that such anti-viral responses to double-stranded RNA in eukaryotic cells would have been understood by those in the art at the time P1 was filed to present barriers to the stability of CRISPR RNA components. (*See* Mirkin Decl., Ex. 3417, ¶ 130.)

According to CVC, because Dr. Mirkin does not know whether degradation is actually a problem with CRISPR-Cas systems in eukaryotic cells, his testimony in support of Broad's argument is merely speculation. (*See* CVC Reply 1, Paper 812, 12:24–13:1, 13:10–12, citing Mirkin Depo., Ex. 4232, 64:24-65:5.) As explained above, we are not persuaded that questions about the ultimate requirements for CRISPR-Cas function in eukaryotes are relevant to the issue of written description because whether a disclosure indicates possession is viewed from what one of ordinary skill in the art would have considered at the time of filing. CVC does not present evidence to contradict Dr. Mikin's testimony about the concerns one would have had, given the lack of discussion of RNA degradation 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).

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

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

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

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

references to show that Group II introns are very inefficient, even unusable in eukaryotes. (*See* Mirkin Decl., Ex. 3417, ¶ 152.) For example, in 2008, Mastroianni[34] (Ex. 4068) states that after injecting fish cells with the components of Group II introns and supplying additional Mg^{+2} ions, "efficient group II intron-based gene targeting reactions have not been demonstrated in eukaryotes." (*See* Mastroianni, Ex. 4068, abstract.) Dr. Mirkin testifies that the technical issues encountered with Group II introns, particularly the need for very high levels of Mg^{2+} ions, would have indicated to one of ordinary skill in the art that CRISPR-Cas systems would not work in eukaryotic cells without a description of specific conditions for adaptation. (*See* Mirkin Decl., Ex. 3417, ¶ 154.)

CVC disputes Dr. Mirkin's testimony about Mastroianni, arguing that it says nothing about deleterious effects of Mg^{2+} ion levels on eukaryotic cells. (*See* CVC Reply 1, Paper 812, 15:6–12.) CVC argues that in contrast, Mastroianni discloses that any reduced efficiency related to Mg^{2+} ions "can be overcome by injecting additional Mg^{2+} or Mg^{2+} in combination with polyamines" (Mastroianni, Ex. 4068, 9), which CVC interprets as simply optimization that one of ordinary skill in the art would have considered in 2012. (*See id.*) In general, CVC argues:

> Contrary to Broad's assertions, no legal authority requires CVC to describe and rule out all theoretical "unique conditions" that are *unnecessary* for practicing the invention. Notably, Broad has not identified *any* "adaptations," "unique conditions," or "specific 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).

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

(CVC Reply 1, Paper 812, 12:16–22.)

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

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

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

Dr. Mirkin testifies further to the problems encountered with T7 polymerase would have indicated to those of ordinary skill in the art that unique circumstances and specific instructions would likely have been needed to show possession of a eukaryotic cell with a CRISPR-Cas system capable of cleaving or editing a target DNA or of modulating transcription, as required in Count 1. (*See* Mirkin Decl., Ex. 3417, ¶¶ 158–161.) Dr. Mirkin explains that T7 polymerase is a prokaryotic protein that transcribes any DNA linked to a T7 promoter, but not when the DNA is present in the chromatin of higher eukaryotes because "of intrinsic differences in chromatin structure between differently evolved eukaryotes or of an integration site that is exceptionally permissive for T7 transcription due to a local accessible chromatin conformation." (Wirtz[35], Ex. 3284, 4626; *see* Mirkin Decl., Ex. 3417, ¶ 160.)

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

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[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).

in P1 were sufficient to demonstrate possession of an embodiment of Count 1. (*See* Mirkin Decl., Ex. 3417, ¶¶ 162–165.) Dr. Mirkin cites to Koseki[36] (Ex. 3294) for its teachings of the problems RNA enzymes, such as ribozymes, can encounter *in vivo*, including colocalization with a target, inhibition of binding to the target by cellular factors (polysomes), and degradation before reaching the target. (*See* Mirkin Decl., Ex. 3417, ¶ 163, citing Koseki, Ex. 3294, 1875–76.) Koseki concludes that "For this reason, colocalization of a ribozyme and its target does not, by itself, guarantee the efficacy of ribozymes in vivo." (Koseki, Ex. 3294, 1876.) Similarly, Link[37] (Ex. 3295) reports that *in vitro* experiments do not predict *in vivo* activity of riboswitches – RNAs that are engineered to control gene activity. (*See* Link, Ex. 3295, 1190 ("Unfortunately, a number of factors intervene to prevent many engineered RNA switches from becoming useful genetic switches. For example, the functions of most aptamers have not been validated in cells, the folding of RNA constructs might differ between test tube and cell, or the ribozyme chosen for RNA switch construction might not be appropriate for controlling gene expression."); *see* Mirkin Decl., Ex. 3417, ¶ 165.)

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

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[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).

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

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

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

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

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

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

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

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

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

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

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

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

Broad argues further that one of ordinary skill in the art would have expected the P1 applicants to address the role of chromatin when adapting the prokaryotic CRISPR-Cas9 system to eukaryotic cells because at the time it was uncertain if Cas9 could access chromatinized DNA. (*See* Broad Opp. 1, Paper 596, 37:16–22.) Dr. Mirkin supports Broad's argument, testifying that is was not predictable whether Cas9 could access chromatinized DNA and citing to discussions in publications about the difficulties researchers encountered when using T7polymerase and the bacteriophage protein, cre, on chromatinized DNA. (*See* Mirkin Decl., Ex. 3417, ¶ 141, citing Ex. 3284, 3285.)

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

time would not have considered chromatin to be a barrier. (*See* CVC Reply 1, Paper 812, 13:1–16, citing Peterson Decl., Ex. 4036, ¶ 189.) Dr. Peterson supports CVC's argument, citing to publications that report success with other prokaryotic proteins and systems, including TALENS, RecA recombinase, Cre recombinase, ϕC31 integrase, Group II introns, restriction nucleases, and chimeric prokaryotic/eukaryotic ZFN nucleases cleave or modify targeted DNA with chromatin structure in a eukaryotic cells. (*See* Peterson Decl., Ex. 4036, ¶ 189, citing Exs. 4039, 4054, 4056, 4057, 4059, 4163, 4119, 4068, 4130, 4134, 4132, 4136, 4109, 4135, 4131, 4133.) Dr. Peterson explains chromatin structures were known to be dynamic and variable, having both open and closed conformations, and it was also known that prokaryotic genomes possess chromatin in the genome, even without a nucleus. (*See* Peterson Decl., Ex. 4036, ¶ 189, citing Exs. 4165, 4168, 4166, 4167.)

Dr. Mirkin and Dr. Peterson present conflicting testimony about how chromatin structure was perceived by those of ordinary skill in the art when designing prokaryotic systems for use in eukaryotic cells. For example, Both Dr. Mirkin and Dr. Peterson cite Sauer[38], published in 1988 (Ex. 3285/4109), which reports site-specific DNA recombination by the bacteriophage Cre recombinase on an artificial circular plasmid introduced into mammalian cells. Sauer demonstrates recombination of a non-chromosome target in a mammalian cell, but asks:

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[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)

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

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

Similarly, Dr. Mirkin cites Wirtz[39] (Ex. 3284), which reports that a bacteriophage polymerase that naturally transcribes DNA into RNA in prokaryotes, T7 RNA polymerase, is unable to fully transcribe higher eukaryotic chromatin because "of intrinsic differences in chromatin structure between 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).

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

In contrast, Dr. Peterson cites to publications regarding prokaryotic restriction enzyme activity in eukaryotic cells. (*See* Peterson Decl., 4036, ¶ 189, citing Carney[40], Ex. 4130, and Morgan[41], Ex. 4133.) CVC also cites Mastroianni (Ex. 4068), which was discussed above in regard to specific Mg^{2+} conditions needed to use a prokaryotic system in eukaryotic cells, but also states that "interference from chromatin with group II intron gene targeting is expected to be mitigated in systems undergoing active transcription or DNA replication." (Mastroianni, Ex. 4068, 11; *see* CVC Reply 1, Paper 812, 13:7–10.)

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

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[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).

Nevertheless, Dr. Mirkin presents evidence of the specific concerns those of ordinary skill would have had about a CRISPR-Cas9 system in a eukaryotic cell at the relevant time by citing statements made by Dr. Dana Carroll, whose technical opinions CVC put forth in the prior '048 interference. (*See* Mirkin Decl., Ex. 3417, ¶ 141, citing Carroll[42], Ex. 3286, 1660; *see* Broad Opp. 1, Paper 596, 37:19–20.) In a September 2012 review of the CVC inventors' results showing DNA cleavage *in vitro* with a CRISPR-Cas9 system, Dr. Carroll stated:

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

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

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

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

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

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

(Jinek 2013[43], Ex. 4137, 1–2.) Similarly, CVC inventor Doudna was credited as saying:

> Our 2012 paper [showing that the Cas9 endonuclease family can be programmed with single RNA molecules to cleave specific DNA 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).

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

(Catalyst[44], Ex. 3287, 3.) Thus, even the CVC inventors, who could be considered to have had more skill than the ordinary artisans, were not sure if the eukaryotic chromatin would allow for a functional CRSIPR-Cas9 system in a eukaryotic cell. The CVC inventors' comments tend to indicate that they did not have possession of a functional CRISPR-Cas9 system in eukaryotic cells until such experiments had been done. "A 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor Ortho Biotech, Inc. v. Abbott Labs.,* 636 F.3d 1341, 1348 (Fed. Cir. 2011).

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

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

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

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

Similarly, we are not persuaded that we require CVC to "describe and rule out all theoretical 'unique conditions' that are *unnecessary* for practicing the

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

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

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

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

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

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

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

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

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

VIII. CVC Miscellaneous Motion 2 to Exclude Evidence

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

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

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

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

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

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

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

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

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

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

IX. Conclusion

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

Broad Motion 1 – denied,

Broad Motion 2 – denied,

Broad Motion 3 – denied,

Broad Motion 4 – granted,

CVC Motion 1 – granted in part,

CVC Motion 2 – dismissed, and

CVC Miscellaneous Motion 2 – granted in part.

As result of the parties' motions to be accorded the benefit of earlier filing dates, CVC remains the junior party, having been accorded benefit of the filing date of 28 January 2013 when its provisional application 61/757,640 was filed. Broad remains the senior party, having been accorded benefit of the filing date of 12 December 2012, when its provisional application 61/736,527 was filed.

In its priority statement[45], CVC asserts that it earliest conception and 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*

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

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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

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Interference 106,115

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

APPENDIX B

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Filed: February 28, 2022

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 Priority
37 C.F.R. § 41.125(a)

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

KATZ, *Administrative Patent Judge.*

Summary

In this interference we determine that The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College ("Broad") have priority over The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier ("CVC") with respect to Count 1 – a single RNA CRISPR-Cas9 system that functions in eukaryotic cells. CVC fails to provide sufficient, persuasive evidence of an earlier reduction to practice or conception, as they are legally defined, of each and every element of Count 1 before Broad's evidence of reduction to practice. Thus, we determine that CVC's currently involved claims are unpatentable under 35 U.S.C. § 102(g).[1] Furthermore, we are unpersuaded by CVC's arguments that Broad's involved claims are unpatentable under 35 U.S.C. § 102(f) for failure to name the correct inventors and we exercise our discretion in declining to take up CVC's arguments regarding inequitable conduct. We enter judgment against CVC, finally refusing CVC's claims involved in this proceeding.

I. Introduction

The same parties were before us previously in Interference 106,048. CVC was involved in that interference based on claims to a CRISPR-Cas9 system that cleaves DNA without restriction to the environment (*e.g.,* encompassing *in vitro* environments outside of a cell and prokaryotic cell environments), whereas Broad

[1] 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).

was involved based on claims that were limited to the system in a eukaryotic environment. (*See* Interference 106,048, Senior Party Clean Copy of Claims, Paper 12, Replacement Broad Clean Copy of Claims, Paper 17, and Decision on Motions, Paper 893, 2:4–7.) That interference was terminated without a determination of unpatentability or judgment against either party because it was held, on motion by Broad, that the parties' involved claims did not interfere. (*See* Interference 106,048, Decision on Motion, Paper 893.) Specifically, it was held that CVC's claims to a CRISPR-Cas9 system without restriction to environment do not anticipate or render obvious Broad's claims limited to a eukaryotic environment. (*See id.*)

Subsequent to an affirmance of that decision by the Federal Circuit,[2] at least some of CVC's involved applications were issued as patents with claims to a method of cleaving DNA with a CRISPR-Cas9 system having a single RNA component, without restriction to the environment. (*See, e.g.,* U.S. Patent 10,266,850; *see* CVC Opp. 5, Paper 2567, 37:4–6.) There is no dispute in this proceeding over the patentability of those claims or that the CVC inventors were the first to invent a CRISPR-Cas9 system with a single guide RNA to cleave DNA in a generic environment.

CVC now presents claims to a CRISPR-Cas9 system having a single RNA component in a eukaryotic cell environment. (*See* Junior Party's Clean Copy of Claims, Paper 7.) These claims were determined to interfere with the same Broad

[2] *See Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286 (Fed. Cir. 2018).

claims involved in Interference 106,048 upon declaration of the current proceeding. (*See* Declaration, Paper 1.) Thus, the priority dispute before us now is which party's inventors were the first to invent a CRISPR-Cas9 system with a single guide RNA able to cleave or edit DNA to affect gene expression in a eukaryotic cell. (*See id.* at 12–13, Count 1.) Our focus is the determination of priority of invention of the subject matter of Count 1 under 35 U.S.C. § 102(g). *See* 35 U.S.C. § 135(a) ("The Board of Patent Appeals and Interferences shall determine questions of priority of the inventions . . . .").

A.

Following the preliminary motions phase of this proceeding, CVC as junior party was accorded benefit of the filing date 28 January 2013 of its provisional application 61/757,640. (*See* Redeclaration, Paper 878.) Broad was accorded benefit of the filing of date 12 December 2012 of its provisional application 61/736,527. (*See id.*) Both parties have filed motions arguing for dates of conception and reduction to practice earlier than their accorded benefit dates. CVC filed Substantive Motion 2 (Paper 1579), which was followed by Broad's opposition (Paper 2569) and CVC's reply (Paper 2744). Broad filed Substantive Motion 5 (Paper 2118), which was followed by CVC's opposition (Paper 2567) and Broad's reply (Paper 2745).

CVC was also authorized to file a motion arguing that Broad's involved patent and application claims are unpatentable for failure to name the correct inventors. CVC filed Substantive Motion 3 (Paper 1558), which was followed by Broad's opposition (Paper 2475) and CVC's reply (Paper 2743).

We take up motions in the order that secures the just, speedy, and inexpensive resolution of the proceeding. *See* 37 C.F.R. § 41.125(a). The parties presented oral arguments on 4 February 2022. (*See* Transcript, Paper 2862.)

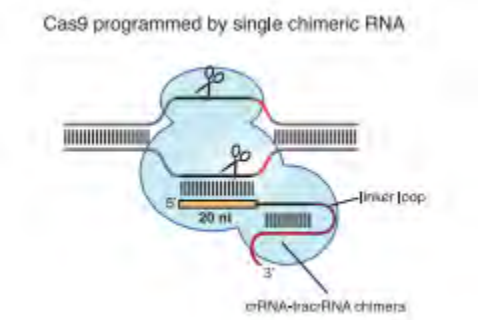
B.

Count 1 is a "McKelvey count,[3]" which includes a claim of an involved Broad application and a claim of an involved CVC application directed to a CRISPR-Cas9 system having a single RNA component, which along with the protein Cas9, can cleave a DNA molecule to alter gene expression or modulate transcription of a targeted gene in a eukaryotic environment. (*See* Declaration, Paper 1, 12–13.)

Briefly, a CRISPR-Cas9 system uses two RNAs and a protein to target a DNA molecule and cleave it at a specific sequence. Count 1 is limited to a system in which the two RNAs are fused into a single RNA molecule, sometimes referred to as a "single guide RNA," "sgRNA," or "chimeric RNA." In Broad's terminology the single guide or chimeric fused RNA comprises a "guide sequence" fused to a "tracr sequence" and in CVC's terminology it comprises a "targeter-RNA" (also called a "crRNA") fused to an "activator-RNA" (also called a "tracrRNA"). Under both parties' terminology, the fused RNA hybridizes to the

[3] *See Melrose v. Graham Packaging Co.,* Interference No. 106,050, 2017 WL 4280697, at *12 (P.T.A.B. Sept. 22, 2017) ("The count is a so-called McKelvey count, now familiar in interferences. Notwithstanding the disjunctive combination of claims, the count represents a single patentable invention.") The use of such a count in interference proceedings was pioneered by the Honorable Frederick E. McKelvey, of the Board.

targeted DNA to achieve specific cutting of the targeted DNA. Jinek 2012[4] (Ex. 3202) provides a schematic figure of the system, which is reproduced below.



(Jinek 2012, Ex. 3202, 820, Fig. 5A.)

Count 1 recites Broad patent 8,697,359, claim 18 or CVC application 15/981,807, claim 156. (*See* Declaration, Paper 1, 12.) Broad patent 8,697,359, claim 18 recites:

> The CRISPR-Cas system of claim 15, wherein the guide RNAs comprise a guide sequence fused to a tracr sequence.

(*Id.* at 12.) Broad patent 8,697,359, claim 15 recites:

> An engineered, programmable, non-naturally occurring Type II CRISPR-Cas system comprising a 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 molecules, 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.

[4] Jinek et al., "A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity," SCIENCE, 337: 816–21 (2012).

(*Id.* at 13.) CVC application 15/981,807, claim 156 recites:

> A eukaryotic cell comprising a target DNA molecule and an engineered and/or non-naturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-—CRISPR associated (Cas) (CRISPR-Cas) system comprising
>
> a) a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein; and
>
> b) a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises:
>
> i) a targeter-RNA that is capable of hybridizing with a target sequence in the target DNA molecule, and
>
> ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,
>
> wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides; and
>
> wherein the single molecule DNA-targeting RNA is capable of forming a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule.

(*Id*.) Both the CVC and Broad portions of Count 1 recite either a "eukaryotic cell comprising" a CRISPR-Cas9 system (claim 156 of CVC application 15/981,807) or a CRISPR-Cas9 system "in a eukaryotic cell" (claim 18 of Broad patent 8,697,359). Both portions also recite the ability of the CRSIPR-Cas9 system to cleave or edit DNA in the eukaryotic cell to alter gene expression. The Broad portion of Count 1 recites "wherein . . . the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered" and the

CVC portion of Count 1 recites "whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule." A complete invention includes these elements of Count 1.

C.

"[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice." *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). When evaluating the testimony of an inventor, we look to corroborative, independent evidence to avoid to safeguard against inventors who might otherwise "be tempted to remember facts favorable to their case." *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341, 1346 (Fed. Cir. 2017).

