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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE,
Patents 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,889,418; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; and 9,840,713; and Applications 14/704,551 and 15/330,876,

Junior Party,
v.

TOOLGEN, INC.,
Application 14/685,510,

Senior Party

Patent Interference No. 106,126 (DK)

Decision – Motions
37 C.F.R. § 125(a)

Before, SALLY GARDNER LANE, DEBORAH KATZ, and RACHEL H. TOWNSEND, *Administrative Patent Judge.*

KATZ, *Administrative Patent Judge*.

I. Introduction

This interference was declared between Junior Party, The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College ("Broad"), and Senior Party, ToolGen, Inc. ("ToolGen"), to determine priority under 35 U.S.C. § 102(g)[1] of invention of the subject matter recited in Count 1. (*See* Declaration, Paper 1.) Count 1 is directed to CRISPR-Cas9 systems, which are a combination of protein and ribonucleic acid ("RNA") that can alter a targeted genetic sequence of an organism.

Several other interferences have been declared regarding similar subject matter and naming Broad as a party. Most recently, the same Broad claims involved in the current interference were involved in an interference with The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier ("CVC"). CVC's claims were held to be unpatentable under 35 U.S.C. § 102(g), and finally refused in that proceeding after a priority contest. (*See* Interference 106,115, Papers, 2863, 2864.) CVC has appealed that decision and judgment to the Federal Circuit and the appeal is currently pending. (*See* Interference 106,115, Paper 2866.) Broad has cross-appealed on certain issues. (*See id.*, Paper 2867.) That interference involves a count very similar to Count 1 of this proceeding – reciting the same Broad patent 8,697,359, claim 18, included in Count 1 of this proceeding. (*See id.,* Paper 1.)

[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).

The judgment in Interference 106,115 is final as to our tribunal. Even though legal conclusions that we made in that proceeding could be reversed by the Federal Circuit and remanded to us for further consideration, which might ultimately lead to Broad's claims being held to be unpatentable under 35 U.S.C. § 102(g), that hypothetical result has yet to come to pass, and we continue with the current proceeding to prepare for a priority contest by deciding issues newly presented in the parties' preliminary motions. Doing so is in the interests of efficiency. *See* 37 C.F.R. § 41.1(b) ("The provisions of Part 41 shall be construed to secure the just, speedy, and inexpensive resolution of every proceeding before the Board.")

In addition to Interference 106,115, Broad is also involved in Interference 106,133, which has a count similar to Count 1 of this proceeding. Broad is Junior Party and Sigma-Aldrich Co., LLC, is senior party in that proceeding. (*See* Interference 106,133, Paper 1.)

ToolGen is involved in Interference 106,127, again with a count similar to Count 1, and with CVC as junior party. (*See* Interference 106,127, Paper 1.)

Preliminary motions in an interference 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. 13 § 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.").

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

a motion to change the count (Broad Motion 1, Paper 72), which we deny;

a contingent motion to have additional claims designated as corresponding to the count (Broad Motion 2, Paper 70), which we dismiss; and

a motion to designate claims as not corresponding to the count (Broad Motion 3, Paper 73), which we deny.

ToolGen has filed a substantive motion for accorded benefit (ToolGen Motion 1, Paper 31), which we dismiss as being moot.

ToolGen also filed a miscellaneous motions to exclude evidence relied upon by Broad, which we dismiss as being moot. (*See* ToolGen Misc. Motion 1, Paper 349.)

We take up these motions in the order that secures a just, speedy, and inexpensive determination of the proceeding. *See* 37 C.F.R. 17 § 41.125(a).

II. Broad Motion 1 – To Substitute Proposed Count 2

Broad argues that Count 1 in this proceeding should be replaced with Proposed Count 2, which is broader than Count 1, encompassing dual and single-molecule RNA configurations. (*See* Broad Motion 1, Paper 72, 1:2–5.) We are not persuaded that Broad has met its burden of proof and should be granted the

relief sought. *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.").

Broad's Proposed Count 2 recites Broad application 15/160,710, claim 1 or ToolGen application 14/685,510, claim 85. (*See* Broad Motion 1, Paper 72, 3:17–20.) ToolGen application 14/685,510, claim 85 is the same as the ToolGen part of Count 1, and thus does not change the scope of the count as being limited to "a chimeric guide RNA comprising a CRISPR RNA (crRNA) portion and a transactivating crRNA (tracrRNA) portion." (*See* Declaration, Paper 1, 12–13.)

Broad argues that "[t]he the only substantive difference between Count 1 and Proposed Count 2 is that Proposed Count 2 is not limited to single-molecule RNA and is thus broader than Count 1." (Broad Motion 1, Paper 72, 24:2–4.) Broad application 15/160,710, claim 1 recites:

> An engineered CRISPR-Cas system in a eukaryotic cell having a DNA molecule, the CRISPR-Cas system comprising:
> I. a Cas9 or a nucleotide sequence encoding the Cas9, and
> II. an RNA or a nucleotide sequence encoding the RNA, the RNA comprising
> (a) *a first RNA* comprising (i) a guide sequence capable of hybridizing to a target sequence of the DNA molecule adjacent to a Protospacer Adjacent Motif (PAM) in the eukaryotic cell and (ii) a tracr mate sequence, and
> (b) *a second RNA* comprising a tracr sequence capable of hybridizing to the tracr mate sequence,
> wherein the guide sequence directs the Cas9 to the target sequence, whereby the DNA molecule is cleaved or edited in the eukaryotic cell.