As senior party, the Broad inventors are presumed to have invented the subject matter of the count before junior party CVC. (*See* 37 C.F.R. § 41.207(a).) Each party, though, bears the burden of providing a showing, supported by appropriate evidence, of the motions it asserts. (*See* 37 C.F.R. § 41.208(b) and § 41.121(b).) We evaluate the parties' arguments and evidence of dates of conception and reduction to practice to determine whether the preponderance of the evidence supports the presumptions of junior and senior party. (*See* 37 C.F.R. § 41.2017(a)(2).)

II. CVC Motion 2 - Priority

CVC asserts an earliest date of actual reduction to practice date (9 August 2012) and conception date (1 March 2012) before Broad's accorded benefit date (12 December 2012). (*See* CVC Motion 2, Paper 1579; *see* Redeclaration, Paper 878.) We look to the evidence presented by the parties of the activities and ideas of CVC's named inventors, Jennifer Doudna, Ph.D., Martin Jinek, Ph.D., Emmanuelle Charpentier, Ph.D., and Krzysztof Chylinski, Ph.D., to determine if the preponderance of evidence supports these dates.

A.

An actual reduction to practice requires proving that the inventors constructed an embodiment of the count, meeting all its limitations, and that they determined the invention would work for its intended purpose. *Cooper*, 154 F.3d at 1327, citing *UMC Elecs. Co. v. United States*, 816 F.2d 647, 652 (Fed.Cir.1987). "[W]hen testing is necessary to establish utility, there must be recognition and appreciation that the tests were successful for reduction to practice to occur." *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 594–95 (Fed.Cir.1997). Because testing is necessary to know whether a CRISPR-Cas9 system cleaves or edits DNA, we look to whether the evidence CVC presents shows that the inventors recognized and appreciated the results of the 9 August 2012 experiment as an embodiment meeting all the limitations of Count 1.

CVC first argues that an embodiment of Count 1 was actually reduced to practice by 9 August 2012 in an experiment in zebrafish embryos performed by Florian Raible, Ph.D., who reportedly was the research group leader at the Center of Molecular Biology at the University of Vienna in 2012. (*See* CVC Motion 2,

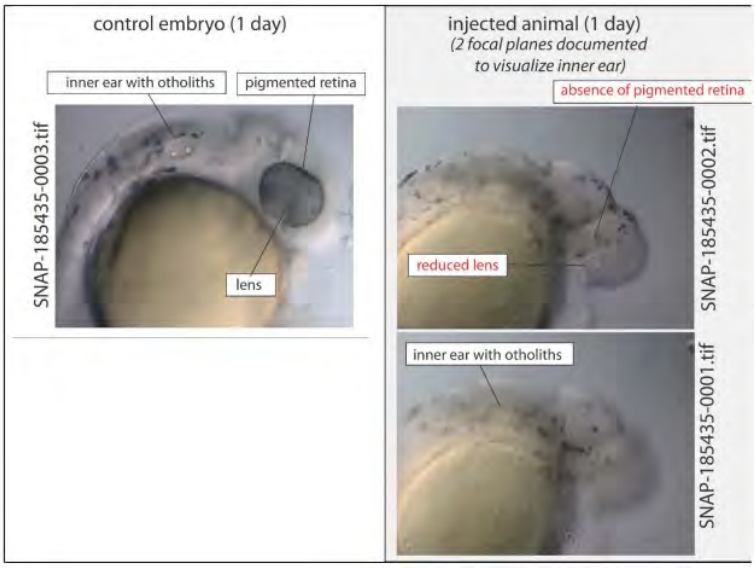
Paper 1579, 22:1–27:15; *see* Raible Decl., Ex. 4294, ¶ 2.) Dr. Raible testifies that he had significant first-hand experience with other gene editing systems such as zinc-finger nuclease (ZFN) technology and transcription activator-like effector nucleases (TALE nucleases or TALENs), including microinjecting them into fertilized eggs of the zebrafish. (Raible Decl., Ex. 4294, ¶ 7.)

Dr. Raible testifies that on 28 June 2012, he sent an e-mail to Dr. Charpentier to show his interest in using the sgRNA CRISPR system in a fish model. (*See* Raible Decl., Ex. 4294, ¶ 14, citing Exs. 4799, 4801, 4802.) Exhibit 4799 is a copy of an e-mail dated 28 June 2012, reflecting Dr. Raible's testimony that he agreed to experiments in an *in vivo* context. (*See* Ex. 4799.) CVC presents the testimony of Dr. Charpentier and a corroborating copy of an email dated 29 June 2012, as evidence that Dr. Doudna approved these experiments. (*See* CVC Motion 2, Paper 1579, 22:5–6, citing Charpentier Decl., Ex. 4351, ¶ 62, Ex. 4804.)

CVC presents evidence of the plans Dr. Chylinski and Dr. Raible made to design CRISPR systems, including the required "NGG" sequence adjacent to the target DNA sequence (called the "PAM sequence"), for targeting the *rx3* gene (also called *chokh/chk*), which regulates eye formation. (*See* CVC Motion 2, Paper 1579, 22:7–23, citing Ex. 4810, Ex. 4294, ¶¶ 21–27.) Mutation of the *rx3/chokh/chk* gene is reported to result in a specific, diagnostic eyeless phenotype, which could be distinguished from generalized developmental problems due to causes other than the disruption of a specific gene. (*See* Raible Decl., Ex. 4294, ¶¶ 22–26.)

CVC argues that in July 2012, Dr. Chylinski and Dr. Raible did preliminary studies and that by 19 July 2012, Dr. Raible performed a first test of a CRISPR-Cas9 system in zebrafish. (*See* CVC Motion 2, Paper 1579, 22:19–25, citing Raible Decl., Ex. 4294, ¶¶ 33–49.) Dr. Raible testifies that he did not detect the expected phenotype from this first test, but instead found some non-specific developmental effects, such as the lack of a head. (*See* Raible Decl., Ex. 4249, ¶ 49, citing Ex. 4337.)

CVC cites further to Dr. Raible's and Dr. Chylinski's testimony about experiments using the fish model with a new *rx3* target sequence. (*See* CVC Motion 2, Paper 1579, 22:25–23:7, citing Raible Decl., Ex. 4294, ¶¶ 52–53, Chylinski Decl., Ex. 4348, ¶¶ 123–124.) On 8 August, 2012, Dr. Raible reportedly performed a second zebrafish experiment and on 9 August 2012 he reportedly identified at least one fish allegedly with the targeted mutation. (*See* CVC Motion 2, Paper 1579, 23:8–16.) In his supporting testimony, Dr. Raible's indicates that one of the 30 embryos he injected with one concentration of the test solution showed the characteristic eyeless morphological phenotype expected for the homozygous *rx3*/*chokh*/*chk* mutant fish. (*See* Raible Decl., Ex. 4294, ¶¶ 54–55.) Dr. Raible testifies that he documented the mutant embryo and the wild type embryo, citing to several different exhibits. (*See* Raible Decl., Ex. 4294, ¶ 55, citing Exs. 4913–4915.) Dr. Raible provides a compilation of several images from these exhibits, which is reproduced below.



(Raible Decl., Ex. 4294, ¶ 55, citing Exs. 4913–4915.)

In his declaration, Dr. Raible summarizes that he

> prepared [the animal with the homozygous *rx3/chokh/chk* phenotype] on August 8, 2012, on behalf of the CVC inventors by injecting into the animal a preformed complex of the Cas9 protein and two single-guide RNAs that included crRNA and tracrRNA sequences where the crRNA sequence targeted the *rx3/chokh/chk* locus. This fish indicated to me that there was successful site-specific DNA cleavage in a zygote injected with the inventors' CRISPR-Cas9 system. The inventor's CRISPR-Cas9 system thus worked as predicted in zebrafish using previously known methods for delivery and analysis.

(Raible Decl., Ex. 4294, ¶ 56.) Dr. Raible testifies that within a few days of obtaining the results he informed Dr. Chylinski. (*See* Raible Decl., Ex. 4249, ¶¶ 57–58.) CVC does not direct us to contemporaneous evidence showing that Dr. Raible considered the results of the 9 August 2012 experiment to have been successful. Although Dr. Raible is not an inventor and, therefore, his testimony does not necessarily need to be corroborated, contemporaneous evidence carries

more weight in supporting his understanding at the time of the experiment, particularly where CVC argues that his understandings inure to the inventors' benefit. (*See* CVC Motion 2, Paper 1579, 26:16–24.)

Dr. Chylinski testifies that he learned of Dr. Raible's results on 9 August 2012 and e-mailed Dr. Charpentier about them. (*See* Chylinski Decl., Ex. 4348, ¶ 127, citing Ex. 4911.) Dr. Charpentier testifies that on a phone call Dr. Chylinski conveyed to her, "consistent with his email," that Dr. Raible had reported positive results of an eyeless phenotype in zebrafish, reflecting successful gene modification using the sgRNA CRISPR-Cas9 system. (Charpentier Decl., Ex. 4351, ¶ 70, citing Exs. 4911, 4912.) Exhibit 4911 is a copy of an e-mail from Dr. Chylinski to Dr. Charpentier, dated 9 August 2012. In the e-mail Dr. Chylinski states:

> Potentially good news about fish. We tested the NLS-tagged Cas9 that we just got from Martin as the normal protein was not giving anything conclusive. It looks like GFP expression in medaka is much lower in the embryo although there are still problems with toxicity and so on, so it will require some more optimization form their site. Anyway, there is a hint it might work but we shouldn't be overexcited now.

(Ex. 4911.) In a reply e-mail, Dr. Charpentier responded "ok. i give you a call now then." (Ex. 4912.)

Broad argues that Dr. Chylinski's e-mail of 9 August 2012 does not indicate he appreciated or recognized that the results of Dr. Raible's zebrafish experiment were successful. (*See* Broad Opp. 2, Paper 2569, 48:15–49:13.) First, Broad argues that the e-mail refers to experiments in "medaka," a type of fish distinct from the zebrafish embryos Exhibits 4913–4915. (*See* Raible Decl., Ex. 4294,

¶¶ 52–55.) Furthermore, Broad argues that Dr. Chylinski never characterized the fish experiments he discusses as being a success. Instead, he refers to a "hint" and cautions about being "overexcited now." (Exs. 4911, 4912.)

We agree with Broad that Dr. Chylinski's 9 August 2012 e-mail to Dr. Charpentier does not characterize any fish experiment as successful and that it is not clear to which results Dr. Chylinski refers because he mentions medaka, not zebrafish. We agree with Broad that by itself, neither Dr. Chylinski's e-mail of 9 August, nor Dr. Charpentier's response demonstrates that either recognized and appreciated Dr. Raible's 9 August 2012 experiment was an actual reduction to practice of an embodiment of Count 1. The e-mail of Exhibit 4911 also fails to adequately support Dr. Raible's declaration testimony that he considered the experiment of 9 August 2012 to be successful at the time.

CVC cites further to Exhibit 5139 as evidence supporting Dr. Charpentier's and Dr. Chylinski's appreciation that the fish embodiment worked for its intended purposes and met all the limitations of Count 1. (*See* CVC Motion 2, Paper 1579, 23:17–21.) Exhibit 5139 is a copy of an e-mail dated 29 August 2012, from Dr. Charpentier to recipients including Dr. Chylinski, asking for a slide presentation summarizing strategies for *in vivo* targeting in bacteria and fish that had been done so far. (*See* Ex. 5139.) We agree with Broad that Exhibit 5139 only requests information and does not provide any indication of the results of these experiments or the inventors' understanding of them. (*See* Broad Opp. 2, Paper 2569, 49:14–20.)

Dr. Chylinski testifies that on 31 August 2012 he prepared a slide for Dr. Charpentier that included a summary of the strategies for *in vivo* targeting in

fish at the time. (*See* Chylinski Decl., Ex. 4348, ¶ 129, citing Ex. 4916; *see* CVC Motion 2, Paper 1579, 23:18–23.) Dr. Chylinski testifies:

> We believed that these effects were the result of our sgRNA CRISPR-Cas9 system's activity in the fish, though we had not confirmed an effect on the targeted regions by sequencing. Ex. 4916. While my fish experiment result summary noted that the effects of possible incomplete GFP loss in the medaka might be the result of "heterozygotes" or "unspecific" effects, the zebrafish eyeless phenotype indicated that we had successfully used our sgRNA CRISPR-Cas9 system to target and cleave target DNA within the zebrafish. Ex. 4916. The reference to repeating experiments indicated that a journal publication would require multiple experiments and a second molecular detection assay.

(Chylinski Decl., Ex. 4348, ¶ 129.) Exhibit 4916 is a copy of an e-mail dated 31 August 2012, from Dr. Chylinski to Dr. Charpentier, with an attached slide presentation. Page 10 of Exhibit 4916 is reproduced below.

Fish experiment results

- Pretty high toxicity observed (death or misdevelopment)
- Small amount of putative mutants (1 in 30-50) seen in some of the experiments
- „Less green" embryos for Medaka, no eyes or misdeveloped eyes for Zebrafish – might be heterozygotes, might be unspecific
- Mutants tested for the mutations in the gene by PCR amplification of the targeted regions (repair of dsDNA breaks is usually connected with trimming of the DNA) – no effect visible
- Experiments are still being repeated

This slide states that "a small amount of putative mutants" were seen in some experiments, states that the "no eyes or misdeveloped eyes for Zebrafish," which

"might be heterozygotes, might be unspecific," and indicates that there is no visible effect of testing for mutations by PCR. (*See* Ex. 4916, 10.)

We are not persuaded that Exhibit 4916 supports Dr. Chylinski's testimony that he recognized the zebrafish eyeless phenotype "indicated that we had successfully used our sgRNA CRISPR-Cas9 system to target and cleave target DNA within the zebrafish." (Chylinski Decl., Ex. 4348, ¶ 129.) CVC argues that Exhibit 4916 shows that Dr. Chylinski summarized the positive results as indicating "'putative mutants' including 'no eyes or misdeveloped eyes for zebrafish,'" but fails to mention that Dr. Chylinski included the possibility that these mutants were "unspecific." Exhibit 4916 does not indicate that Dr. Chylinski favored the explanation of heterozygosity over unspecific effects or that he was convinced the phenotype was due to specific editing of the *rx3* gene by a CRISPR-Cas9 system. We agree with Broad and find that, contrary to CVC's argument, Exhibit 4916 does not indicate an acknowledgement of positive results by Dr. Chylinski. (Broad Opp. 2, Paper 2569, 43:2–14.) Exhibit 4916 does not indicate that Dr. Raible informed Dr. Chylinski of any experiments he believed were successful as of the end of August 2012.

CVC cites to Dr. Chylinksi's testimony on cross-examination that he recalled Dr. Raible "describing the phenotypes he observed." However CVC does not direct us to any part of Dr. Chylinski's deposition that indicates he considered Dr. Raible's results to show that the CRISPR-Cas9 system had cleaved DNA in a zebrafish embryo to cause an alteration of gene expression in a zebrafish embryo. (*See* CVC Reply 2, Paper 2744, 25:9–13, citing Chylinski Depo., Ex. 6202, 101:14–102:3.)

CVC also argues that by 9 August 2012 Drs. Chylinski and Charpentier appreciated that a fish cell embodiment of the count worked for its intended purpose. (*See* CVC Motion 2, Paper 1579, 23:15–16.) In its Reply Brief,[5] CVC argues that Dr. Charpentier stated she was "convinced" the CRISPR/Cas9 system would work in Dr. Raible's fish experiments. (*See* CVC Reply 2, Paper 2744, 13:14–18, 22:6–8.) In support, CVC cites to a statement in Dr. Charpentier's declaration citing Exhibit 4807. (*See* Charpentier Decl., Ex. 4351, ¶ 60.)

Dr. Charpentier reports that Exhibit 4807 is a copy of an e-mail that was reportedly never sent, but has a date of 28 June 2012 and appears to be from Dr. Charpentier to Dr. Raible, among other cc'ed recipients. (*See* Charpentier Decl., Ex. 4351, ¶ 60; *see* Ex. 4807.) The message is in response to Dr. Raible's offer to collaborate and his plan for experiments using a CRISPR/Cas9 system in fish, as well as a worm model, including a plan for experiments. (*See* Ex. 4807.) Dr. Raible refers to what might be expected "if the stunning efficiency of the CRISPR/Cas system you observed in vitro translates to the in vivo scenario . . . ." (*Id*.) Apparently in reply, Dr. Charpentier indicates she is glad that Dr. Raible is interested in doing fish experiments as a collaboration and then states: "Wit[h] regard to the system, we are indeed convinced." (*Id*.) Dr. Raible does not refer to any actual results. Nor does Dr. Charpentier.

[5] We note that CVC relied on Exhibit 4807 for the first time in it Reply Brief as support for an argument that Dr. Charpentier was "convinced" the system would work in fish cells, even though the exhibit was available when CVC Motion 2 was filed. (*See* Motion 2, Paper 1579, I-24.)

Neither Dr. Charpentier nor CVC provides an explanation why Dr. Charpentier's words in Exhibit 4807 indicate she was convinced of positive results for Dr. Raible's fish experiments. Instead, Dr. Charpentier and CVC merely quote the words "indeed convinced" without relating them back to Dr. Raible's message. Without further explanation of how Dr. Charpentier's comment relates to positive results using a CRISPR-Cas9 system in a fish cell, the e-mail fails to corroborate Dr. Charpentier's testimony or to support CVC's argument that Dr. Charpentier was "convinced" that the fish system would work. We note further that CVC does not direct us to comments by any of the CVC inventors that they were "convinced" or similarly persuaded that the CRISPR-Cas9 system had worked *after* Dr. Raible presented his results to Dr. Chylinski.

In general, we find that CVC over-emphasizes isolated words by its inventors to argue that they recognized and appreciated Dr. Raible's results. We are further persuaded that CVC over-interprets the inventors' recognition and appreciation of Dr. Raible's results because neither Dr. Doudna nor Dr. Jinek remembers learning of them at the time. (*See* Doudna Depo, Ex. 6204, 169:10–15; *see* Jinek Depo., Ex. 6207, 75:16–78:9; *see* Broad Opp. 2, Paper 2569, 47:17–48:5.) It is unlikely that Dr. Doudna or Dr. Jinek was told of results understood by Drs. Chylinski and Charpentier to be the first successful gene modification in a eukaryotic cell by a CRISPR-Cas9 system and forgot it. (*See* Doudna Depo., Ex. 6204, 269:16–22 (Q Okay. All right. Well, you would have been keenly interested in learning if there had been success since you were working as quickly as possible to try and show that CRISPR-Cas9 worked in eukaryotic cells for genome editing, right? A I would have been interested in all of the experiments we

had underway at the time.").) Instead, Dr. Doudna testified that getting the genome editing a CRISPR-Cas9 system to work in a fish cell would have been of broad interest and would be publication-worthy in a high-impact journal in 2012. (*See* Doudna Depo., Ex. 6204, 163:3–12.) Thus, if Dr. Doudna had been told that Dr. Raible's experiment in August 2012, or at any other time, was successful, she would have remembered it. We note, too, that no zebrafish experiments were included in CVC's provisional applications filed 19 October 2012 and 28 January 2013. (*See* Broad Opp. 2, Paper 2569, 50:5–8.) The lack of communication by Drs. Chylinski and Charpentier regarding Dr. Raible's 9 August 2012 zebrafish experiment and lack of reference to it later indicates to us that the CVC inventors did not consider it to be a success or a reduction to practice of Count 1 because Dr. Raible did not communicate any success to them.

Both parties present the opinion testimony of witnesses who have experience with zebrafish models. CVC presents the testimony of Cecilia Moens, Ph.D. (*see* CVC Motion 2, Paper 1579, 24:1–26:15, citing Moens Decl., Ex. 4343) and Broad presents the testimony of Phillippe Mourrain, Ph.D. (*see* Broad Opp. 2, Paper 2569, 45:1–46:22, citing Mourrain Decl., Ex. 3447). Neither party disputes the qualifications of the other's witness, but the witnesses provide divergent opinions on the results of Dr. Raible's 9 August 2012 experiment.

Dr. Moens testifies that the eyeless phenotype Dr. Raible obtained in the 9 August 2012 zebrafish experiment was consistent with cleavage of the *rx3* gene and demonstrated that the CRISPR-Cas9 system he injected into the embryos was capable of cleaving or editing a target DNA to modulate transcription of at least one gene encoded by the target DNA. (*See* Moens Decl., Ex. 4343, ¶¶ 45–58, 70–

72.) Dr. Moens testifies that visual verification of the phenotype is sufficient to prove, with a high level of confidence that the *rx3* gene was successfully targeted, even without molecular analysis, such as PCR, to verify cleavage. (Moens Decl., Ex. 4343, ¶ 49.)

Dr. Mourrain testifies that Dr. Raible and others in the field would have used genetic testing to confirm mutations of the *rx3* gene. (*See* Mourrain Decl., Ex. 3447, ¶¶ 23–60.) Dr. Mourrain testifies further that the phenotype shown in the images from Dr. Raible's 9 August 2012 experiment was not what would have been expected from targeted cleavage of the *rx3* gene because a combination of characteristics were not present. According to Dr. Mourrain, the pictures presented by Dr. Raible were taken earlier in development than when these characteristics would be assessed. (*See* Mourrain Decl., Ex. 3447, ¶¶ 94–102.) In general, Broad argues that Dr. Raible's 9 August 2012 zebrafish experiment was a failure. (*See* Broad Opp. 2, Paper 2569, 40:11–47:10.)

Although both witnesses appear to be qualified in light of their credentials and experience, we need not determine which witness is correct because "there is no conception or reduction to practice where there has been no recognition or appreciation of the existence of" new subject matter. *Silvestri v. Grant*, 496 F.2d 593, 597 (CCPA 1973). Expert testimony can shed light on what the inventors did, such as whether their results demonstrate every limitation of a count, but we look for an appreciation of the results *by the inventors* or their agents. Thus, even if, as Dr. Moens testifies, one zebrafish embryo demonstrated targeted mutation of the *rx3* gene by a CRISPR-Cas9 system, if her testimony does not indicate the CVC inventors or Dr. Raible recognized or appreciated this result, the one embryo

would not indicate a reduction to practice by the inventors. In *Heard v. Burton*, 333 F.2d 239, 1505 (CCPA 1964), the court held that there was no reduction to practice where Heard never recognized what he had made, even though years later, after Burton's filing date, his company tested it and determined it was a particular form of alumina recited in the count. *See also Invitrogen Corp. v. Clontech Lab'ys, Inc.*, 429 F.3d 1052, 1065 (Fed. Cir. 2005) ("it is not enough that a party adduce evidence that objective test results comport with an inventor's testimony concerning his state of mind. Rather, there must also be evidence that the junior party timely interpreted or evaluated the results, and understood them to show the existence [of] the invention."). Because neither party's witness can testify to what the CVC inventors or Dr. Raible were thinking at the time, we are not persuaded that either's testimony sheds light on whether the CVC inventors reduced an embodiment of Count 1 to practice by 9 August 2012.

In addition to not being persuaded that the CVC inventors recognized and appreciated the results of Dr. Raible's experiment, we are not persuaded by the contemporaneous evidence, specifically Dr. Raible's subsequent work, that Dr. Raible appreciated these results. (*See* Broad Opp. 2, Paper 2569, 44:14–23, 46:23–47:7.) According to his testimony, Dr. Raible attempted at least two other experiments using an sgRNA CRISPRCas9 system to target the *rx3* gene. (*See* Raible Decl., Ex. 4294, ¶¶ 70–73.) One experiment produced an eyeless embryo that also had non-specific development delay, which Dr. Raible characterized in his declaration as "more likely than not the product of successful DNA cleavage." (*See* Raible Decl., Ex. 4294, ¶ 72.) The other experiment "did not yield clearer results" than the previous experiment. (*See id.* at ¶ 73.)

But then, by 12 September 2012, Dr. Raible ended the project without any publication identified to us by CVC. He testifies:

> While I was happy to have helped the inventors validate their sgRNA CRSIRPCas9 system in zebrafish, I did not believe that merely showing successful cleavage in a eukaryote using only routine techniques, with no special parameters to introduce a nuclease into eukaryotic cells, would be a publication-worthy discovery. That was a trivial and expected result. I felt that to justify expending additional resources on these experiments, I needed results suggesting that the efficiency of CRISPR-Cas9 *in vivo* could compete with ZFNs and TALENs. I believed that other labs with more resources would likely generate such data before I would be able to, for instance by being able to perform massive parallel sequencing on targeted gene loci, bypassing the need to rely on the presence of length variants identified by PCR.

(*See id.* at ¶ 74.) This testimony contrasts sharply with Dr. Raible's views in June 2012, when he stated:

> Given the massive interest in simple methods for genome editing, we would expect that the establishment of a CRISPR/CAS-based genome editing system in any fish system would be of broad interest, and therefore a short article in a high-impact journal would not be unlikely as a result (provided the results match the expectations based on the in vivo data).

(Ex. 4799, 2.) It also contrasts with CVC's representation that there was a "race to publish on the implementation of CVC's sgRNA CRISPR-Cas9 system . . . ." (CVC Opp. 5, Paper 2567, 2:8–9.) Given the apparent importance of the experiments Dr. Raible was performing it is unclear why he abandoned them if he believed the CRISPR-Cas9 system designed by the CVC inventors was producing positive results in fish cells. It seems more likely that Dr. Raible's abandonment of

the project indicates that he did not recognize any success in 2012. (*See* Broad Opp. 2, Paper 2569, 47:1–7.)

CVC fails to direct us to persuasive evidence that any of the CVC inventors or Dr. Raible recognized or appreciated the results of the 9 August 2012 zebrafish experiment as demonstrating specific cleavage of a targeted DNA with an sgRNA CRISPR-Cas9 system to affect gene expression in a eukaryotic cell. Although Dr. Raible testified for this proceeding that one fish embryo indicated the CVC inventors' system had worked as predicted, no other evidence highlighted by CVC demonstrates he had this understanding in August 2012. (*See* Raible Decl., Ex. 4294, ¶ 56.) The evidence CVC presents shows that Drs. Chylinski and Charpentier were aware of Dr. Raible's results, but does not show that they considered the results to show success or that they relayed this information to either Dr. Doudna or Dr. Jinek. CVC does not direct us to evidence, beyond his testimony for this proceeding, that Dr. Raible communicated his understanding that the experiments were successful to any of the CVC inventors. Furthermore, Dr. Raible continued his allegedly successful experiment with only two other experiments and then abandoned the project, despite, in his words, the "massive interest" in field. (Ex. 4799; *see* Raible Decl., Ex. 4294, ¶¶ 70–74.)

Without persuasive evidence that either the inventors or Dr. Raible recognized the 9 August 2012 zebrafish experiment was successful, we are not persuaded that any inurement indicates an actual reduction to practice of an embodiment of Count 1. (*Contra* CVC Reply 2, Paper 2744, 16:2–4.) *See Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 593, 595 (Fed. Cir. 1997) (where there was not sufficient or persuasive evidence that the workers actually communicated

the results or had a basis to know whether the results were positive, their work did not inure to the benefit of the inventors or prove reduction to practice).

Accordingly, we are not persuaded that the CVC inventors or Dr. Raible actually reduced to practice an embodiment of Count 1 by 9 August 2012.

CVC asserts later dates of actual reduction to practice by 31 October 2012, 1 November 2012, 5 November 2012, and 18 November 2012. (*See* CVC Motion 2, Paper 1579, 27:16–35:9.) As discussed below, we are persuaded that the Broad inventors reduced to practice an embodiment of Count 1 by 5 October 2012 – a date prior to any of CVC's other asserted dates. Thus, we need not render a decision on CVC's later dates because even if we found the evidence supporting them to be persuasive, they would not change our overall analysis of priority. Instead, we look to whether CVC presents evidence to persuade us that it had a date of conception earlier than Broad. *See Cooper*, 154 F.3d at 1327 ("[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice.").

B.

CVC argues that its inventors had a complete conception of an embodiment of Count 1 by 1 March 2012. (*See* CVC Motion 2, Paper 1579, 4:13–20:23.) Conception requires a "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986); *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200,

1206 (Fed. Cir. 1991) ("Conception requires both the idea of the invention's structure and possession of an operative method of making it."). "An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." *Burroughs Wellcome Co. v. Barr Lab., Inc*., 40 F.3d 1223, 1228 (Fed. Cir. 1994).

The inventor need not know that the invention will work for conception to be complete because determining it works is part of reduction to practice. *See id.* Even when the invention is in an uncertain or experimental art, where the inventor cannot reasonably believe an idea will be operable until some result supports that conclusion, "[a]n inventor's belief that his invention will work or his reasons for choosing a particular approach are irrelevant to conception." *Id*. Thus, we do not base a determination of conception on facts regarding the state of the art or the inventor's beliefs of what will happen, but on the facts of how specific and settled the inventor's ideas were at the time asserted.

Under facts "where results at each step do not follow as anticipated, but are achieved empirically by what amounts to trial and error" there has not been a complete conception. *Alpert v. Slatin,* 305 F.2d 891, 894 (CCPA 1962). "Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Burroughs*, 40 F.3d at 1228. Similarly, a conception may not be complete "if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and

permanent reflection of the complete invention as it will be used in practice." *See id.* at 1229. "When a research plan requires extensive research before the inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred." *Hitzeman v. Rutter*, 243 F.3d 1345, 1357 (Fed. Cir. 2001).

In such cases it is the factual uncertainty about whether the idea was complete in the mind of the inventor, rather than a generalized uncertainty surrounding experimental sciences or a specific field of art, that undermines conception. *See id.* For example, under the facts of *Hitzeman* it was not the general state of the art, but statements made by the inventor during prosecution and subsequent publications that revealed he had not conceived of the complete subject matter of the count and considered it not to have been reasonably expected by one of ordinary skill in the art. *Id.* at 1357. The *Hitzeman* court found that claiming the result of a biological process with "no more than a hope, or wish," that the process would be performed, when it had never before been achieved, was insufficient to establish conception. *Id.* at 1356–57.

CVC begins by asserting that before 1 March 2012, its inventors had identified the necessary and sufficient components of a CRISPR-Cas9 cleavage complex that could cleave any chosen target DNA *in vitro*. (*See* CVC Motion 2, Paper 1579, 5:6–6:10.) CVC states that the inventors learned that the PAM sequence was necessary and learned that they could truncate the lengths of the crRNA and tracrRNA, while maintaining a functional *in vitro* CRISPR-Cas9 system. (*See id.* at 6:21–7:7.) According to CVC, the inventors understood before

1 March 2012 that they could program their system to target and cleave any target DNA molecule of choice. (*See id.* at 7:8–13.)

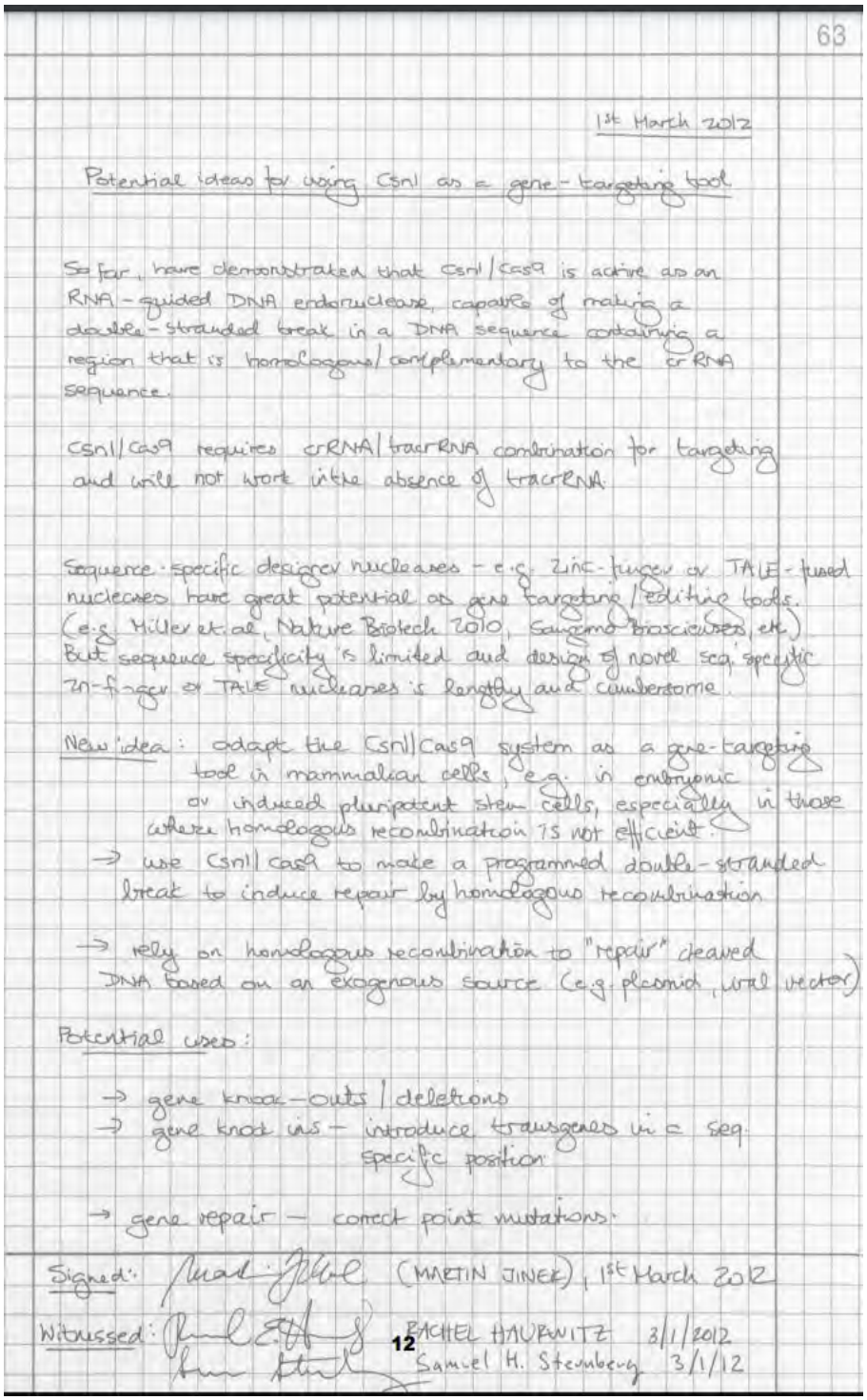
CVC continues with the argument that by 1 March 2012 the inventors had conceived of a CRISPR-Cas9 system in eukaryotic cells. (*See* CVC Motion 2, Paper 1579, 7:17–13:2.) CVC relies on the testimony of Dr. Doudna and Dr. Jinek that by 1 March 2012 they had discussed and developed a schematic diagram of a CRISPR-Cas9 system including a single guide RNA or "sgRNA," or "chimeric RNA" with the crRNA and tracrRNA present on a single RNA molecule. (*See* CVC Motion 2, Paper 1579, 7:18–23, citing Jinek Decl., Ex. 4349, ¶¶ 30–32; *see* Doudna Decl., Ex. 4350, ¶¶ 41–44.) This single RNA would form a complex with Cas9 to target and cleave DNA that is complementary to the protospacer region of the crRNA. (*See id.*) Dr. Doudna testifies that she "believed that the engineered sgRNA CRISPR-Cas9 system we had designed could target and modify DNA in both prokaryotes and eukaryotes, including mammalian cells." (*Id.*, ¶ 44.)

In support of their testimony, Drs. Jinek and Doudna cite to Exhibit 4406, which is e-mail correspondence between them dated 1 March 2012. In the e-mail, Dr. Doudna states: "I'm very excited about the Csn-1/Cas9-based genome targeting ideas we discussed yesterday, this will be fabulous if it works." (Exs. 4406 and 4405.) Dr. Doudna states further that she thought "it would be good to demonstrate that the single-RNA guide works to direct DNA cleavage by Csn1/Cas9 in vitro ASAP, . . . and then proceed with the experiments necessary to show that this strategy will actually work in mammalian cells." (Exs. 4406 and 4405.) The e-mails between Drs. Jinek and Doudna demonstrate that they planned experiments to show that the single-guide RNA CRISPR/Cas9 system would work

in mammalian cells.

CVC, as well as Drs. Jinek and Doudna, cite further to pages of Dr. Jinek's notebook memorializing their ideas on 1 March 2012. The pages are reproduced below.

Interference 106,115



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1st March 2012

Potential ideas for using CsnI as a gene-targeting tool

So far, have demonstrated that CsnI/Cas9 is active as an RNA-guided DNA endonuclease, capable of making a double-stranded break in a DNA sequence containing a region that is homologous/complementary to the crRNA sequence.

CsnI/Cas9 requires crRNA/tracrRNA combination for targeting and will not work in the absence of tracrRNA.

Sequence-specific designer nucleases - e.g. Zinc-finger or TALE-fused nucleases have great potential as gene targeting/editing tools. (e.g. Miller et al, Nature Biotech 2010, Sangamo biosciences, etc) But sequence specificity is limited and design of novel seq. specific Zn-finger or TALE nucleases is lengthy and cumbersome.

New idea: adapt the CsnI/Cas9 system as a gene-targeting tool in mammalian cells, e.g. in embryonic or induced pluripotent stem cells, especially in those where homologous recombination is not efficient.

→ use CsnI/Cas9 to make a programmed double-stranded break to induce repair by homologous recombination

→ rely on homologous recombination to "repair" cleaved DNA based on an exogenous source (e.g. plasmid, viral vector)

Potential uses:

→ gene knock-outs/deletions
→ gene knock ins - introduce transgenes in a seq. specific position

→ gene repair - correct point mutations.