(Braod Motion 1, Paper 72, 4:3–14 (emphasis added).) This claim recites two RNAs, in contrast to claim 85 of ToolGen application 14/685,510, which recites

one chimeric RNA.[2] Although Broad fails to provide a thorough analysis of the language of Proposed Count 2, ToolGen does not dispute that it is broader than Count 1 because the Broad part of Proposed Count 2 encompasses both the dual- and single-molecule RNA configurations.

ToolGen argues, instead, that Broad's Proposed Count 2 is excessively broad. (*See* ToolGen Opp. 1, Paper 276, 18:1–9:20.) ToolGen notes that Proposed Count 2 adds the words "or edited" to the Broad portion of Count 1 so that the proposed version states: "the guide sequence directs the Cas9 to the target

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[2] Claim 85 of ToolGen application 14/685,510, which is part of Count 1, recites:

> An isolated mammalian cell comprising a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system for site specific, cleavage of a double-stranded target nucleic acid sequence in the isolated mammalian cell, wherein the CRISPR/Cas system comprises:
>
> a) a nucleic acid encoding a Cas9 polypeptide, wherein the Cas9 polypeptide comprises a nuclear localization signal and wherein said nucleic acid is codon-optimized for expression in mammalian cells, and
>
> b) *a chimeric guide RNA* comprising a CRISPR RNA (crRNA) portion and a transactivating crRNA (tracrRNA) portion,
>
> wherein the target nucleic acid sequence comprises a first strand having a region complementary to the crRNA portion of the chimeric guide RNA and a second strand having a trinucleotide protospacer adjacent motif (PAM), and
>
> wherein the Cas9 polypeptide and the chimeric guide RNA form a Cas9/RNA complex in the isolated mammalian cell and mediate double stranded cleavage at the target sequence.

(Declaration, Paper 1, 12–13 (emphasis added).)

sequence, whereby the DNA molecule is cleaved ***or edited*** in the eukaryotic cell." (*See id.* at 18:10–12.) In addition, ToolGen notes that Proposed Count 2 also eliminates the phrase "expression of at least one gene product is altered" from the Broad portion. (*See id.* 19:12–14.)

Whether or not these changes are broadening, we agree with ToolGen that Broad has included differences between Count 1 and Proposed Count 2 without explaining why these changes are necessary. Broad argues in its Reply that it does not oppose modification of Proposed Count 2 to delete the term "or edit," and to add back the term "wherein expression of the at least one gene product is altered," but Broad carried the burden of persuading us the count should be changed to Proposed Count 2 in its motion. *See* 37 C.F.R. § 41(b)(2). Because we decline to make a change in the proposed count "for change's sake" we deny Broad's request on this basis alone. *See Louis v. Okada*, 59 U.S.P.Q.2d 1073, 1076 (BPAI 2001) (precedential) ("As the moving party, Sauer must demonstrate, in its preliminary motion, a genuine need to change the count, and not simply cause a change for change's sake.").

Nevertheless, we address Broad's arguments in support of its motion to substitute the count. Broad argues that Count 1 should be replaced with Proposed Count 2 because "Count 1 does not describe the full scope of the interfering subject matter and excludes Broad's best proofs." (Broad Motion 1, Paper 72, 17:12–15.) According to Broad, the "fundamental invention" at issue in this proceeding is the use of CRISPR-Cas9 in eukaryotic cells, regardless of whether a dual-molecule or single-molecule RNA is involved. (*See id.* at 17:18–18:7.) Broad argues that implementing Count 1 in a priority contest would be unjust

because it would restrict Broad from using its "best and earliest dual-molecule RNA proofs to support its proof of prior invention, while putting Broad's claims to that same generic subject matter at risk of cancellation." (*Id.* at 18:5–7; 20:12–21.)

Broad argues further that it has involved claims directed to "generic RNA eukaryotic CRISPR-Cas9 systems and methods," which are not limited to single-molecule RNA systems. (Broad Motion 1, Paper 72, 17:15–18.) In its Motion 2, which is contingent on the grant of Motion 1, Broad seeks to add more claims asserted to encompass RNA components without limitation to their configuration to the interference. (*See id.* at 13:15–14:3.)