Signed: (MARTIN JINEK), 1st March 2012

Witnessed: RACHEL HAURWITZ 3/1/2012
Samuel H. Sternberg 3/1/12

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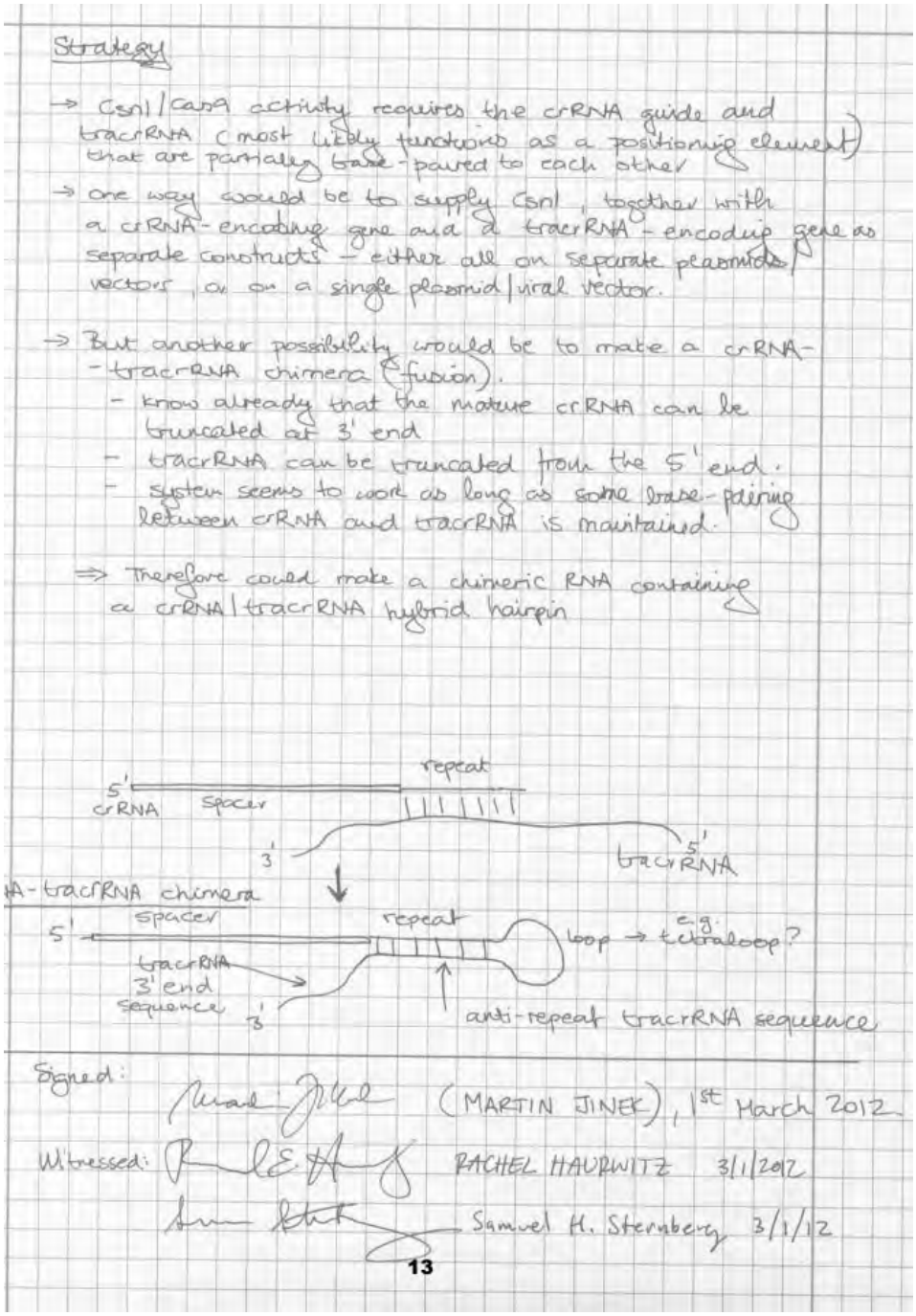
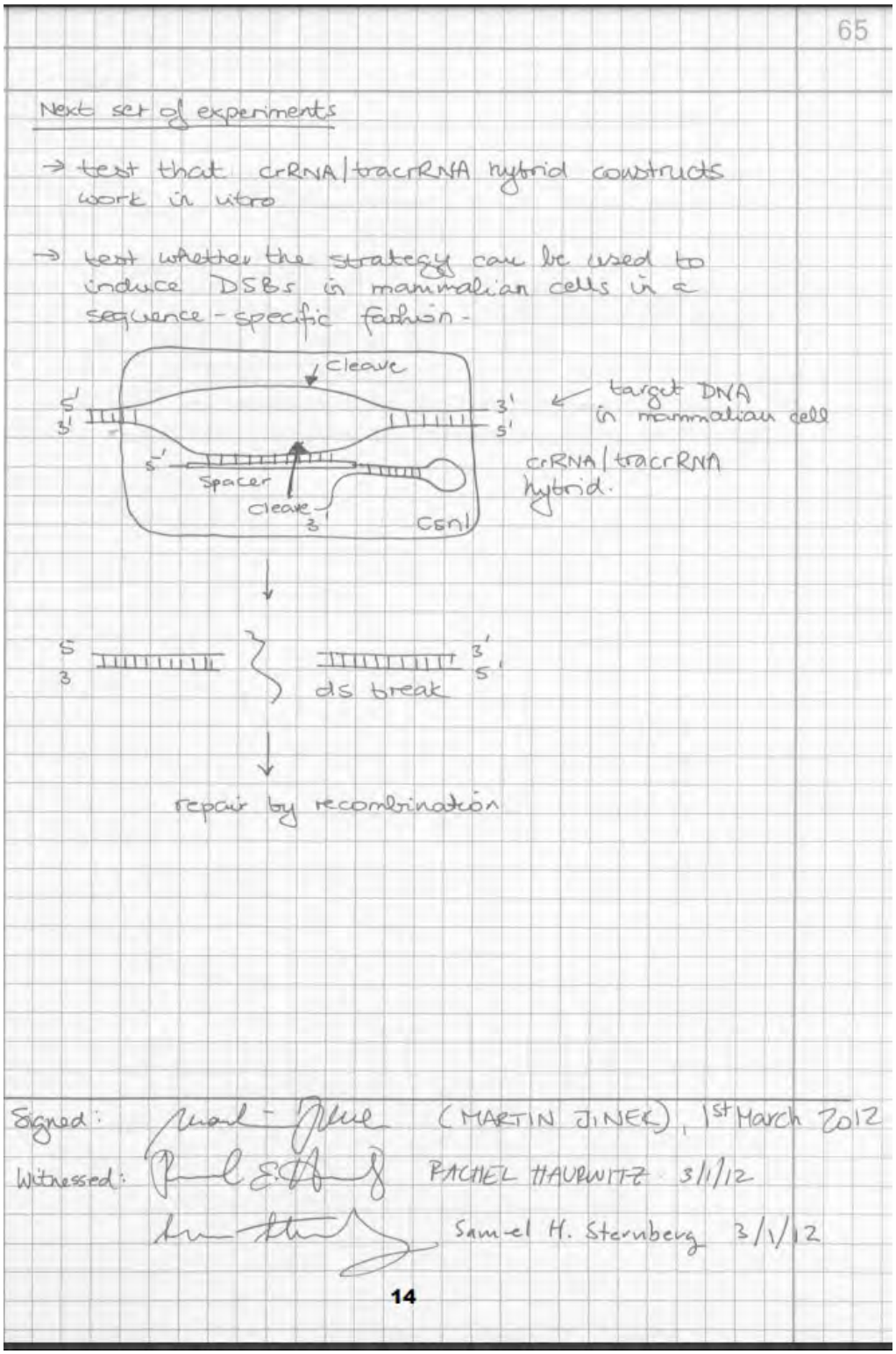
Interference 106,115



Interference 106,115



(Ex. 4381, 12–14.) These notebook pages corroborate the CVC inventors' testimony that they had developed a CRISPR-Cas9 system, including a crRNA-tracrRNA fusion, for targeting a sequence homologous or complementary to the crRNA sequence. (*See* Ex. 4381, 12–13.) The pages indicate that Drs. Jinek and Doudna had the "New idea" of "adapt[ing] the Csn1/Cas9 system as a gene-targeting took in mammalian cells, e.g. in embryonic or induced pluripotent stem cells . . . ." (Ex. 4381, 12.) The pages also indicate that the CVC inventors had a plan to "test whether the strategy can be used to induce DSBs in mammalian cells in a sequence-specific fashion." (Ex. 4381, 14.)

CVC cites to the testimony of Yannick Doyon, PhD.,[6] to support the argument that its inventors' conception was complete because each element of Count 1 was included in Dr. Jinek's notebook pages. (*See* CVC Motion 2, Paper 1579, 8:17–12:8, citing Doyon Decl., Ex. 4345, ¶¶ 70–82.) Specifically, Dr. Doyon testifies that the system the CVC inventors depicted has a Cas9 protein and a single molecule DNA-targeting RNA capable of hybridizing to a target sequence to cleave the DNA. (*See* Doyon Decl., Ex. 4345, ¶¶ 74–76.) CVC cites further to Dr. Doyon's opinion that Dr. Jinek's notebook shows evidence of having

[6] Dr. Doyon terrifies that he is an Associate Professor in the Department of Molecular Medicine at Université Laval, Québec, Canada. (*See* Declaration of Yannick Doyon, Ph.D. ("Doyon Decl."), Ex. 4345, ¶ 13.) Dr. Doyon testifies that he has extensive experience in the field of genome editing using ZFNs, TALENs, and CRISPR-Cas9 systems and his publications, patents, and grants reflect his testimony. (*See id.* at ¶ 14; *see* Ex. 4346.) Broad does not raise any objection to Dr. Doyon's qualifications. We find him to be qualified to present opinion testimony on the subject of interference.

conceived of a "eukaryotic cell comprising a target DNA molecule and an engineered Type II CRISPR-Cas system," because statements in the notebook refer to "mammalian cells," "embryonic or pluripotent cells," and gene knock-outs/deletions" as well as "gene knock-ins" and "gene repair." (*See* Doyon Decl., Ex. 4345, ¶¶ 77–80; *see* CVC Motion 2, Paper 1579, 9:3–12.)

CVC argues that its inventors' conception was definite and permanent as of 1 March 2012 because it did not change between conception and subsequent reduction to practice. (*See* CVC Motion 2, Paper 1579, 12:9–13:2.) Specifically, CVC argues that the sgRNA CRISPR-Cas9 system depicted in Dr. Jinek's notebook is a "blueprint" of the sgRNA design that was published by the inventors in Jinek 2012 (Ex. 3202), used in their reductions to practice, and disclosed in their patent applications. (*Id.* citing Doyon Decl., Ex. 4345, ¶¶ 83–85.) CVC presents a side-by-side comparison of diagrams depicting an sgRNA from Dr. Jinek's notebook entry of 1 March 2012 (Ex. 4381), Figure 5B of the Jinek 2012 publication (Ex. 3202), and Figure 38A of CVC provisional application 61/757,640 ("P3," Ex. 3004), which it argues are the same. (*See* CVC Motion 2, Paper 1579, 12:13–18.) Dr. Doyon supports this argument by testifying that "[t]he single-guide CRISPR-Cas9 system for eukaryotic cells that the CVC inventors contemplated by March 1, 2012 is the same as the single-guide CRISPR-Cas9 system that the CVC inventors later used to induce double- strand breaks in the DNA of mammalian cells using ordinary skill and routine techniques." (Doyon Decl., Ex. 4345, ¶ 83.)

CVC argues that further evidence of its inventors' conception on 1 March 2012 occurred on 11 April 2012, on 28 May 2012, and on 28 June 2012, after the inventors were diligently working towards a reduction to practice. (*See*

CVC Motion 2, Paper 1579, 14:2–20:23.) First, CVC asserts that by 4 April 2011 the inventors had conducted the first *in vitro* test confirming an sgRNA could form a functional DNA-cleavage complex with Cas9 and cleave targeted DNA. (*See id.* at 14:8–10, citing Jinek Notebook, Ex. 4381, 84–86 (indicating that "chimeras A are all functional").) After that test, CVC highlights an invention disclosure form ("IDF") reportedly drafted by Dr. Jinek on 11 April 2012, as evidenced by a copy of an e-mail from Dr. Jinek to Dr. Doudna with that date. (*See* CVC Motion 2, Paper 1579, 14:11–16, citing Ex. 5105.)

CVC asserts that the IDF "shows that the inventors understood the PAM sequence and its expected role in CRISPR-Cas9-mediated DNA cleavage in a eukaryotic cell" because it referred to using a CRISPR-Cas9 system in eukaryotic cells such as oocytes, embryos, human ES cells, and iPSC lines (CVC Motion 2, Paper 1579, 15:8–10, citing Ex. 5105, 18, 23–28, Jinek Decl., Ex. 4349, ¶¶ 72–74; Doudna Decl., Ex. 4350, ¶ 60.) CVC asserts further that by 11 April 2012, its inventors had selected truncated crRNA and tracrRNA components for a CRISPR-Cas9 system. (*See* CVC Motion 2, Paper 1570, 15:17–16:15.)

CVC argues that the IDF provides conventional techniques for reducing the invention to practice and optimizing it. (*See* CVC Motion 2, Paper 1579, 16:16–17:1, citing Ex. 5105, 23–24.) The IDF lists techniques of introducing DNA or RNA encoding components of the system into cells, by direct microinjection of oocytes, and embryos, transfection of cultured cells, electroporation of cultured cells, transduction of cells using viral vectors and *Agrobacterium*-mediated transformation of plants. (*See* Ex. 5105, 24.)

Broad argues that the IDF "simply consists of laundry lists of methods for

introduction and generic statements" regarding useful components without any definite or permanent idea for implementation of the invention. (Broad Opp. 2, Paper 2569, 32:17–20.) Broad cites to Dr. Jinek's cross-examination testimony that as of 1 March 2012, he understood achieving sgRNA and Cas9-mediated genome editing in eukaryotic cells would only require expressing or delivering these components to the cell "using straightforward application of basically methods for expression of RNAs and proteins in eukaryotic cells," such as had been used for TALENs and zinc finger techniques. (Jinek Depo., Ex. 6207, 92:6–9; *see, generally, id.* at 92:10–95:1; *see* Broad Opp. 2, Paper 2569, 32:15–33:2.) CVC does not direct us to more explanation or details of the processes that the CVC inventors understood, at the time, would be needed to achieve a functional sgRNA CRISPR-Cas9 system in a eukaryotic cell.

The IDF demonstrates that the CVC inventors planned to use their sgRNA CRISPR-Cas9 system in eukaryotic cells, but does not provide many details of how the inventors envisioned such a system would be operable. Instead, the IDF and Dr. Jinek's testimony indicates that as of 1 March 2012 the inventors assumed that what was known about other genome editing systems such as TALENs and zinc fingers would be applicable to a CRISPR-Cas9 system.

CVC cites further to experimental work supporting the asserted conception date of 1 March 2012, noting that "[w]hile diligently working towards an [actual reduction to practice], the inventors understood that the Doudna and Charpentier labs were not equipped to do testing in eukaryotic cells, but collegial labs at [University of California] and [University of Vienna] would be able to test the system in eukaryotes much faster." (CVC Motion 2, Paper 1579, 17:2–4.) The

CVC inventors testify that they contacted other scientists: David Drubin and Aaron Cheng to test sgRNA CRISPR-Cas9 in human cells and Florian Raible to test sgRNA CRISPR-Cas9 in zebrafish cells. (*See* Doudna Decl., Ex. 4350, ¶ 62, Jinek Decl., Ex. 4349, ¶ 75, 78; Charpentier Decl., Ex. 4351, ¶¶ 57–58; Chylinski Decl., Ex. 4348, ¶¶ 115.)

CVC argues that by 28 May 2012 its inventors had constructed sgRNAs for programming CRISPR-Cas9 systems to target genes from eukaryotic organisms adjacent to PAM sequences in eukaryotic cells, specifically in human cells. (*See* CVC Motion 2, Paper 1579, 17:11–19:9.) Dr. Jinek's testimony and his notebooks, cited by CVC, show that he had a plan to use his sgRNA constructs to target the CTLA gene in human cells. (*See* Jinek Decl., Ex. 4348, ¶¶ 124–128; Jinek Notebook, Ex. 4382, 1, 2.) CVC argues that this CLTA-targeting sgRNA CRISPR-Cas9 construct is the same system the inventors used to ultimately reduce an embodiment of Count 1 to practice in human cells. (*See* CVC Motion 2, Paper 1579, 19:7–9.) CVC argues further that a first year graduate student was able to reduce the invention to practice in human cells using conventional methods with only a few weeks of training. (*See* CVC Motion 2, Paper 1579, 13:23–14:1.)

CVC next points to evidence from 28 June 2012 as further support for the inventors' conception. (*See* CVC Motion 2, Paper 1579, 19:10–20:23.) CVC cites to e-mails between Drs. Charpentier, Chylinski, and Raible on that date discussing a plan to inject sgRNA/Cas9 into zebrafish embryos as an RNA/protein complex. (*See* CVC Motion 2, Paper 1579, 19:19–20:12, citing Ex. 4799; Chylinski Decl., Ex. 4348, ¶¶ 115–1116, Charpentier Decl., Ex. 4351, ¶¶ 57–59, Raible Decl., Ex. 4294, ¶¶ 14–16.) According to CVC, the inventors' reduction to practice in

zebrafish required only routine injection of sgRNA and Cas9 protein into zebrafish embryos. (*See* CVC Motion 2, Paper 1579, 13:8–14.)

Broad opposes CVC's arguments regarding conception, arguing, in general, that the CVC inventors lacked a "definite and permanent idea of the complete operative invention" as it would have been applied in practice. (Broad Opp. 2, Paper 2569, 30:13–39:16.) According to Broad, the 1 March 2012 diagram in Dr. Jinek's notebook was merely a "naked idea," without a definite plan. (*See id.* at 32:1–4.) Broad also asserts that the CVC inventors encountered multiple failures throughout 2012 when they attempted to use their sgRNA CRISPR-Cas9 system in human cells and zebrafish embryos. (*See id.* at 30:13–39:16.)

According to Broad, these failures prompted them to consider changing material aspects of the system in an attempt to find a strategy that could work. (*See id.*) Broad argues that these failures also indicate the CVC inventors had not expressed their ideas in such clear terms as to enable those skilled in the art to make the invention. (*See id.* at 33:24–34:5, citing *Coleman v. Dines,* 754 F.2d 353, 359 (Fed. Cir. 1985) ("Conception must be proved by corroborating evidence which shows that the inventor disclosed to others his 'completed thought expressed in such clear terms as to enable those skilled in the art' to make the invention.").)

Broad argues that instead of providing directions sufficient to reduce to practice a functional sgRNA CRISPR-Cas9 system in human cells by 28 May 2012, the CVC inventors were "merely guessing at solutions to fundamental problems." (Broad Opp. 2, Paper 2569, 35:2–37:19.) Broad first cites to a copy of e-mail correspondence dated 16 August 2012, with the subject line "Re: unfortunate results," in which Dr. Cheng reported to Dr. Doudna, Jinek,

and Drubin that experiments targeting the eukaryotic gene CTLA in cells failed. (*See* Ex. 4943; *see* Broad Opp. 2, Paper 2569, 35:13–15.) The exhibit shows a response from Dr. Doudna: "Shucks! I guess it would have been too easy of it worked the first time . . . I'll think on this and get back to you - my quick take is maybe try again with improved Cas9 expression?" (Ex. 4943.)

Broad cites further to a copy of e-mail correspondence dated 14[7] September 2012, with the subject line "Re: no good news," in which Dr. Cheng wrote to Dr. Doudna: "Unfortunately no cleavage for any RNA chimeras despite using the codon-optimized Cas9 constructs this time See attached." (Ex. 4988; *see* Broad Opp. 2, Paper 2569, 35:16–36:1.) The exhibit shows that Dr. Doudna responded with generalized suggestions about repeating the experiment with increased amounts of plasmid, concluding:

> Since there are so many variables in these experiments I think we have to try to move forward in a stepwise fashion as much as possible.
>
> As for RNA localization I think we're hoping that the Cas9 protein binds the RNA such that the RNP is transported into the nucleus I wonder if having a too-efficient NLS on Cas9 is actually counterproductive if it means that Cas9 is transported before it has a chance to find and bind the guide RNA. . . Thoughts?

(Ex. 4988.)

[7] The quoted language is from an e-mail dated "Sep 15, 2012 at 4:03 AM," but the response from Dr. Doudna is dated "Friday, September 14, 2012 6:43 PM." (Ex. 4988.) Although it is not clear whether different time zones account for this discrepancy, it does not change our analysis of the inventors' ideas in mid-September.

In a copy of an e-mail dated 11 October 2012, Dr. Doudna responded to news about a failed experiment with codon-optimized and non-codon optimized Cas9 with a CLTA6 RNA chimera, stating:

> Hi Alex and Aaron - thanks for sending your results although it's disappointing not to see Cas9-mediated cleavage in these experiments. Aaron I'm wondering if you think there is anything different about the way you did the experiment back in August when it appeared that there was some cleavage with the CLTA6 guide? Or could that result have been due to a contamination, say with the ZFN sample -? And it will be interesting to see the result from the RNA transfection experiment. Is it worth trying the transfections again with the codon-optimized Cas9? As we have discussed I still think the problem may be with the assembly and localization of the Cas9 RNP - either due to degradation of the guide RNA failure to assemble with Cas9 or failure of the RNP nuclear localization. I will think on this on my way back to SF tonight and we can meet soon to discuss.

(Ex. 5043; *see* Jinek Decl., Ex. 4349, ¶ 230.)

Broad cites yet further to a copy of e-mail correspondence also dated 11 October, in which Dr. Jinek wrote to Dr. Doudna:

> Re mammalian cells - Based on the latest set of results, I suspect we have a problem with our RNA design. Either we are not targeting the right piece of DNA (due to chromatin structure etc), or the problem lies with the RNA design per se. Given that the ZFN has no problems cleaving the same region (+/- 30 bp), the former is probably the lesser concern at this point. On the other hand, there could be a number or reasons for the latter including:
>
> -RNA is not made at sufficient levels
>
> -RNA is expressed strongly but turns over too fast to associate with Cas9 posibly due to degradation by exonucleases
>
> -RNA is stable but does not associate with Cas9 at the right place and at the right time.

> For the next set of experiments I think we should switch to CMV vectors cloning today and explore alternatives to our first-generation RNA design - e.g. modify the hairpin length introduce extensions at the 5' and 3' termini. Or possibly block potential degradation from either end by introducing hairpins etc.

(Ex. 5041; *see* Broad Opp. 2, Paper 2569, 36:2–6.) Dr. Doudna responded:

> As for Cas9 in mammalian cells I completely agree with your analysis and suspect that one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic.
>
> It would be great to test some alternate designs of the guide RNA in vitro - perhaps this is something Alex could do using target plasmids you already have available? Maybe we could also try this in cell extracts? We can discuss further tomorrow - 10 am OK?

(Ex. 5041.) And Dr. Jinek responded:

> I agree that we should explore various alternate RNA designs for targeting in cells. As for the in vitro experiments - I thought that this was what Steve Lin was going to do. Maybe it would be good to bring him on board for this as well at this stage. Then things could be parallelized and Alex could focus more on the mammalian cell work. When Enbo gets back he could then help out with IPs and Northerns because we will need to check whether the RNAs are associating with Cas9 in vivo. Anyway, let's talk tomorrow.

(Ex. 5041.)

Broad cites to a copy of further e-mail correspondence dated 17 October 2012, in which Dr. Doudna wrote to Dr. Jinek, Dr. Cheng, and other scientists at Berkley:

> I think that doing the experiment with cell extracts to test whether the

> transfected Cas9 is active is a critical control. We should perhaps also be preparing some of the other Cas9's for mammalian expression in case they work better for some reason (i.e. folding or faster/better RNP assembly).

(Ex. 5053; *see* Broad Opp. 2, Paper 2569, 36:6–10.)

From these e-mails, Broad concludes that instead of having a definite and permanent idea of an embodiment of Count 1, the CVC inventors were engaged in "guesswork" and "returned to the drawing board." (Broad Opp. 2, Paper 2569, 36:10–11.) According to Broad the CVC inventors had to redesign their components and strategy beyond what would have been routine techniques for one of ordinary skill in the art and did not have a definite and permanent idea of the invention by 1 March 2012. (*See id*. at 37:18–19.)

CVC does not directly address these e-mail statements in its Reply Brief, arguing only that Broad "cites correspondence with its colleagues *as evidence of CVC's reasonable diligence*, which . . . Broad barely challenged." (CVC Reply 2, Paper 2744, 18:15–17.) CVC does not provide any reason why these communications are not also evidence the inventors' thoughts and understandings around CVC's asserted conception date.

CVC asserts that the 28 June 2012 design of a CRISPR-Cas9 system complex for use in zebrafish embryos is evidence of the 1 March 2012 conception. (*See* CVC Motion 2, Paper 1579, 19:10–20:23.) As discussed above, we are not persuaded that the CVC inventors' recognized and appreciated the result of Dr. Raible's zebrafish experiments. Although CVC argues that the inventors' design of sgRNAs to target genes in zebrafish is evidence of their earlier

conception, we are not persuaded that these designs represent a definite and permanent idea of the invention because we are not persuaded the CVC inventors understood that reducing the invention to practice in zebrafish using this design would have required only routine skill by 28 June 2012. (*See* CVC Motion 2, Paper 1579, 20:18–23.) Thus, we agree with Broad that CVC's evidence of conception by 28 June 2012 in the design of sgRNAs for a CRISPR-Cas9 system in zebrafish is not persuasive evidence of a definite and permanent idea of the invention by the CVC inventors due to the, at least perceived, subsequent experimental failures of this design.

In general, CVC argues that Broad "fabricates an illusion of doubt in the inventors' minds by cataloging snippets from various CVC documents . . . . These simply reflect that the inventors understood and considered these routine implementation issues during the process and, at all stages, had a plan to address them." (CVC Reply 2, Paper 2744, 10:12–15.) We disagree, given the inventors' actual statements about problems with design and questions about what to do next. CVC cites to the inventors' declarations as evidence that they had a plan to address the issues they encountered, but their statements prepared for this proceeding do not reflect these contemporaneous communications.

For example, CVC cites to Dr. Doudna's declaration statement that her "familiarity with multiple systems that had been used successfully to target and modify genes in eukaryotes made it clear to [her], before March 1, 2012, that the CRISPR-Cas9 system that [they] had engineered would work in eukaryotes." (Doudna Decl., Ex. 4350, ¶ 40; *see* CVC

Reply 2, Paper 2744, 10:15–16.) But her contemporaneous statements on 11 October 2012 that "one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic" (Ex. 5041) or that there was contamination from controls (Ex. 5043), as well as suggestions to "test some alternate designs of the guide RNA" (Ex. 5041), does not indicate she knew how to solve this problem to make a functional system at the time.

> Similarly, Dr. Jinek testified for this proceeding that his
>
> experience with RNAi and knowledge of RNA biology led me understand that issues such as potential degradation and nuclear localization are the types of problems that could be addressed though routine experimentation by, for example, adjusting the amount of RNA, modifying the RNA to improve expression or stability, or optimizing the delivery method.

(Jinek Decl., ex. 4349, ¶ 230; *see* CVC Reply 2, Paper 2744, 10:15–16.) But, his contemporaneous statements on 11 October 2012 of "a problem with our RNA design" and suggestions to "switch to CMV vectors cloning today and explore alternatives to our first-generation RNA design – e.g. modify the hairpin length introduce extensions at the 5' and 3' termini. Or possibly block potential degradation from either end by introducing hairpins etc." do not indicate he had a definite and permanent idea of a function system at the time. (Ex. 5041.)

Dr. Chylinski (Ex. 4348, ¶¶ 22–24) and Dr. Charpentier (Ex. 4351, ¶ 26) also testify to their knowledge of using RNAs in eukaryotic cells and of other gene editing systems, such as TALENs and zinc fingers, but CVC does not direct us to anything other than these generalized statements to show specific instructions for

overcoming the problems encountered through October 2012. (*See* CVC Reply 2, Paper 2744, 10:15–16.) For example, CVC does not direct us to evidence that either Dr. Chylinski or Dr. Charpentier provided Dr. Raible with specific instructions that would have produced positive results in his fish embryo experiments. CVC does not direct us to evidence that any of the inventors had a definite and permanent idea of an sgRNA CRISPR-Cas9 system that would work to edit DNA in a eukaryotic cell, particularly when they encountered what was perceived as design problems in their system at that time. (*Contra* CVC Reply 2, Paper 2744, 10:15–16.)

CVC argues further that its inventors did not encounter "perplexing intricate difficulties arising every step of the way" or "unduly extensive research or experimentation" when applying CVC's sg RNA CRISPR-Cas9 system in eukaryotic cells. (*See* CVC Reply 2, Paper 2744, 17:19–23, quoting *Rey-Bellet v. Englehardt*, 493 F.2d 1380, 1386 (CCPA 1974) and *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994).) Given the inventors' comments from August to October of many "unfortunate results" (Ex. 4943), "problem with our RNA design" (Ex. 5041), and "so many variables in these experiments" (Ex. 4988) it is not clear how CVC comes to this conclusion.

CVC argues that "[i]t is irrelevant whether . . . some experiments performed by CVC's colleagues in other eukaryotic cell types (e.g., nematodes) had not yet succeeded," whether there were doubts about the results of other experiments (citing experiments in medaka fish), or whether collaborations in yeast, mice, or plants had not yet started. (CVC Reply 2, Paper 2744, 18:1–5.) CVC argues that "[t]he question is not whether some colleagues' experiments succeeded or failed,

but rather whether the inventors' conception of Count 1 was complete." (*Id.* at 18:5–7.) We agree with this last statement – the relevant question is whether the inventors had a complete conception of Count 1. But, we disagree that the other facts are irrelevant to that question and that they cannot provide insight into what the inventors were thinking at the asserted date of conception. We disagree that reports of repeated failures and correspondence reviewing the possible problems, searching for solutions, and questioning their designs do not provide an insight into what the inventors thought on 1 March 2012 and after.

We find the facts related to the CVC's inventors' asserted conception on 1 March 2012 and the further evidence of 11 April 2012, 28 May 2012, and 28 June 2012 to be different from the facts of inventorship presented in *Burroughs*. In that case, the confirmatory testing was "brief" and followed the "normal course of clinical trials." *Burroughs*, 40 F.3d at 1230. In contrast, CVC argues its inventors had the materials for an actual reduction to practice in human cells on 28 May 2012, but allegedly completed it, after diligent work, on 31 October 2012 – over five months later – after encountering many problems and trying many times. (*See* CVC Motion 2, Paper 1579, 17:11–19:9, 27:16–33:23.) Contrary to CVC's argument, we find that the CVC inventors engaged in a "prolonged period of extensive research, experiment, and modification" following the alleged conception on 1 March 2012. *Burroughs*, 40 F.3d at 1230. The evidence shows that, at best, the CVC inventors encountered one unrecognized positive result and several failures with zebrafish embryos and several months of failed experiments and doubt with human cells. Given that the scientists performing these experiments were of at least ordinary skill, we are persuaded that the

communications surrounding these experiments reflect "uncertainty that so undermines the specificity of the inventor's idea that it [was] not yet a definite and permanent reflection of the complete invention as it [would] be used in practice." *Id.* at 1229.

We do not base our decision on a lack of reasonable expectation of success by the CVC inventors that the system would be capable of editing DNA in a eukaryotic cell. (*See* CVC Reply 2, Paper 2744, 4:6–19, 19:14–20.) And we agree with CVC that the decision in the prior interference 106,048, which determined that those of ordinary skill in the art would not have been a reasonable expectation of success in a functional eukaryotic CRISPR-Cas9 at the time, is not directly relevant to the inquiry before us now. (*See id.*, 4:23–5:3.) Accordingly, we are not persuaded by either party's evidence of what those in the art expected at the time. (*See* Broad Opp. 2, Paper 2569, 18:23–24:12; *see* CVC Reply 2, Paper 2744, 22:18–24:6.)

Instead, we base our decision on the facts that the CVC inventors encountered multiple experimental failures before they recognized any success, even as late as mid-October 2012. Although the CVC inventors developed a system on 1 March 2012 that they hoped would work in eukaryotic cells, the preponderance of the evidence demonstrates that they did not have a definite and permanent idea of how to achieve that result as of that date or by the later dates CVC asserts support that date because of their perception of these multiple failures.

CVC argues that a system with the same sgRNA sequence, promoter, nuclear localization sequence, cell type and methods asserted to be evidence of conception when designed on 28 May 2012 were ultimately shown to be functional

in Example 2 of its provisional application 61/757,640 ("P3"), filed 28 January 2013, which we determined to be a constructive reduction to practice. (*See* CVC Motion 2, Paper 1579, 17:11–19:9; *see* CVC Reply 2, Paper 2744, 7:6–21.) CVC argues that this evidence is therefore necessarily sufficient to demonstrate conception, citing *Haskell v. Colebourne*, 671 F.2d 1362 (CCPA 1982). (*See* CVC Reply 2, Paper 2744, 7:9–14.)

Haskell, though, presented a much simpler fact pattern, wherein the disclosure in a pre-filing patent application draft was held to be adequate evidence of conception when nearly the same application, filed a few days later, was a sufficient constructive reduction to practice. *See id.* at 1366–67. There was no evidence of experimental failures and uncertainty between the drafting of the application and the filing of the final application days later in *Haskell*. We decline to interpret *Haskell* as a creating a blanket rule that when elements are later shown to be sufficient to establish a constructive reduction to practice in a benefit application, conception must necessarily have occurred, as CVC asserts. (*See* CVC Reply 2, Paper 2744, 7:9–14.) Rather we look to all of the evidence presented, including evidence of experimental failures and uncertainty to determine what the inventors understood about the system at the dates asserted. The inventors' activities in the eight months from their initial description of the materials on 28 May 2012 to the constructive reduction to practice allegedly using these materials on 28 January 2013 indicates to us they had sufficient uncertainty that undermines CVC's arguments of a definite and permanent idea of an sgRNA CRISPR-Cas9 system to be used in a eukaryotic cell.

We acknowledge CVC's argument that in the end only routine materials and techniques, as described by the CVC inventors, were required for a sgRNA CRISPR-Cas9 that can edit DNA in eukaryotic cells, but we look to what the CVC inventors understood as evidence of their conception, not what others might have understood later. (CVC Reply 2, Paper 2744, 7:15–10:11.) The *Hitzeman* court explained:

> *Nunc pro tunc* conception involves the situation where an inventor actually possessed a claimed device at the time of his alleged conception, but failed to recognize the device's inventive features at that time. As articulated in cases such as [*Heard v. Burton*, 333 F.2d 239, 242–44 (1964)], an inventor who failed to appreciate the claimed inventive features of a device at the time of alleged conception cannot use his later recognition of those features to retroactively cure his imperfect conception.

Hitzeman, 243 F.3d at 1358–59; *see also Cooper*, 154 F.3d at 1331 ("The rule that conception and reduction to practice cannot be established *nunc pro tunc* simply requires that in order for an experiment to constitute an actual reduction to practice, there must have been contemporaneous appreciation of the invention at issue by the inventor." (citing *Estee Lauder,* 129 F.3d at 593).)

Count 1 requires not just the mechanics of a CRISPR-Cas9 system (RNAs, vectors, transfection or microinjection techniques), but also that the system causing "expression of the at least one gene product is altered" in a eukaryotic cell or a system that "is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule" in a eukaryotic cell. (*See* Declaration, Paper 1, 12–13.) Therefore, it is not sufficient for CVC to show only that its inventors conceived of the mechanics

of a CRISPR-Cas9 system. To have conceived of an embodiment of Count 1 they must have had a definite and permanent idea of an operative invention, that is of a system they knew would produce the effects on genes in a eukaryotic cell recited in Count 1.

C.

There is no dispute in this proceeding that the CVC inventors conceived of a generic sgRNA CRISPR-Cas9 system by 1 March 2012 and we note that CVC's patent rights to that invention are not at issue here. (*See* CVC Opp. 5, Paper 2567, 37:4–6.) Rather, the issue before us now is CVC inventor's conception of a CRISPR-Cas9 system that works in eukaryotic cells. CVC fails to direct us to persuasive evidence that the testing of CVC's CRISPR-Cas9 system was merely confirmative as in *Burroughs Wellcome.* Instead, we find the subsequent course of experimentation, especially repeated failures, reveal the inventor's uncertainty, which undermines a definite and permanent idea. Thus, CVC fails to persuade us that its inventors had a conception of an embodiment of Count 1 by 1 March 2012.

As explained above, we are also not persuaded that the CVC inventors either reduced to practice an embodiment of Count 1 by 9 August 2012 or that Dr. Raible performed experiments that inured a reduction to practice to them by that date.

Accordingly, we DENY CVC Motion 2 for priority.

III. Broad Motion 5 – For judgment based on priority

Broad argues that its inventors actually reduced to practice an embodiment of Count 1 by 5 October 2012. (*See* Broad Motion 5, Paper 2118, 20:10–21:12, 36:11–39:15.) Broad asserts earlier dates in July and August 2012 as well, but we

need not consider whether Broad's evidence regarding these dates is sufficient because, in light of our decisions in regard to CVC's priority arguments, an actual reduction to practice by the Broad inventors by 5 October 2012 demonstrates priority before any post-9 August 2012 date CVC asserts. That is, if we determine that the Broad inventors had an actual reduction to practice of an embodiment of Count 1 by 5 October 2012, Broad will have persuaded us that it is entitled to priority over CVC.