Broad does not, though, identify any ToolGen claims involved in this proceeding that are broader than single-molecule CRISPR-Cas9 systems. (*See* Broad Reply 1, Paper 335, B-8:19–22, Response to ToolGen's Additional Material Facts ("43. ToolGen's involved claims are not generic or directed to dual-molecule RNA; the claims are limited to a single-molecule RNA configuration. Paper 1 (Declaration of Interference), 12–13. **RESPONSE**: Admitted.") Broad only argues that "ToolGen sought non-limited claims and disclosed dual-molecule RNA systems in its patent applications." (*See* Broad Motion 1, Paper 72, 15:12–13, *et seq*.) According to Broad, ToolGen is currently prosecuting "generic RNA claims," citing claim 58 of application 17/004,355. (*See id.* at 22:15–19; 17:17–18; 18:14–15.) These ToolGen claims have not been allowed and are not involved in the current interference. Instead, ToolGen confirms that its only involved claims are limited to single-molecule RNA systems. (*See* ToolGen Opp. 1, Paper 276, 4:24–5:3.) Thus, Broad cannot, and does not argue that both parties

claim subject matter outside of the scope of Count 1. (*See* ToolGen Opp. 1, Paper 276, 4:14–5:19.)

Rather, Broad's argument is that because its *own* claims and proofs are outside the scope of Count 1, the count is too narrow. According to Broad, this is unjust because it puts Broad's generic RNA invention at risk, while excluding Broad's best proofs, which are based on dual-molecule RNA systems. (*See* Broad Motion 1, Paper 72, 1:21–2:4.) Broad argues that ToolGen suffers no prejudice from Proposed Count 2 because it still includes ToolGen's claim 85 as half of the count and ToolGen can submit the same proofs to a single-molecule RNA system. (*See id.* at, 3:4–6.) But given Broad's complaint that its own generic claims could be put at risk if its dual-molecule proofs are excluded, Broad fails to explain why it would be just to put ToolGen's involved claims, limited to a single-molecule system, at risk with proofs to a dual-molecule system, unless both are the same patentable invention.

We are not persuaded that the count should be broadened as Broad argues because Broad fails to establish by a preponderance of the evidence why the single- and dual-molecule CRISPR-Cas9 systems should be included in one count. The interference rules state that a count is "the Board's description of the interfering subject matter that sets the scope of admissible proofs on priority" and require that "[w]here there is more than one count, each count must describe a patentably distinct invention." 37 C.F.R. § 41.201. Although not expressly stated, the rules indicate that a count is generally drawn to one patentable invention, where two counts can be used if the parties claim interfering subject matter that encompasses two patentable inventions.

Broad argues that "[i]t is a well-established interference practice that a party may request broadening of an interference count on the ground that it fails to describe the interfering subject matter and excludes the party's best proofs." (Broad Motion 1, Paper 72, 18:16–22.) In support Broad cites several interference cases, none of which is binding precedent. In *Grose v. Plank*, 15 USPQ2d 1338, 1342 (BPAI 1990), Plank proposed the substitution of the counts to include a limitation describing the invention in a different way than recited in the original count, facilitating earlier priority proofs. In addition, though, "Plank urged that the two alternative limitations defined the same patentable invention . . . ." Similarly, in *Kondo v. Martel*, 220 USPQ 47, 49 (BPAI 1983), Kondo requested to broaden the count to include an "additional and non-patentably distinct species" in order to provide the best proofs of priority. In the third case cited by Broad, *Nelson v. Drabek*, 212 U.S.P.Q. 98 (Comm'r 1979), no substantive decision on a motion to substitute the count was provided, merely a decision on petition for transmission of the motion to the Primary Examiner, under the interference procedures in use at that time.

Thus, although Broad is correct that counts may be substituted to allow a party to present its best proofs, Broad fails to cite support, precedential or non-precedential, that a count should be broadened to include more than one patentable invention for the purpose of allowing a party to present its best proofs. Broad fails to address the discussion in *Lee v. Mcintyre*, 55 USPQ2d 1137, 1142 (BPAI 2000), a precedential case, that

> it should be manifest to all that there is no *per se* rule that the count ultimately must be as broad as the broadest patent claim designated as

> corresponding to the count. During the course of an interference, a count may be narrowed to exclude patentable subject matter within the scope of a claim designated as corresponding to the count *where the claim is directed to more than one patentable invention*.

Id. (emphasis added). In *Lee*, the Board determined that even though the parties both disclosed the same three species, because the Examiner determined each species to be patentably distinct inventions, a count encompassing all three would allow the party who proved the earliest date of invention as to any of the species to be awarded priority as to the entire count, i.e., as to all three species. *See id.* The Board cited to the reasoning in *Godtfredsen v. Banner*, 598 F.2d 589, 592 (CCPA 1979), that "[i]t is not considered that such a result would be consonant with the primary purpose of an interference or with the intent of 35 U.S.C. 135, since there would be no determination of priority as to each of the common [patentably distinct] inventions claimed by the parties." *Lee,* 55 USPQ2d at 1142.

In the Reply Brief, Broad cites *Lee*, arguing that it is "longstanding interference practice (previously codified in 37 CFR § 1.606) that the count must be as broad as any claim designated claim of either party" corresponding to the count." (*See* Broad Reply 1, Paper 335, 7:19–8:5, citing *Lee*, 55 USPQ2d at 1142 (referring to prior rule 37 C.F.R. § 1.606).) Broad cites no corresponding current interference rule that carries forward what may have been a longstanding practice codified under 37 CFR § 1.606, i.e., that the count in the initial declaration must be equal to the full scope of a party's claims designated as corresponding to the count. Indeed, that former "practice" that "presumed, subject to a motion under Section 1.633(c)" that a claim designated as corresponding to the count did not contain

separate patentable inventions (37 C.F.R. 1.606) is not consistent with the current rules. Under the "Presumption" rules governing this interference, claims correspond to a count when the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of a claim – a one-way test. *See* 37 C.F.R. § 41.207(b)(2). A species count may anticipate a genus claim. Therefore, a generic claim that is anticipated or rendered obvious by a count is properly designated as corresponding to the count. Under the rules governing this interference, designation of claim correspondence to the count thus does not equate to a presumption that the scope of the count is equal to the full scope of the designated claims. In short, there is no presumption here that the species count is the same patentable invention as any genus claims designated as corresponding to the count.

We note that the test for whether parties' claims interfere is a different test – the two-way test, wherein one party's claim must anticipate or render obvious the other party's claim "and vice versa." 37 C.F.R. § 41.203(a); *see Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington*, 334 F.3d 1264, 1270 (Fed. Cir. 2003) ("Accordingly, we hold that the Director's interpretation of 37 C.F.R. § 1.601(n) as establishing a two-way test for determining whether two parties are claiming the "same patentable invention" is neither plainly erroneous nor inconsistent with the language of the regulation."). Thus, the determination of whether claims correspond to a count is distinct from the determination of interfering subject matter. Neither the two-way test for interference-in-fact nor the one-way test for

claim correspondence under the current rules provides a presumption that the dual- and single-molecule RNA configurations are the same patentable invention.

Broad fails to meet its burden in Motion 1 because it fails to present argument or direct us to evidence that the dual-molecule and single-molecule CRISPR-Cas9 systems are the same patentable invention. (*See* ToolGen Opp. 1, Paper 276, 1:16–4:12.) In the alternative, Broad fails to present argument or direct us to evidence that the dual-molecule and single-molecule CRISPR-Cas9 systems are separately patentable, but that broadening the count to include them both would not, somehow, result in a priority contest between separate inventions.

Broad argues that "[t]he count in this Interference should resolve the parties' dispute as to who made the breakthrough necessary to make CRISPR-Cas9 systems and methods work in a eukaryotic environment first, regardless of whether they used "dual-molecule" RNA or the analogous "single-molecule" RNA approach." (Broad Motion 1, Paper 72, 17:18–21.) But Broad does not argue that the single-molecule and dual-molecule approach are the same patentable invention.

Broad fails to address the substantive issue of the common or separate patentability of the dual- and single-molecule CRISPR-Cas9 systems in any thorough way. Broad argues that "[t]he dual-molecule and single-molecule RNA approaches are highly analogous in eukaryotic cells" (Broad Motion 1, Paper 72, 6:10–11), but this is not an argument that the different systems are the same patentable invention. Although Broad cites to publications reportedly showing similarities between the systems and testimony that they are "closely related" and "informative" of how the other operates, Broad never argues that either of the two systems is obvious over the other. (*See* Broad Motion 1, Paper 72, 6:10–7:8.)

Broad does not direct us to evidence showing how one of ordinary skill in the art[3] would have understood the factors identified in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966), and whether the factors indicate how the two systems should be evaluated under 35 U.S.C. § 103. (*See* ToolGen Opp. 1, Paper 276, 1:18–22.)

In the absence of argument, Broad leaves the determination of common or separate patentability up to the Board. Broad states:

> If the PTAB determines that single-molecule RNA eukaryotic CRISPR systems are a patentably distinct invention from generic claims that also include dual-molecule RNA eukaryotic CRISPR-Cas9 systems, the PTAB should not proceed on Count 1 with the currently designated claims. The PTAB should either grant this motion and proceed with Proposed Count 2, or designate the generic and dual-molecule RNA claims as not corresponding to Count 1 and proceed with Count 1 with only those claims explicitly limited to single-molecule RNA (*see* Broad Motion 3).

(Broad Motion 1, Paper 72, 23:10–15.) Similarly, Broad asserts: "If the Board refuses to adopt Proposed Count 2, then it must determine that dual-molecule RNA claims are separately patentable." (Broad Reply 1, Paper 335, 16:5–6.) Broad's

[3] The parties do not dispute the level of skill of the ordinary artisan in the motions review. Both Broad's and ToolGen's witnesses testify that one of ordinary skill in the art would have a broad background and strong understanding of the molecular biology and biochemistry techniques with a Ph.D. degree in a life sciences discipline and at least a one year of relevant post-doctoral experience. (*See* Seeger Decl., Ex. 2454, ¶ 30; *see* Declartion of Barry Stoddard, Ph.D., in Support of ToolGen, Ex. 1420, ¶ 19.) Therefore, we find that this characterizes the level of skill of an ordinarily skilled artisan, which is also informed by the teachings available to those in the field at the time.

argument fails to recognize that it is Broad's burden to provide a showing, supported with evidence, to justify the relief it seeks. *See* 37 C.F.R. § 41.208(b). We deny Broad's request to change the count, not because we are persuaded of any specific relationship between a single-molecule and a double-molecule RNA configuration, but because we are *not* persuaded of any such relationship. Broad has failed to persuade us that the single- and dual-molecule RNA configurations are the same patentable invention. Alternatively, Broad has failed to move to add another count directed to a dual-molecule RNA configuration, encompassing what it considers to be its best proofs, and show why such a count would be drawn to a patentably distinct invention from Count 1. *See* 37 C.F.R. § 41.201 ("Where there is more than one count, each count must describe a patentably distinct invention.").