We look to the activities and ideas of the Broad inventors, Feng Zhang, Ph.D., Le Cong, Ph.D., Fei Ran, Ph.D., Patrick Hsu, Ph.D., Randall Platt, Ph.D., and Neville Sanjana, Ph.D., to determine whether the preponderance of the evidence shows that by 5 October 2012 they constructed an embodiment of Count 1, meeting all its limitations and that they recognized and appreciated it would work for its intended purpose. *See Cooper*, 154 F.3d at 1327; *see Estee Lauder Inc.*, 129 F.3d at 594–95. We look to other evidence presented by Broad as background to the asserted reduction to practice on 5 October 2012.

A.

Broad presents the testimony of Dr. Zhang that by 7 February 2011 he had learned of CRISPR systems and was considering them as a tool for genome editing. (*See* Zhang Decl., Ex. 3424, ¶ 50; *see* Broad Motion 5, Paper 2118, 7:18–23.) A copy of e-mails dated 5–7 February 2011, from Dr. Zhang to Le Cong provides a link to a paper in Science magazine and states:

> Let's keep this confidential. I have a feeling that this could work very well in mammalian systems and can completely replace any kind of FokI system. I ordered the cascade and nuclease genes for synthesis so we should be able to test them shortly after you get back. I did a pretty thorough patent search and

> it doesn't seem like anyone has thought about using this as a nuclease system for catalyzing homologous recombination.

(Ex. 3832.) It is not clear from the e-mail that Dr. Zhang is referring to a CRISPR system because it cannot be discerned to which Science magazine paper Dr. Zhang refers, but the e-mail corroborates his testimony that he was contemplating using a non-mammalian nuclease system in eukaryotic cells by February 2011.

Dr. Zhang testifies that in April 2011, after reading a published article by Deltcheva *et al.* (Ex. 3214), he recognized the three components of a CRISPR system were the Cas9 protein, the crRNA, and the tracrRNA. (*See* Zhang Decl., Ex. 3424 ¶¶ 66–67; *see* Broad Motion 5, Paper 2118, 8:11–18.) Deltcheva includes a figure of a model of "tracrRNA-mediated crRNA maturation involving RNase III and Csn1," with a legend stating: "tracrRNA can bind with almost perfect complementarity to each repeat sequence of the pre-crRNA. The resulting RNA duplex is recognized and site-specifically diced by RNase III in the presence of Csn1, releasing the individual repeat-spacer-repeat units (first processing event)." (Deltcheva, Ex. 3214, 605.) Dr. Zhang explains that the "Csn1" protein is the same as the "Cas9" protein, or "cas5" protein, and that he uses the terms interchangeably. (*See* Zhang Decl., Ex. 3424, ¶¶ 60, 66.)

Dr. Zhang testifies that he designed vectors to express chimeric RNA constructs for use in a CRISPR-Cas9 system, which included various configurations of hSpCas9 and chimeric RNA for testing in eukaryotic cells. (*See* Zhang Decl., Ex. 3424, ¶¶ 133–140.) Dr. Zhang presents a plasmid map of the hSpCas9 system with chimeric RNA, which he asserts was used successfully. (*See* Zhang Decl., Ex. 3424, ¶ 141, citing Ex. 3770, 128.) Exhibit 3770 is a copy of an

e-mail, dated 17 July 2012, from Dr. Zhang to Grace Gao and Dr. Cong, with attachments, including the plasmid diagram named "pLenti2-U6-target1-EF1a-hSpCsn1-GFP-NLS-WPRE.sbd" on page 128 and reproduced below.

Andrew Ellington, Ph.D.,[8] Broad's witness, explains that the map of plasmid

[8] Dr. Ellington testifies that he is a Professor in the Department of Molecular Biosciences at the University of Texas and in the Howard Hughes Medical Institute. (Ellington Decl., Ex. 3430, ¶ 11.) Dr. Ellington testifies that he has

pLenti2-U6- target8-EF1a-hSpCsn1-GFP-NLS-WPRE includes a sequence called "Chimeric RNA" in the upper, right-hand side, which has a 20 nucleotide guide sequence capable of hybridizing to a target sequence in the genome, a tracr mate sequence, a GAAA linker, and tracr RNA sequence, all of which would be expected to be expressed from the U6 promoter. (*See* Declaration of Technical Expert Andrew Ellington in Support of Broad ("Ellington Decl."), Ex. 3430, ¶¶ 33, 34; *see* Broad Motion 5, Paper 2118, 24:13–17.)

Broad cites to the testimony of both Dr. Zhang and Dr. Cong about experiments starting on 17 July 2012 to target the mTH gene, a gene Dr. Zhang testifies he was studying in regard to neuronal and brain function, using vectors to express hSpCas9, with nuclear localization signals, and chimeric RNA in mouse cells. (*See* Broad Motion 5, Paper 2118, 13:14–18, citing, *e.g.*, Zhang Decl., Ex. 3424, ¶ 143, and Cong Decl., Ex. 3425, ¶ 25; *see* Zhang Decl., Ex. 3424, ¶ 124.) According to Broad and the inventors' testimony Dr. Cong transfected separate cultures of mouse cells, incubated them, and lysed them to obtain genomic DNA for a Surveyor assay[9] to show genetic modification. (*See* Cong Decl., Ex. 3425,

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extensive experience in the fields of biomolecular engineering and synthetic biology, particularly with engineering nucleic acid and protein systems. (*See id.* at ¶ 10.) Dr. Ellington's publications, patents, and grants reflect his testimony. (*See* Ex. 3431.) CVC does not raise any objection to Dr. Ellington's qualifications. We find him to be qualified to present opinion testimony on the subject of interference.

[9] Dr. Ellington explains that the Surveyor assay was used to detect and quantify cleavage of the mTH genomic target used in the CRISPR-Cas9 experiments by the Broad inventors. (*See* Ellington Decl., Ex. 3430, ¶ 36.) Briefly, the Surveyor assay detects small insertions or deletions (called "indels") using an enzyme to cleave DNA at such mismatches and then imaging the resulting fragments,

¶ 25.) Drs. Zhang and Cong reportedly obtained results from these experiments on 20 July 2012 and from further experiments on 21 July 2012, which Dr. Cong allegedly characterized as "very promising . . . but because the second gel is 1%, it's hard to tell." (Ex. 3773; *see* Broad Motion 5, Paper 2118, 13:14–14:5, citing Zhang Decl., Ex. 3424, ¶¶ 140–149; *see* Cong Decl., Ex. 3425, ¶¶ 26–33.)

Broad presents another e-mail dated 22 July 2012, in which Dr. Cong wrote to Dr. Zhang: "For CRISPR, the expected size for the particular target seq of No.7 of mTH is 250bp + 380bp, and our faint band at least one of them is just below the 400bp marker, the other one is also seems to be around 250bp, so it's very promising." (Ex. 3775; *see* Broad Motion 5, Paper 2118, 13:19–14:5; *see* Zhang Decl., Ex. 3424, ¶ 151; s*ee* Cong Decl., ¶ 32.) Broad argues further that on 23 July 2012, Dr. Zhang wrote that the "the most critical thing for us to do now is to verify that we are indeed getting cutting with the U6::mTH-l/EFla::2xNLS-Csnl-GFP construct. Once that is confirmed we will be able to plan the rest of the experiments much more easily." (*See* Ex. 3777; *see* Broad Motion 5, Paper 2118, 13:19–14:1; *see* Zhang Decl., Ex. 3424, ¶ 153.)

Broad argues that in addition to visualizing results on gels, the inventors also analyzed the activity of the chimeric RNA CRIPR-hSpCas9 system on the mTH gene with sequencing analysis. (*See* Broad Motion 5, Paper 2118, 15:1–16:13, citing Zhang Decl., Ex. 3424, ¶¶ 163–69; Cong Decl., Ex. 3425, ¶¶ 44–57.) Broad relies on Dr. Cong's testimony that by 28 July 2012 samples from colonies

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separated by size, on a gel. (*See id.*)

containing genomic DNA fragments of the 27 July 2012 experiment were submitted to Genwiz for sequencing. (*See* Cong Decl., Ex. 3425, ¶¶ 44 and 46, citing Exs. 3781 and 3782.) Exhibits 3781 and 3782 are copies of e-mails dated 30 July 2012 from a Genwiz e-mail address to Dr. Cong indicating that samples had been received. (*See* Exs. 3781 and 3782.)

Dr. Zhang testifies that on 31 July 2012 he accessed and analyzed the sequencing results from the 25 July 2012 mTH target experiment and recognized that two colonies showed small insertions or deletions, or "indels," at the expected modification site. (*See* Zhang Decl., Ex. 3424, ¶ 165, citing Ex. 3784.) He also testifies that he understood that these indels would result in a frameshift in the DNA target sequence that would result in a change in expression when the mTH target was expressed, such as by introducing a premature stop-codon. (*See id.*) Exhibit 3784, which is a copy of an e-mail, dated 31 July 2012, sent by Dr. Zhang to Dr. Cong, states in part: "Hi Le, I took a look at the data. It is very promising. There are two clones that had modifications. See attached. Feng." (Ex. 3784.) Exhibit 3830 is a copy of an e-mail, dated 31 July 2012, in which Dr. Cong responds to Dr. Zhang, stating: "There is a better example in plate 3 sequencing results! Will send you summary later. I am looking at the results with David." (Ex. 3830.)

CVC argues that this evidence, as well as evidence of earlier asserted reductions to practice, is insufficient to establish it as an actual reduction to practice. (*See* CVC Opp. 5, Paper 2567, 46:7–51:20.) In general, CVC argues that Broad fails to provide contemporaneous evidence, such as laboratory notebooks or electronic notes of the experimental design, protocol, conditions, or other details of

the experiment, fails to provide contemporaneous evidence that Dr. Zhang appreciated that the embodiment worked for its intended purpose, and fails to provide sufficient corroboration of the inventors' testimony. (*See id.*) CVC argues further that the results of the experiments reported were not properly controlled, were contaminated, and that the electronic notebook records have no associated metadata and are unreliable. (*See id.*)

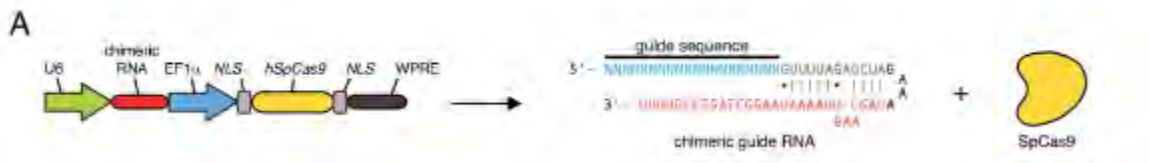
We note that much of the inventors' testimony we cite above is supported by copies of e-mails presented by Broad, while other testimony Broad presents appears to lack corroboration. Nevertheless, as discussed above, we need not review the evidence Broad presents regarding these experiments as a reduction to practice in July 2012 because we need only consider the assertions of an actual reduction to practice on 5 October 2012 to evaluate Broad's priority case. Accordingly, we do not make a determination of the sufficiency of this evidence alone to support Broad's priority argument, but look to it for background to the asserted 5 October 2012 reduction to practice.

Broad argues that Dr. Zhang reported the results for the July 2012 experiments in the 5 October 2012 manuscript submitted to Science magazine. (*See* Broad Motion 5, Paper 2118, 16:21–23, 36:12–39:15, citing Ex. 3564.) Exhibit 3564 is a copy of a manuscript entitled "CRISPR-Assisted Mammalian Genome Engineering," and naming Le Cong, David Cox, F. Ann Ran, Shuailiang Lin, Robert Barretto, Wenyan Jiang, Luciano Marraffini, and Feng Zhang as authors. (*See* Exhibit 3564.) Exhibit 3564 has the header "Submitted Manuscript: Confidential" and the date "October 5, 2012." (Ex. 3564.)

According to Broad, the manuscript is evidence that the experiments

presented were done at least prior to 5 October 2012. (*See* Broad Motion 5, Paper 2118, 37:1–7.) Broad argues further that Dr. Zhang's decision to prepare a manuscript for submission to the journal Science, which would then undergo extensive peer review, indicates he recognized and appreciated that his results demonstrated successful use of a chimeric RNA CRISPR-Cas9 system to cleave DNA in a eukaryotic cell. (*See id*.)

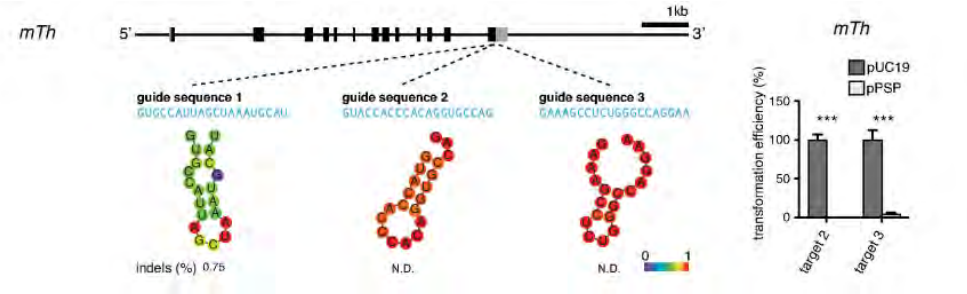
Broad cites to Dr. Zhang's testimony that one of the systems he described in the manuscript (Ex. 3564) is an "hSpCas9" system with chimeric RNA. (*See* Zhang Decl., Ex. 3424, ¶ 180.) Dr. Zhang points to Figure 2A of the manuscript, which is reproduced below.



(Ex. 3564, 15; *see* Zhang Decl., Ex. 3424, ¶ 180.) Dr. Zhang testifies that he designed this system earlier, citing to the e-mail dated 17 July 2012, to Dr. Cong and other Broad personnel, including plasmid maps and sequences as attachments. (*See* Zhang Decl., Ex. 3424, ¶ 182, citing Ex. 3770.) Dr. Zhang testifies further that his chimeric RNA design differed from that in Jinek 2012 (Ex. 3202), authored by CVC inventors, by having four extra U nucleotides on the 3' end of the tracr segment because he used a U6 promoter. (*See* Zhang Decl., Ex. 3424, ¶ 180.)

Broad argues, citing to Dr. Zhang's testimony, that the 5 October 2012 manuscript memorializes the July 2012 mouse cell experiments. (*See* Zhang Decl., Ex. 3424, ¶¶ 173–175; *see* Broad Motion 5, Paper 2118, 17:7–18:3, 37:11–16.)

Broad points to a portion of Figure 2B of the manuscript, which is reproduced below.



(Ex. 3564, 15.) The legend for Figure 2B indicates that it is a

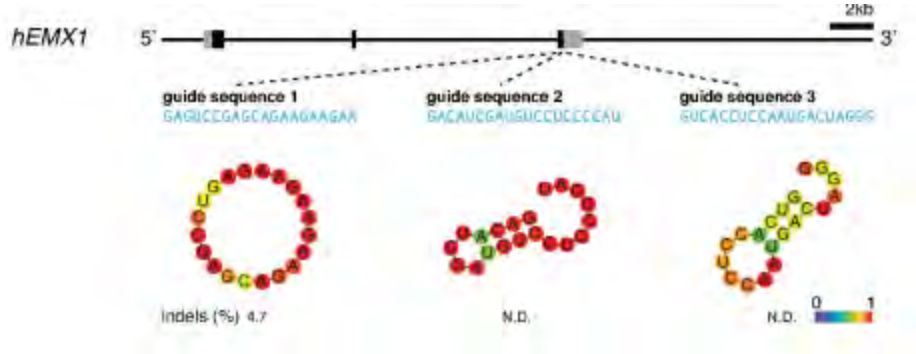
> [s]chematic showing guide sequences targeting the human EMXJ, PVALB, and mouse Th loci as well as their predicted secondary structures. The modification efficiency at each target site is indicated below the RNA secondary structure drawing (EMXJ, n = 216 amplicon sequencing reads; PVALB, n = 224 reads; Th, n = 265 reads). Each base is colored according to its probability of assuming the predicted secondary structure, as indicated by the rainbow scale.

(Ex. 3564, 12.) Broad points to the notation of an indels (%) of 0.75 for one of the constructs targeting the mTH gene. (*See* Broad Motion 5, Paper 2118, 37:11–13.)

Broad argues that the indel % of 0.75 reported in the 5 October 2012 manuscript is consistent with the two positive results received from sequencing data for the repeat experiment in July 2012 because two positive results out of 265 sequencing reads provides a percentage of 0.75. (*See* Broad Motion 5, Paper 2118, 18:1–3; *see* Cong Decl., Ex. 3425, ¶ 57: "The indel% of 0.75 listed in the manuscript for the first mTH target sequence is consistent with the two positive results we received in the Genewiz data, divided by the 265 reads (i.e., 2/265 =

0.0075) that were reported. This is consistent with my recollection that we included our successful use of Dr. Zhang's hSpCas9 system with chimeric RNA to target the mTH target sequence 1 in our manuscript.").)

Broad argues further that Dr. Zhang described other experiments in human cells with his hSpCas9 system and chimeric RNA in the 5 October 2012 manuscript, citing to other portions of Figure 2B relating to the hEMX1 target in a human cell. (*See* Broad Motion 5, Paper 2118, 38:7–39:2.) This portion of Figure 2B is reproduced below.



(Ex. 3564, 15.) The text of the 5 October 2013 manuscript supporting this portion of Figure 2B recites:

> We then explored the generalizability of CRISPR-mediated cleavage in eukaryotic cells by targeting additional genomic loci in both human and mouse cells by designing chimeric RNA targeting multiple sites in the human EMXJ, PVALB, as well as the mouse *Th* loci. We achieved 6.3% and 0.75% modification rate for the human *PVALB* and mouse *Th* loci respectively, demonstrating the broad applicability of the CRISPR system in modifying different loci across multiple organisms (Figure 2B, Table 1). However, we were only able to detect cleavage with one out of three spacers for each locus.

(Ex. 3564, 5.) The manuscript indicates that indels (%) of 0.75 for one construct targeting the mTH gene and an indels (%) of 4.7 for one construct targeting the hEMX1 gene demonstrate that the CRISPR system works for modifying different loci across multiple organisms.

Broad argues that acceptance of and reviewers' comments about the 5 October 2012 manuscript are evidence that Dr. Zhang's experiments were successful and achieved the biological function required in Count 1: "the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered" or "cleaving or editing the target DNA molecule." (Declaration, Paper 1, 13; *see* Broad Motion 5, Paper 2118, 39:3–13.) Specifically, Broad cites to comments including:

> The authors report for the first time the milestone implementation of a bacterial CRISPR system in human cells, and show it can be used for RNA-guided DNA cleavage and genome engineering. Specifically, Le Cong et al. show that two distinct type II CRISPR-Cas systems (based on Cas9 from primarily S.pyogenes and to a lesser extent S. thermophilus) can cleave several targets in human (EMX1, PVALB) and mouse (Th) cell lines. Results show compellingly and thoroughly that the system they developed based on Cas9, crRNA and tracr RNA, or on Cas9 and chimeric RNA is functional and efficient in vivo, for cleavage and inducing mutations at the target site.

(Ex. 3836, 3.) Broad cites further to another comment:

> Jinek et al. (2012) and Gasiunas et al. (2012) showed recently that the Cas9-crRNA complex of the type II CRISPR-Cas system acts as an RNA-guided DNA nuclease where the specificity is programmed by crRNA and Cas9 executes cleavage. The flexibility in RNA programming coupled with a Cas9 ability to generate doublestranded DNA breaks (DSB) set a stage for genome editing using Cas9-crRNA

> complexes. Le Cong et al. now provide experimental evidence that Cas9-crRNA complex can be employed for the mammalian genome engineering. This is a breakthrough paper which may be a game changer in the genome editing field. Le Cong et al reconstituted Cas9-crRNA interference system in mammalian cell lines and show that Cas9 nuclease introduces DSB at the sites targeted by crRNA. They obtained a functional Cas9-crRNA complex in mammalian cells through the heterologous expression of individual components and showed that they are transported to the nucleus and introduce a DSB in DNA. Authors show that Cas9-crRNA cleavage results in the formation of indels which support repair through the error-prone NHEJ pathway. To make precise edits in the genome authors used a nicking Cas9 mutant to stimulate homologous recombination which is an error-free gene repair pathway. Work is technically sound, experiments make a logical flow and in general paper reads well.

(Ex. 3836, 3–4.) The reviewers' comments indicate to us that not only did the Broad inventors recognize and appreciate the positive results of an engineered Type II CRISPR-Cas system targeting DNA in eukaryotic cells to specifically cleave DNA molecules and alter gene expression, others in the field confirmed the results.

Broad cites to Dr. Ellington's testimony to show that the experiments of July 2012 are reported in the 5 October 2012 manuscript show an actual reduction to practice of each and every element of the half of Count 1 that recites claim 18 of Broad patent 8,697,359. (*See* Broad Motion 5, Paper 2118, 24:17–20, citing Ellington Decl., Ex. 3430, Charts A and B.) Dr. Ellington testifies that the description of Figure 2(A) in the manuscript meets the element of an engineered, programmable, non-naturally occurring Type II CRISPR-Cas9 system. (*See* Ellington Decl., Ex. 3420, 62, 67, 85, Chart A.) Dr. Ellington explains that

Figure 2(A) provides a schematic diagram of a vector that can be programmed to target multiple genomic loci by driving the expression of a synthetic crRNA-tracrRNA chimera (chimeric RNA), having a 20-bp guide sequence corresponding to the protospacer in the genomic target site, as well as a SpCas9, which do not naturally occur together. (*See id.*)

Dr. Ellington also cites to Figure 2B of the 5 October 2012 manuscript, specifically the results provided for targeting of the mTH gene as evidence that the inventors' work meets the element of a CRISPR-Cas9 system with a chimeric RNA and Cas9 protein that achieve "targeting and hybridizing to a target sequence of a DNA molecule." (*See* Ellington Decl., Ex. 3430, 69, Chart A.) Dr. Ellington quotes the language of the manuscript: "Schematic showing guide sequences targeting the human EMX1, PV ALB, and mouse Th loci as well as their predicted secondary structures." (*Id.*)

Dr. Ellington cites further to the use of HEK 293FT or N2A cells in the manuscript as evidence of the inventors' reduction to practice of a CRISPR-Cas9 system as recited in Count 1 in a eukaryotic cell. (*See id.* at 74, citing Ex. 3564, October 5, 2012 manuscript, Ex. 3564, 20.) In support of the element of the Cas9 protein cleaving the DNA molecule of a gene expressed in a eukaryotic cell and altering expression of at least one gene product, Dr. Ellington again cites to the statement in the 5 October 2012 manuscript that:

> We then explored the generalizability of CRISPR-mediated cleavage in eukaryotic cells by targeting additional genomic loci in both human and mouse cells by designing chimeric RNA targeting multiple sites in the human . . . as well as the mouse Th loci. We achieved 6.3% and 0.75% modification rate for the human PVALB and mouse Th loci

respectively.

(Ellington Decl., Ex. 3430, 80, 83, Chart A, quoting 5 October 2012 manuscript, Ex. 3564, 5.) Dr. Ellington cites further to the statement in the manuscript that "[t]he modification efficiency of each target site is indicated below the RNA secondary structure drawing" in support of the element of the Cas9 protein cleaving DNA molecules. (Ellington Decl., Ex. 3430, 80, 83, Chart A, quoting 5 October 2012 manuscript, Ex. 3564, 12.) And Dr. Ellington cites to Table 1 of the 5 October 2012 manuscript, which reports the results of gene targeting with two different species of Cas9 protein, in three different genes, representing mouse and human, with indel % ranging from 0.75 to 6.4. (*See* Ellington Decl., Ex. 3430, 84, Chart A, quoting 5 October 2012 manuscript, 18, Table 1.)

Dr. Ellington provides similar testimony regarding the half of Count 1 that recites claim 156 of CVC application 15/981,807. (*See* Ellington Decl., Ex. 3430, 93, 94, 99, 101, 109, 111, Chart B.)

CVC does not put forth an argument, or direct us to evidence to support an argument, that the 5 October 2012 manuscript prepared by the CVC inventors fails to memorialize an actual reduction to practice of each and every element of Count 1 as of that date.[10] Nor does CVC put forth an argument, or direct us to

[10] CVC denies Broad's statements of material fact ("SMFs") regarding the 5 October 2012 manuscript, but fails to explain why or cite evidence to the contrary in its opposition. (*See* CVC Opp. 5, Paper 2567, Appendix 2-11, response to Broad SMF 53 ("Dr. Zhang also reported his successful results with his hSpCas9 system in the October 5, 2012 Manuscript submitted to Science. . . .

evidence in support of an argument that the 5 October 2012 manuscript does not represent experiments performed by the Broad inventors. In the absence of such arguments, we are not persuaded that any deficiencies CVC asserts regarding Broad's evidence of reductions to practice before 5 October 2012, for example in July, negate the evidence of the submitted manuscript as representing an actual reduction to practice by the Broad inventors by 5 October 2012. (*See* CVC Opp. 5, Paper 2569, 44:6–51:20.) As Broad argues, the manuscript itself is corroboration that the Broad inventors performed the experiments reported therein and appreciated the results and the reviewers' comments indicate that the experiments were conducted at least to standards acceptable to those of ordinary skill in the art. Because Broad presents persuasive evidence that the 5 October 2012 manuscript memorializes each and every element of a system and eukaryotic cell as recited in Count 1, which CVC does not dispute, we are persuaded that it is sufficient evidence of an actual reduction to practice by the Broad inventors.

B.

CVC opposes Broad's motion for priority, in general, on the asserted basis that the CVC inventors derived the system of Count 1 entirely from CVC.[11] (*See* CVC Opp. 5, Paper 2567, 1:2–3.)

To prove derivation a party must "establish prior conception of the claimed

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Response: Denied."); *see also id.* at Appendix 2-11 – 2-14, responses to Broad SMFs 54, 55, 65–69.)

[11] Broad argues that CVC's arguments are untimely and improper because they should have been presented as a substantive motion for judgment under 35 U.S.C. § 102(f). (*See* Broad Reply 5, Paper 2745, 1:10–13, 8:20–10:9.) Whether or not

subject matter and communication of the conception to the adverse claimant." *Price v. Symsek,* 988 F.2d 1187, 1190 (Fed. Cir. 1993) (explaining that although the ultimate question of whether a patentee derived an invention from another is one of fact, the determination of whether there was a prior conception is a question of law, which is based upon subsidiary factual findings). "Communication of a complete conception must be sufficient to enable one of ordinary skill in the art to construct and successfully operate the invention." *See Hedgewick v. Akers*, 497 F.2d 905, 908 (CCPA 1974). Thus, to prove derivation, CVC must first establish that its inventors conceived of the claimed subject matter before the Broad inventors.

In its Opposition, CVC argues that its inventors conceived of the invention of Count 1 before Broad's asserted conception date of 26 June 2012 and that Drs.

CVC's derivation argument was properly presented as an opposition, CVC bears the burden of proving its elements. We note that CVC mischaracterizes the Board's Memorandum of 25 March 2021, by stating "the PTAB instructed CVC not to file a separate motion." (CVC Reply 2, Paper 2744, 28:23–24.) Instead, when asked whether CVC should raise its derivation allegations in a separate motion, the Board "offer[ed] no opinion" and directed CVC to the Interference Rules and Standing Order for guidance. (*See* Memorandum, Paper 2474.) The Board also noted that because the schedule was well underway, a request to file a motion would likely have been denied. (*See id.*) The Memorandum did not indicate that derivation is properly raised in an opposition if, as Broad argues, the facts on which the allegation is based were known when the parties had an opportunity to seek authorization for proposed motions at the outset of the interference. (*See* Broad Reply 5, Paper 2745, 9:23–10:9; *see* Junior Party List of Intended Motions, Paper 19 (not requesting or mentioning a motion for derivation).)

Doudna and Charpentier received the Nobel Prize for their work. (*See* CVC Opp. 5, Paper 2567, 1:7–14, 31:9–33:11.) In support of this earlier date of conception, CVC refers to the evidence it presents in CVC Motion 2, arguing for priority, stating that "[b]y June 26 [Broad's asserted date of conception], the CVC inventors had not only filed CVC's first provisional application, but were well on their way towards an actual reduction to practice in eukaryotes . . . ." (*See* CVC Opp. 5, Paper 2567, 31:22–23.) CVC does not direct us to evidence that overcomes our determination, discussed above, that the CVC inventors encountered multiple experimental failures before they recognized any success in eukaryotic cells, even as late as mid-October 2012. CVC does not address its inventors' experimental failures in its opposition.

CVC argues that "the completeness of CVC's conception before June 26 is further confirmed by the fact that Zhang claims to have quickly and easily applied CVC's sgRNA CRISPR-Cas9 system in eukaryotic cells, once he learned of CVC's invention from Marraffini." (CVC Opp. 5, Paper 2567, 33:4–7; *see also* 6:1–22.) As explained above, though, neither conception nor reduction to practice can be established *nunc pro tunc*. *See Hitzeman*, 243 F.3d at 1358–59; *see also Cooper*, 154 F.3d at 1331. Regardless of any success by the Broad inventors, the preponderance of the evidence presented by the parties demonstrates that the CVC inventors' experimental failures reveal uncertainty undermining a definite and permanent idea of an sgRNA CRISPR-Cas9 system that edits or cleaves DNA in a eukaryotic cell. CVC attempts to shift our focus to the activities of other, competing inventors, rather than on the activities of its own inventors. We are not

persuaded that these other activities are evidence of the CVC inventors' ideas or of their conception.

Similarly, we are not persuaded by CVC's argument that because the Broad inventors were able to reduce to practice an embodiment of Count 1 "quickly and easily," the CVC inventors had a complete conception. (*See* CVC Opp. 5, Paper 2567, 6:1–6:12.) The Broad inventors' activities and ideas do not inure to CVC, at least because CVC never submitted anything to the Broad inventors for testing. *See Genentech, Inc. v. Chiro Corp.*, 220 F.3d 1345, 1353 (Fed. Cir. 2000) (inurement requires at least (1) conception by the inventor, (2) expectation of success by the inventor, and (3) "the inventor must have submitted the embodiment for testing for the intended purpose of the invention."). None of the facts presented by either party indicates that the CVC and Broad inventors worked together on a eukaryotic CRISPR-Cas9 system and CVC raises derivation only as an opposition to Broad's priority motion. *See Applegate v. Scherer*, 332 F.2d 571, 573 (CCPA 1964) ("An originality or derivation case . . . is quite unlike a case involving independent invention, between whom true priority must be decided.").

CVC cites to *Applegate* to argue that a party who identifies a compound, not the party who tested it and showed that it worked, is the inventor. (*See* CVC Opp. 2, Paper 2567, 4:5–16; 34:20–35:23.) CVC argues that under *Applegate*, there is no rule requiring proof that a biological invention works before there can be conception. (*See id.*) We agree. We disagree, though, that *Applegate* is otherwise informative in light of the facts before us. There is no issue in *Applegate* of whether Scherer fully conceived of the subject matter of the count because the evidence shows he named the compound of interest, he asked Scherer to test it for

its intended purpose, and Scherer obtained the results in the normal course of testing. *See id.* at 572–73. Unlike the facts before us, *Applegate* does not address repeated experimental failures and their effect on a determination of conception or derivation.

Furthermore, we also decline to accept CVC's argument that the Broad inventors contributed nothing to the invention of Count 1. (*See* CVC Opp. 5, Paper 2567, 6:23 ("The record shows that Zhang contributed *none* of the elements of Count 1."). Broad raises technical reasons why the Broad inventors had success when other eukaryotic CRISPR-Cas9 systems failed. (*See, e.g.,* Broad Opp. 2, Paper 2569, 36:18–37:14 (arguing that Dr. Zhang chose to use a U6 promoter that would produce a tracrRNA in eukaryotic cells that was four nucleotides longer than the tracrRNA the CVC inventors in their *in vitro* experiments); *see* Broad Motion 5, Paper 2118, 12:4–9.) Although CVC fails to dispute the difference between these technical details of the parties' systems, we need not make a determination on the merits of Broad's arguments because CVC's failures before Broad's success by 5 October 2012 indicate there must have been differences.

According to CVC, any technical aspects of Broad's system were merely routine techniques used by those of ordinary skill and were not inventive. (*See* CVC Opp. 5, Paper 2567, 20:20–22:10.) CVC argues further that any choices made by Dr. Zhang, such as choice of promoter, codon optimization, addition of nuclear localization signals, are not recited in Count 1 and are not required for reduction to practice. (*See* CVC Opp. 5, Paper 2567, 22:11–30:15.) CVC's argument discredits the limitation in Count 1 of a *functional* fused or covalently linked RNA CRISPR-Cas9 system in eukaryotic cells that alters the expression of

at least one gene product, cleaves or edits a target DNA molecule, or modulates transcription of a one gene encoded by the target DNA molecule. (*See* Declaration, Paper 1, 13.) Although Count 1 does not recite the various technical features that are needed to obtain this function, conception and reduction to practice require any necessary technical features. Therefore, we disagree with CVC that the determination of the necessary technical features of a system are irrelevant to conception or reduction to practice, even if each feature, in isolation, was known to those of ordinary skill. We disagree that the Broad inventors' ideas of the necessary features of a functional eukaryotic system as recited in Count 1 are irrelevant to a determination of priority.

Even if CVC invented a generalized sgRNA CRISPR-Cas9 system, for which they hold numerous patents undisputed in this proceeding (*see* CVC Opp. 5, Paper 2657, 37:4–6; *see* Broad Reply 5, Paper 2745, 3:18–19), and they had an intention and hope that a CRISPR-Cas9 system would work in eukaryotic cells (*see* CVC Opp. 5, Paper 2657, 10:1–18:17), we are not persuaded that the determination of technical features necessary to achieve success is irrelevant. Instead, determination of those features indicated that the Broad inventors had a definite and permanent idea of a system in eukaryotic cells, which lead them to an actual reduction to practice earlier than the CVC inventors.

CVC argues that even if the Broad inventors contributed the "eukaryotic aspect of Count 1 . . . Zhang cannot be an inventor of Count 1 because the eukaryotic element is just one of several features, including the sgRNA feature." (CVC Opp. 5, Paper 2567, 5:1–7.) According to CVC, to win an interference, a party must have invented the entire invention as embodied in the combination of

elements recited in the count. (*See id.* at 5:7–11.) CVC cites to *Alexander v. Williams*, 342 F.2d 466, 468 (CCPA 1965), where Bendix inventors were found to have not conceived of the entire count when it had been disclosed to them by General Electric inventors. (*See* CVC Opp. 5, Paper 2567, 5:1–11; 36:9–23.)

We do not see how this case or argument benefits CVC because even though the Broad inventors learned of a guide RNA comprising a guide sequence fused to a tracr sequence from a public presentation given by CVC inventors in June 2012 (*see* CVC Opp. 5, Paper 2567, 1:7–13; *see* Marraffini Depo., Ex. 5262, 38:4–10 (confirming that the linker sequence Dr. Marraffini disclosed to Dr. Zhang was presented publicly by the CVC inventors)), the CVC inventors had only used this system *in vitro* at the time.

Given the subsequent failures and lack of a clear plan by the CVC inventors to achieve a functional CRISPR-Cas9 system in eukaryotic cells, it is not clear to us why CVC now emphasizes the need to have conceived of the entire count to prevail on priority. (*See* Broad Reply 5, Paper 2745, 24:1–17.) Unlike the facts of *Alexander*, and as explained above, we determine that to show conception of Count 1 a party must show conception of the count element of a CRISPR-Cas9 system that achieves cleavage or editing of a gene to alter expression from a gene in a eukaryotic cell. *Compare Alexander*, 342 F.2d at 470–71 (finding that the count element of mounting cams on a common shaft was not "the essence of the invention" and was the losing party's only contribution). Because we find that the CVC inventors did not conceive of every element of Count 1 on 1 March 2012, we are not persuaded that the CVC inventors could have divulged the complete subject matter of Count 1 to the Broad inventors. *Contra Alexander*, 342 F.2d at 468

("One undisputed fact of great significance, we think, is that the General Electric inventors were the first to conceive the invention defined by the count."), *see also id.* at 471 ("In this case Bendix had not even rendered partial aid since the General Electric inventors had first conceived every element of the count.").

CVC's arguments and evidence presented in its opposition to Broad Motion 5 do not persuade us that its inventors had a complete conception of the invention of Count 1 prior to 5 October 2012 – the date that we are persuaded the Broad inventors achieved a reduction to practice of the invention of Count 1. Without a prior conception, CVC's argument that Broad derived the system recited in Count 1 entirely from CVC fails.

C.

Broad has persuaded us that its inventors achieved an actual reduction to practice of an embodiment of Count 1 by 5 October 2012. CVC has failed to persuade us that its inventors achieved either an actual reduction practice or a complete conception of an embodiment of Count 1 before that date. CVC also fails to persuade us that Broad derived the invention of Count 1 from the CVC inventors.

Accordingly, we GRANT Broad Motion 5.

Judgement against CVC will be entered separately.