Broad acknowledges that "[t]he Board has repeatedly recognized that it is 'not right or fair' to proceed with an interference where there are two patentably distinct inventions at issue yet proof of priority to just one of them will defeat the opponent's right to both inventions . . . ." (Broad Reply 1, Paper 335, 16:6–12 ("'If a count includes within its scope two patentably distinct inventions, say invention A and invention B, then priority proof of either invention A or invention B would defeat the opponent's right to both A and B. That is not right or fair.' *Ashurst v. Stampf*, Interference 105,482 McK, 2008 WL 2781979, at *22 (B.P.A.I. July 16, 2008) (citing *Godtfredsen v. Banner*, 598 F.2d 589, 592 (CCPA 1979)).") Yet Broad fails to direct us to evidence that Proposed Count 2 does not encompass more than one patentably distinct invention.

We note that in Motion 3, Broad argues that its involved claims not limited to a single-molecule RNA should be designated as not corresponding to Count 1.

(*See* Broad Motion 3, Paper 73, 20:18–31:21.) As we discussed above, claims are designated as corresponding to a count when "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). As in Motion 1, Broad fails to present evidence or argument regarding the obviousness of its "non-limited" claims over Count 1, which is limited to a single-molecule RNA system in Motion 3, arguing instead that designating the "non-limited" claims as corresponding to Count 1 would be unfair. (*See* Broad Motion 3, Paper 73, 29:1–31:19.) Broad does not present Motion 1 or Motion 3 as being contingent on the other. Rather, Broad argues for relief that would involve contradictory reasoning – in Motion 1 that the single- and dual molecule CRISPR-Cas9 systems are the same patentable invention and in Motion 3 that a "non-limited" CRISPR-Cas9 system is separately patentable from a single-molecule CRISPR-Cas9 system – without directing us to evidence in either context. Broad expects us to choose a basis for relief based on no evidence. We decline to do so because Broad fails to meet its burden in both motions. We note that the fairness of the proceeding to both parties depends on whether the single-molecule and dual-molecule systems are the same patentable invention or are separately patentable. We are not persuaded of either result by any of Broad's arguments.

Broad argues further that "[t]he rules do not require a proposed count to be directed to the same patentable invention as the original count." (Broad Reply 1, Paper 335, 1:13–14; *see id.* at 1:10–2:16, 4:9–5:9.) We do not base our decision on argument or evidence regarding the relationship of the proposed count and the original count, but rather on Broad's failure to argue and direct us to evidence that

the proposed count encompasses one separately patentable invention or that it does not. We determine that Broad has failed to meet its burden because Broad fails to provide a basis on which we can decide whether Proposed Count 2 is appropriate.

According to Broad, the "the relevant question would be whether a *generic* RNA genus is directed to the same invention as the single-molecule RNA species." (Broad Motion 1, Paper 335, 2:15–16.) We disagree. The relevant question is the scope of Proposed Count 2 itself – whether it encompasses more than one patentable invention and whether it satisfies the intent of 35 U.S.C. § 135 to determine priority as to the common, patentably distinct inventions claimed by the parties.

Broad argues:

> Moreover, there was no need for Broad to "prove" that generic RNA claims are anticipated by or obvious in view of the single-molecule RNA Count 1, because this assumption is inherent in the structure of this Interference. Specifically, Broad's generic RNA claims stand designated to the single-molecule RNA Count 1 because the PTAB has preliminarily concluded they are anticipated by or obvious in view of Count 1. ToolGen agrees, arguing that that Broad's generic RNA claims should remain designated as corresponding to Count 1—another tacit admission that Broad's generic RNA claims (like Proposed Count 2) are directed to the same patentable invention as Count 1 under the interference rules as applied by the PTAB.

(Broad Reply 1, Paper 335, 2:17–3:2.) In this argument, Broad uses ToolGen's arguments to avoid the burden of presenting sufficient argument and evidence. Broad again fails to take a position on whether Proposed Count 2 encompasses more than one patentable invention and to support that position with argument and evidence. We are not persuaded that ToolGen's arguments in opposition to a

different motion (Broad Motion 3) is evidence in support of Broad's current motion. Further, to the extent relevant, ToolGen's position in its Opposition 3 is not inconsistent with its position here. As explained above, the standard for whether subject matter is directed to the same patentable invention is based on a two-way test while claim correspondence only requires that the count anticipate or render obvious the claim, i.e., a one-way test.

Because Broad fails to meet its burden under 37 C.F.R. § 41.208(b) we deny Broad Motion 1.

III. Broad Contingent Motion 2

Broad filed Motion 2, requesting to have certain claims of its own applications 15/160,710 and 15/430,260 designated as corresponding to the count if Broad Motion 1 were granted, substituting Proposed Count 2 for Count 1. (*See* Paper 70.)

Because we deny Broad Motion 1 and do not change the count, we dismiss Broad Motion 2 as being moot.

We note that Broad asserts "that in the event that the PTAB denies Broad Motion 1 and proceeds with Count 1, claim 41 of [application 15/160,710] and claim 95 of [application 15/430,260] are both limited to single-molecule RNA ('sgRNA') configurations and thus also correspond to Count 1." (Broad Motion 2, Paper 70, 1:12–14.) Because Broad was not authorized to file a motion to have additional claims designated as corresponding to Count 1, we decline to review these claims. Given Broad's argument, though, Broad has a duty to disclose its argument and the status of this procedure in the prosecution of the recited

applications. *See* 37 C.F.R. § 1.56.

IV. Broad Motion 3

Broad argues that certain claims were improperly designated as corresponding to Count 1 and requests that they be designated as not corresponding. (*See* Broad Motion 3, Paper 73, 1:2–12.) According to Broad, these claims are patentably distinct from Count 1. (*See* Broad Motion 3, Paper 73, 2:19–20.) Broad argues that these claims also fail to correspond to proposed Count 2, but because we deny Broad Motion 1 to substitute Count 1 for that count, we need not consider Proposed Count 2.

"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.

At the outset of our analysis, we note that the success of whether a CRISPR-Cas9 system would be able to cleave DNA and alter gene expression in a eukaryotic cell, as well as other limitations of Count 1, is considered to be taught in the prior art under the presumption of 37 C.F.R. § 41.207(b)(2) because such limitations are recited in Count 1. (*See* ToolGen Opp. 3, Paper 274, 2:15, n.1.)

A. Estoppel

Broad argues that claims directed to SaCas9, claims directed to a CRISPR-Cas9 system with multiple nuclear localization signals, and claims not limited to an RNA configuration should be designated as not corresponding to Count 1. (*See*

Broad Motion 3, Paper 73, 9:7–13:17, 15:6–18:19, 20:18–31:21.) Broad argued and we reviewed the same issues in the prior '115 Interference.

The count in the '115 Interference, like Count 1 in the current proceeding, included the same Broad claim – claim 18 of Broad patent 8,697,359. (*See id*.; *see* '115 Interference, Declaration, Paper 1, 12.) In that proceeding, the Board determined that Broad claims requiring two or more NLSs were properly designated as corresponding to the count. (*See* '115 Interference, Decision on Motions, Paper 877, 62:7–67:2.) The Board also decided that Broad claims reciting SaCas9 were properly designated as corresponding to the count in the '115 Interference. (*See* '115 Interference, Decision on Motions, Paper 877, 53:6–62:6.) And the Board determined that claims not limited to a single-molecule RNA configuration were properly designated as corresponding to the count. (*See id.* at 42:7–53:5.) The count in the '115 Interference, like Count 1 in the current proceeding, included the same Broad claim – claim 18 of Broad patent 8,697,359. (*See id*.; *see* '115 Interference, Declaration, Paper 1, 12.) Thus, the Board previously determined that Broad failed to persuasively show that a CRISPR-Cas9 system using SaCas9, including two or more nuclear localization signals, or not limited to a single RNA configuration would not have been obvious over the subject matter of claim 18 of Broad patent 8,697,359.

We decline to decide these issues again under the doctrine of issue preclusion. Issue preclusion by a judgment on the merits in a first suit precludes relitigation in a second suit of issues actually litigated and determined in the first. *Lawlor v. National Screen Serv. Corp.,* 349 U.S. 322, 326 (1955). Issue preclusion precludes a party from relitigating identical issues by switching

adversaries and precludes a party from asserting a claim that the plaintiff had previously litigated and lost against a different party. *See Parklane Hosiery Co. v. Shore*, 439 U.S. 322, 329 (1979). Thus, Broad does not avoid issue preclusion because ToolGen did not oppose Broad's motion regarding claim correspondence in the prior interference. Instead, application of issue preclusion centers around whether an issue of law or fact has been previously litigated. *International Order of Job's Daughters v. Lindeburg & Co.,* 727 F.2d 1087, 1091 (Fed. Cir. 1984). A party who has litigated an issue and lost should be bound by that decision and cannot demand that the issue be decided over again. *Mother's Restaurant, Inc. v. Mama's Pizza, Inc.,* 723 F.2d 1566, 1569 (Fed. Cir. 1983).

We properly apply the doctrine if:

> (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) plaintiff had a full and fair opportunity to litigate the issue in the first action.

A.B. Dick Co. v. Burroughs Corp., 713 F.2d 700, 702 (Fed. Cir. 1983); *see also* Restatement (Second) of Judgments § 27, p. 250 (1980). Broad's requests to have claims limited to SaCas9, claims limited to two or more nuclear localization signals, and claims not limited to a single RNA configuration designated as not corresponding to the count meets each of these requirements.

First, as explained above, these issues in Broad's current Motion 1 are identical to issues the Board decided in Interference 106,115 – claim correspondence to a count in the prior interference and the current interference that recites common subject matter.