IV. CVC Motion for Incorrect Inventorship – CVC Motion 3

CVC argues that judgement should be entered against Broad because all of Broad's involved patents and applications are invalid under 35 U.S.C. § 102(f) for failure to name all of the correct inventors. (*See* CVC Motion 3, Paper 1558.) A

determination of inventorship requires two steps performed as a claim-by-claim analysis: first a construction of each asserted claim to determine the subject matter encompassed and then a comparison of the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to determine whether the correct inventors were named. *See Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1302 (Fed. Cir. 2002). We look to the sufficiency of CVC's evidence in support of its argument that the contributions of the named inventors on Broad's patents and applications does not match the scope and content of the subject matter claimed.

CVC's arguments are ultimately based on a sworn declaration prepared by Thomas J. Kowalski (the "Kowalski Decl.," Ex. 4295), Broad's former prosecuting patent attorney, in an opposition proceeding in the European Patent Office regarding inventorship of PCT application claims. (*See* CVC Motion 3, Paper 1558, 2:17–3:3.) The declaration provides a list of named individuals and their alleged contributions. (*See* Kowalski Decl., Ex. 4295, ¶ 16.) The declaration refers in general to patent applications filed by Broad, but does not provide an analysis of individual claims and does not list or discuss Broad's currently involved patents or applications. (*See* Kowalski Decl., Ex. 4295, ¶ 14.)

CVC provides Chart 1, which lists PCT application claim language allegedly corresponding to reported inventive contributions, as well as CVC's interpretation of the "corresponding representative claim language in Broad's involved U.S. patents or application." (*See* CVC Motion 3, Paper 1558, 4:9–5:2.) Neither Chart 1, not specific claim phrases, appear in the Kowalski Declaration.

CVC argues that the inventors named on Broad's involved patents and application is inconsistent with Mr. Kowalski's findings. (*See* CVC Motion 3, Paper 1558, 6:11–9:2.) CVC provides Chart 2, which lists Broad's involved patents and application and the individuals who CVC asserts should have been named. (*See id.* at 7:3–9:2.)

We are not persuaded that the Kowalski Declaration is sufficient evidence that Broad's involved patents and applications incorrectly name inventors because CVC never compares the alleged contributions of the people named in Kowalski declaration with Broad's involved patent and application claims, as properly interpreted. CVC repeatedly notes that Broad's PCT application and Broad's involved patents and application claim priority to the same original provisional application and, thus, "originate from a common source." (*See* CVC Motion 3, Paper 1558, 6:12–14, 11:14–16, *see also id.* at 12:12–13, 13:6–7, 13:22–23.) To the extent CVC is asserting that the Kowalski Declaration is relevant to Broad's involved claims, this argument is unpersuasive. Claiming benefit to the same provisional application says nothing about what is claimed in later applications. Broad's involved patents and application may claim different inventions from the PCT applications, regardless of their lineages. Without an actual analysis of Broad's involved claims and the alleged contributions of each asserted co-inventor, CVC's argument is completely unpersuasive.

Furthermore, neither CVC nor the Kowalski Declaration provides a detailed explanation of the contributions done by the people named. Mr. Kowalski testifies that he "review[ed] the claims as a statement of inventive concepts disclosed in the application and for a provisional application the subject matter in the disclosure

(and claims, if present)." (*See* Kowalski Decl., Ex. 4295, ¶ 5.) Mr. Kowalski then states that he conducted interviews and "invite[d] the individual to provide any additional information, e.g., additional documents, that support his contribution to the invention or inventions." (*Id.* at ¶ 9.) Mr. Kowalski concludes that he assessed all of the information, considering "the nature of the invention, e.g., whether the invention requires simultaneous conception and reduction to practice and the state of the prior art, and who did what when." (*Id.* at ¶ 10.) But none of this information is included in the declaration. The declaration includes only brief conclusions, of no more than a sentence, indicating to which inventions the named individuals "contributed in a not insubstantial manner. . . ." (*See id*. at ¶ 16.)

For example, the declaration states that Dr. Cong and Randall Platt contributed to "CRISPR-Cas9 system adapted in for uses in eukaryotic cells," but that Patrick Hsu, Fei Ran, and Shuailiang Lin, contributed to "the CRISPR-Cas9 system for *certain* uses in eukaryotic cells." (Kowalski Decl., Ex. 4295, ¶ 16 (emphasis added).) Mr. Kowalski did not provide an explanation of the difference between "uses in a eukaryotic cell" and "*certain* uses in a eukaryotic cell," if there is any difference. He provided no more substantive information beyond the short phrases and did not compare these contributions to any specific claim language.

CVC acknowledges this lack of information for at least some of the people identified by Mr. Kowalski, stating: "The declaration does not specify precisely to which systems and methods of use in eukaryotes Ran, Hsu, and Lin contributed, but, in the absence of clarification, it is reasonable to assume that whatever aspects they did contribute are reflected in the claims of PCT/US2013/074611." (CVC Motion 3, Paper 1558, 10:22–25.) We decline to adopt the CVC attorney's

assumptions. Furthermore, we do not find CVC's arguments to be persuasive of any contribution regarding Broad's currently involved patent and application claims.

CVC cites to the testimony of Scott Bailey, Ph.D., to support its argument that a skilled artisan would have found that inventive contribution by Platt, Cong, Ran, Hsu, and Lin, as identified in the Kowalski Declaration and claimed in Broad's application PCT/US2013/074611, is also claimed in Broad's involved patents and application. (*See* CVC Motion 3, Paper 1558, 11:1–4, citing Bailey Decl., Ex. 4341, ¶¶ 30-35.) Dr. Bailey is an Associate Professor in the Department of Biochemistry and Molecular Biology at Johns Hopkins Bloomberg School of Public Health. (*See* Bailey Decl., Ex. 4341, ¶ 9.) Dr. Bailey does not testify to any particular expertise in patent law, instead applying "U.S. legal principles that have been provided to me by counsel." (Bailey Decl., Ex. 4341, ¶ 17.) In fact, Dr. Bailey has never done an inventorship analysis. (*See* Bailey Depo, Ex. 6208, 18:7–11 ("Q. Have you ever conducted an inventorship analysis for purposes of patents or applications filed in the United States Patent and Trademark Office? A. I have not."), *see* Broad Opp. 3, Paper 2475, 18:3–23.) We do not find Dr. Bailey to be qualified to testify about the legal aspects of inventorship. Thus, we give his conclusions little weight. His testimony is, though, that he works in the field of molecular mechanisms of CRISPR systems, and his publications and grants support this. (*See* Bailey Decl., Ex. 4341, ¶ 14; *see* Bailey *Curriculum Vitae*, Ex. 4342.) Thus, to the extent he testifies about what one of skill in the art would have understood at the time, we find him qualified.

Dr. Bailey's testimony highlights the vagueness of the Kowalski Declaration. Dr. Bailey testifies that Mr. Kowalski determined that "Ran, Hsu, and Lin made inventive contributions to 'certain' uses of or methods of using the CRISPR-Cas9 systems in eukaryotic cells, although he [presumably Mr. Kowalski] does not specify what 'certain' means." (Bailey Decl., Ex. 4341, ¶ 31.) According to Dr. Bailey, "it is reasonable to assume that whatever aspects Ran, Hsu, and Lin did contribute are reflected in the claims of [the PCT application], which do not recite specific uses that are distinct from the basic use of CRISPR-Cas9 systems in eukaryotic cells." (Bailey Decl., Ex. 4342, ¶ 31.) Thus, even though Dr. Bailey does not understand Mr. Kowalski's conclusions, he accepts that Ran, Hsu, and Lin are inventors of uses of CRISPR-Cas9 systems in eukaryotic cells.

Dr. Bailey continues, testifying that "the contributions regarding the use of CRISPR-Cas9 systems in eukaryotic cells, as identified in the Kowalski Declaration and claimed in [PCT application], are also claimed in the involved Broad patents and application." (Bailey Decl., Ex. 4341, ¶ 33.) To come to this conclusion, Dr. Bailey provides a chart listing "Inventive Contributions According to Kowalski Declaration," being "in eukaryotic cells," and matches this phrase to claim language in Broad's involved claims that refers to eukaryotic cells. (Bailey Decl., Ex. 4341, ¶ 33.)

Dr. Bailey concludes:

> as a technical matter, I view the claims of the [the PCT application] and claims of the involved Broad patents and application as being directed to the same invention, even if they use different words. So, if Mr. Kowalski is correct that Platt, Cong, Ran, Hsu, and Lin "contributed in a not insubstantial manner" to the subject matter claimed in [the PCT application],

> they must necessarily also have "contributed in a not insubstantial manner" to the subject matter claimed in the above-listed involved Broad patents and application.

(Bailey Decl., Ex. 4341, ¶ 35.) CVC argues that it "presented the—now unrebutted—testimony of its scientific expert, Dr. Bailey, that those same technical contributions Kowalski identified are recited in the claims of the Broad's involved patents and application." (CVC Reply 3, Paper 2743, 1:10–12.)

Because Dr. Bailey testifies that he is not certain of the technical contributions Mr. Kowalski identified, beyond the short phrases Mr. Kowalski used, and because Dr. Bailey merely matches words in Broad's involved claims, we are not persuaded that his testimony indicates anything about the contributions of the named people or Broad's claims or what one of ordinary skill would have understood about them. Neither Dr. Bailey nor CVC explains, for example, how the "certain uses in eukaryotic cells" referred to by Mr. Kowalski compare to the scope of Broad's involved claims.

Dr. Bailey's testimony, to the extent he is qualified to give it, is unpersuasive because it is not supported by any explanation or reasoning other than a blind acceptance of the vague conclusions in the Kowalski Declaration and a comparison to isolated phrases in Broad's involved claims. Furthermore, the Kowalski Declaration does not refer to or provide an analysis of Broad's involved patent or application claims. Thus, we give little to no weight to either Dr. Bailey's testimony or the Kowalski Declaration in regard to the inventorship of Broad's currently involved claims having the phrase "eukaryotic cells."

The Kowalski Declaration is similarly unpersuasive regarding the phrases "co-delivery to the nucleus," "*in vivo* applications," and "ortholog design." (Kowalski Decl., Ex. 4295, ¶ 16; *see* CVC Motion 3, Paper 1558, 11:18–13:24.) Mr. Kowalski provided no more substantive information beyond these short phrases and did not compare these contributions to any specific claim language. Again, there is no discussion of Broad's involved claims or even of the specific claim language of the PCT applications to which Mr. Kowalski refers. Dr. Bailey again provides only a blind acceptance of the vague conclusions in the Kowalski Declaration and a comparison to isolated phrases in Broad's involved claims. (*See* Bailey Decl., Ex. 4341, ¶¶ 37–54.) Neither Mr. Kowalski nor Dr. Bailey provide an actual analysis of what the named individuals did and how those contributions contribute to subject matter within the scope of Broad's involved claims as properly interpreted.

CVC argues that Broad does not present evidence or information to respond substantively to CVC's arguments and does not explain why it did not identify the people named in the Kowalski Declaration as inventors. (*See* CVC Reply 3, Paper 2743, 1:21–2:1.) Broad need not do so because CVC carries the burden of proving the inventorship of Broad's patents and applications is incorrect. *See* 37 C.F.R. § 41.208(b) ("To be sufficient, a motion must provide a showing, supported with appropriate evidence, such that, if unrebutted, it would justify the relief sought. The burden of proof is on the movant."). CVC fails to do so.

CVC argues that because Mr. Kowalski was Broad's own attorney and he provided sworn testimony "based on subject matter—and not on a claim-by-claim basis," on which Broad previously relied in European opposition proceedings,

Broad cannot argue that the analysis is insufficient and must be bound by it here. (*See* CVC Reply 3, Paper 2743, 5:11–19.) CVC argues further that Mr. Kowalski's Declaration is an admission that can be used against Broad in this proceeding. (*See id.* at 6:20–9:23.) These arguments are unpersuasive because the Kowalski Declaration does not persuade us that the findings therein are necessarily relevant to Broad's involved claims. CVC argues that Dr. Bailey's analysis determined that the "relevant claims as a whole" recite the same features as the claim language and specification disclosure of the relevant PCT applications, but as explained above, we find Dr. Bailey's analysis to be insufficient because he merely matched words in Mr. Kowalski's determinations with the words in Broad's currently involved claims. (CVC Reply 3, Paper 2743, 12–23.) Neither Dr. Bailey nor CVC provides an analysis of Broad's involved claims, beyond the recitation of some words. Thus, their declarations do not provide us with sufficient evidence of who invented Broad's involved claims.

Patent issuance creates a presumption that the named inventors are the true and only inventors. *See Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998). CVC's burden is to overcome this presumption with sufficient evidence. CVC fails to meet its burden and to persuade us that we should determine any of Broad's issued patent claims, or pending application claims, are unpatentable under 35 U.S.C. § 102(f).

Accordingly, we DENY CVC Motion 3. This decision renders Broad Contingent Responsive Motion 6 moot.

V. CVC Miscellaneous Motion 7 – To Exclude Evidence

CVC requests that certain exhibits submitted by Broad be excluded. (CVC Motion 7, Paper 2789.) Specifically, CVC argues that the following declarations should be excluded: Benjamin Davies (Ex. 3435), Mark Kay (Ex. 3436), Alan Lambowith (Ex. 3437); Paul Simons (Exs. 3438 and 3440); Erez Lieberman Aidan (Ex. 3439), Greg Hannon (Ex. 3441 and 3442), Mark Isalan (Ex. 3443), Caixao Gao (Ex. 3446); Adam Bogdanove (Ex. 3449), Thierry VandenDriessche (Ex. 3450), Bryan Cullen (Ex. 3451), Paula Cannon (Ex. 3452), portions of the Third Declaration of Ronald Breaker (Ex. 3448). (*See id.* at 1:19–2:22.) CVC asserts that either the declarants were not made available for cross-examination or the declarations contain statements of in admissible hearsay. (*See id.* at 3:5—9:12.)

We do not rely on any of these declarations to reach our decisions. Thus, CVC's request is moot.

CVC also asserts that Exhibits 3681, 6107, and 6116 should be excluded because they are third party books and are inadmissible hearsay. (*See id.* at 9:15–10:23.) Again, we do not rely on any of these exhibits to reach our decisions. Thus, this request is also moot.

Accordingly, we DISMISS CVC's motion to exclude evidence.

VI. Broad Miscellaneous Motion 9 – To Exclude Evidence

Broad requests that portions of the re-direct testimony of Dr. Phillip Zamore should be excluded as being outside the scope of cross examination. (*See* Broad Motion 9, Paper 2793.)

Because we deny CVC's motions and grant Broad Motion 5 without relying on Dr. Zamore's cross-examination, Broad's request is moot.

Accordingly, we DISMISS Broad's motion to exclude.

VII. Inequitable conduct

CVC asserts inequitable conduct during prosecution of the applications that became the involved Broad patents and requests authorization to file a motion arguing that it renders Broad's claims unpatentable. (*See* Junior Party's List of Intended Motions, Paper 19, 15:15–22:12; *see* CVC's Additional Justifications Supporting Authorizing a Motion for Unpatentability Due to Inequitable Conduct, Paper 2856, 1:13–5:8.) Specifically, CVC asserts that Dr. Zhang made affirmative material misstatements during prosecution of the applications that became Broad's involved patents and applications by submitting allegedly false declarations. (*See id.*)

Under the circumstances of this case, we decline to take up CVC's arguments of inequitable conduct because they are not directly related to the issue of priority for the subject matter of the current count. CVC filed claims that provoked an interference, a proceeding primarily to determine priority between parties. Our mandate is to determine priority, whereas determinations of unpatentability for other reasons is discretionary. *See* 35 U.S.C. § 135(a) ("The

Board of Patent Appeals and Interferences shall determine questions of priority of the inventions and may determine questions of patentability.").

CVC has had an opportunity to oppose any facts presented by Broad in this proceeding with contrary evidence. Thus, if the facts CVC asserts regarding inequitable conduct are related to Broad's priority case, CVC has had an opportunity to present them. CVC does not allege any inequitable conduct by counsel for Broad or any of Broad's named inventors during this proceeding. Instead, CVC's basis for asserting inequitable conduct would seek to cancel Broad's claims for reasons unrelated to Broad's arguments for priority. Accordingly, in this proceeding, we exercise our discretion to decline to consider issues that are not related to priority.

No further motions are authorized.

VIII. Conclusion

We deny CVC Motion 2 for judgment based on priority.

We deny CVC Motion 3 for judgment based on improper inventorship.

We grant Broad Motion 5 for judgment based on priority.

We dismiss as moot Broad Motion 6 for correction of inventorship.

We dismiss as moot CVC Motion 7 to exclude evidence.

We dismiss as moot Broad Motion 9 to exclude evidence.

We enter judgment separately in accordance with these decisions.

Interference 106,115

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Interference 106,115

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APPENDIX C

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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)

Judgment
37 C.F.R. § 41.127(a)

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

KATZ, *Administrative Patent Judge.*

In the Decision on Priority issued concurrently, we deny Motion 2 filed by The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier ("CVC") (Paper 1579) and grant Motion 5 filed by The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College ("Broad") (Paper 2118), both seeing seeking judgment based on priority under 35 U.S.C. § 102(g).[1] (*See* Paper 2863.) We also deny Motion 3 filed by CVC (Paper 1558), seeking judgment based on improper inventorship named on Broad's involved patents and application. (*See id.*)

According, it is

ORDERED that judgment on priority is entered against CVC as to Count 1, the sole count of the interference (*see* Redeclaration, Paper 23, 11:30–13:12);

FURTHER ORDERED that the following claims of CVC are finally refused:

Application 15/947,680 – Claims 156–185;

Application 15/947,700 – Claims 156–185;

Application 15/947,718 – Claims 156–185;

Application 15/981,807 – Claims 156–185;

Application 15/981,808 – Claims 156–170 and 172–185;

Application 15/981,809 – Claims 156–170 and 172–185;

Application 16/136,159 – Claims 156–184;

Application 16/136,165 – Claims 156–184;

[1] 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).

Application 16/136,168 – Claims 156–184;
Application 16/136,175 – Claims 156–184;
Application 16/276,361 – Claims 3–31;
Application 16/276,365 – Claims 3–32;
Application 16/276,368 – Claims 3–31;
Application 16/276,374 – Claims 3–32.

(*See* 35 U.S.C. § 135(a); *see* Redeclaration, Paper 23, 13:16–14:9.)

FURTHER ORDERED that the parties are directed to 35 USC § 135(c) and 37 C.F.R. § 41.205 regarding the filing of settlement agreements;

FURTHER ORDERED that a party seeking judicial review timely serve notice on the Director of the United States Patent and Trademark Office; 37 C.F.R. §§ 90.1 and 104.2. See also 37 C.F.R. § 41.8(b);[2] and

FURTHER ORDERED that a copy of this judgment be entered into the administrative records of CVC 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; and Broad 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.

[2] Attention is directed to *Biogen Idec MA, Inc., v. Japanese Foundation for Cancer Research*, 785 F.3d 648, 654–57 (Fed. Cir. 2015) (determining that pre-AIA § 146 review was eliminated for interference proceedings declared after 5 September 2012).

Interference 106,115

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