The second requirement, that the issue was actually litigated, is also met because it is "generally satisfied if the parties to the original action disputed the issue and the trier of fact resolved it." *See Continental Can Co. v. Marshall,* 603 F.2d 590, 596 (7th Cir.1979). Under long-standing Supreme Court holdings, when an administrative agency is acting in a judicial capacity and resolves disputed issues of fact properly before it, which the parties have had an adequate opportunity to litigate, *res judicata* can be applied to enforce repose. *See B & B Hardware, Inc. v. Hargis Indus., Inc.*, 575 U.S. 138, 148–49 (2015). The Board had jurisdiction and resolved the parties' dispute regarding benefit of priority in Interference 106,115.

The third requirement, that the issue be essential to the judgment is also met because our determinations in the '115 Interference were not merely incidental or or collateral.

> [T]he requirement that a finding be "necessary" to a judgment does not mean that the finding must be so crucial that, without it, the judgment could not stand. Rather, the purpose of the requirement is to prevent the incidental or collateral determination of a nonessential issue from precluding reconsideration of that issue in later litigation.

Mother's, 723 F.2d at 1571. Although Broad's claims were not ultimately canceled in the judgment of the prior interference, the issue of claim correspondence was before the Board and had to be decided in the preliminary motions phase to set the proceeding for priority, even though the determination was not ultimately used in the judgment. *See id.* ("This is not a case where the court reached out to make determinations as to issues which were not before it. The issue of the [trademark confusion] was the focus of the parties' pleadings and was

fully litigated in the state court."). The determination of claim correspondence was not hypothetical or dicta, even if the judgement was not ultimately entered against Broad in the '115 Interference. Rather the determination could have been necessary to the judgment, if Broad had not prevailed. We note that Broad has filed a motion seeking the same relief in this interference, indicating that, again, the finding will be necessary for judgment if that judgment is against Broad. We see no reason why Broad should continue to get additional bites of the apple merely because it ultimately prevailed in an earlier proceeding.

We note that decisions and judgment in the '115 Interference are still on appeal at the Federal Circuit, but that does not impact the finality of our decision for purposes of issue preclusion Nevertheless, in the event that the prior decisions are reversed, we review Broad's arguments below.

B. Non-Limited RNA

Broad argues that if we deny Broad Motion 1, seeking to change the count, it's arguments regarding "non-limiting RNA claims" is "relevant." (*See* Broad Motion 3, Paper 73, 20:20–21.) As explained above, we deny Broad Motion 1.

We reviewed Broad's arguments and determined that claims not limited to a single-molecule RNA configuration were properly designated as corresponding to the count in the prior '115 Interference. (*See* '115 Interference, Decision on Motions, Paper 877, 42:7–53:5.) The count in the '115 Interference, like Count 1 in the current proceeding, included the same Broad claim – claim 18 of Broad patent 8,697,359. (*See id*.; *see* '115 Interference, Declaration, Paper 1, 12.) Thus, the Board previously determined that Broad failed to persuasively show that a CRISPR-Cas9 system not limited to a single RNA configuration would not have

obvious over the subject matter of claim 18 of Broad patent 8,697,359. Even if Broad is not precluded from arguing that its claims limited to two or more NLSs do not correspond to Count 1, Broad fails to persuade us it is entitled to relief. We briefly review Broad's arguments below.

Broad separates the clams it highlights into three different groups: 1) claims that do not require an RNA component at all, 2) claims that are "generic" as to the RNA component and do not use the term "guide RNA," and 3) claims that are "generic" as to the RNA component and use the term "guide RNA." (*See* Broad Motion 3, Paper 73, 20:24–21:3.)

As it argued in Motion 1, Broad argues that "[i]It would be entirely inequitable to award priority to that fundamental invention of eukaryotic CRISPR systems to a party who made only one species of that invention, potentially long after the other party made the broad, fundamental breakthrough," which according to Broad is the successful engineering of CRISPR-Cas9 systems for use in eukaryotic cells, regardless of the particular variation of RNA design. (*Id.* at 29:21–25.) Broad acknowledges that claims correspond to a count when the count, treated as prior art, would have anticipated or rendered obvious the subject matter of the claims, as provided in 37 C.F.R. § 41.207(b)(2), but argues that "[t]his is not, however, a per se rule that must rigidly be applied, even if doing so would work an inequitable outcome." (*Id.* at 29:5–9.)

Broad does not, though, argue or direct us to facts indicating the relationship between claims it asserts are directed to "generic" RNA configurations and the subject matter of Count 1. As ToolGen argues, even if Broad is correct that at least some of its claims are "generic" as to RNA configuration, a count directed to a

species – single-molecule RNA configuration – would anticipate these claims, if treated as prior art. (*See* ToolGen Opp. 3, Paper 274, 32:21–23.) Thus, under 37 C.F.R. § 41.207(b)(2), we know of no facts to rebut the presumption made upon declaration of the interference that such claims correspond to Count 1. Broad fails to argue or direct us to evidence to the contrary.

Furthermore, Broad fails to support its arguments regarding inequity with arguments, supported by evidence, that the single-molecule RNA configuration recited in Count 1 is the same invention as the "generic" RNA configuration to which it asserts its claims are drawn. Broad argues that it could be denied generic claims, if ToolGen establishes that it made the single-molecule RNA species first, even though ToolGen was later to invent the "generic" RNA configuration. However, Broad does not argue or present evidence that the single-molecule RNA configuration is the same invention as the dual-molecule RNA configuration, both of which are embraced in the "generic" RNA configuration. (*See* Broad Motion 3, Paper 73, 30:9–11.) Thus, we do not have a basis to determine whether evidence of an earlier invention of a system using a single-molecule RNA configuration would unjustly deny a party rights to a system using a dual-molecule RNA configuration or not. If the single-molecule and the dual-molecule RNA configurations are not the same invention, Broad's argument of unfairness is not supported. But Broad fails to argue or cite to evidence that both configurations are the same invention.

We note that Broad does not cite to support for using different criteria than provided in 37 C.F.R. § 41.207(b)(2) to determine that claims correspond to a count. Broad cites to discussion during the rulemaking regarding this rule,

regarding the application of estoppels for generic claims lost in an award of priority to a species count. (*See* Broad Motion 3, Paper 73, 29, 7–10, citing 69 Fed. Reg. 49960, 49994 (Comment 186 and Answer), Ex. 2305, 62.) The Office explained a just result could be obtained by determining priority for two counts: a species count and a genus count. (*See id.*) But Broad did not move to add a genus count to the interference, only to substitute the species count with a genus count. (*See* Broad Motion 1, Paper 72.) Because Broad fails to present argument or evidence that each count would describe a patentably distinct invention, Broad fails to persuade us that any relief is required. (*See* 37 C.F.R. § 41.201 (requiring that "[w]here there is more than one count, each count must describe a patentably distinct invention.").)

We are also not persuaded by Broad's reliance on *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F. 3d 1264, 1268 (Fed. Cir. 2003), that relief is warranted. (*See* Broad Motion 3, Paper 73, 30:14–31:9.) That opinion holds that the Office properly implemented a two-way test as the standard for interference-in-fact, which is reflected in 37 C.F.R. § 41.203(a) ("*Interfering subject matter.* An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa."). The court's discussion of claim correspondence in that case was based on the prior interference rules and does not address the current standard recited in 37 C..F.R. § 41.207(b)(2), which provides a one-way test for claim correspondence.

Broad fails to persuade us that the claims it asserts are generic to RNA configuration should be designated as not corresponding to Count 1. Broad argues that "[i]n unpredictable arts, multiple species can be separately patentable," but fails to argue, with supporting evidence, that this is true for the two species of the CRISPR-Cas9 system. (Broad Motion 3, Paper 73, 31:8–9.) Thus, we deny Broad's request regarding its "generic" claims for failure to meet its burden.

C. SaCas9

Broad argues that claims[4] limited to using the *Staphylococcus aureus* Cas9 ("SaCas9") protein, or a nucleotide sequence encoding it, as the Cas9 component of the CRISPR-Cas9 do not correspond to Count 1. (*See* Broad Motion 3, Paper 73, 9:7–13:17.) Broad cites, for example to claim 1 of the involved Broad patent 8,865,406, which provides for "a second regulatory element operable in eukaryotic cell operably linked to a nucleotide sequence encoding a *Staphylococcus aureus* Cas9 protein . . . ." (*Id.* at 9:12–29, citing patent 8,865,406, Ex. 2017, claim 1.) Broad argues that there is no teaching or suggestion in either Count 1 or the prior art to use SaCas9 in a CRISPR-Cas9 system in eukaryotic cells. (*See* Broad Motion 3, Paper 73, 10:6–7.)

Broad argued and we decided the same issue in the prior '115 Interference. (*See* '115 Interference, Decision on Motions, Paper 877, 53:6–62:6.) Specifically, we determined that the Broad claims reciting SaCas9 were properly designated as

[4] Broad asserts that claims 1–30 of patent 8,865,406; claims 1–30 of patent 8,895,308, and claims 1, 16–21, and 30–40 of application 15/330,876 do not corresponding to Count 1 under this ground. (*See* Broad Motion 3, Paper 73, 9:9–11.)

corresponding to the count in that interference. (*See id.*) That count, like Count 1 in this proceeding, included the same Broad claim – claim 18 of Broad patent 8,697,359. (*See id.*; *see* '115 Interference, Declaration, Paper 1, 12.) Thus, we previously determined that Broad failed to persuasively show that a CRISPR-Cas9 system using SaCas9 would not have been obvious over the subject matter of claim 18 of Broad patent 8,697,359.

ToolGen does not argue the doctrine of issue preclusion prevents Broad from relitigating the same issue in the current interference, but ToolGen does argue that Broad's arguments and the evidence cited are the same it presented in the '115 Interference. (*See* ToolGen Opp. 3, Paper 274, 8:13–15.) We agree with ToolGen. Thus, even if Broad is not precluded from arguing that its claims limited to SaCas9 do not correspond to Count 1, Broad fails to persuade us it is entitled to relief. We briefly review Broad's arguments below.

Broad argues, relying on the testimony of Christoph Seeger, Ph.D.,[5] that there is no teaching or suggestion in either Count 1 or the prior art to select

[5] Dr. Seeger testifies that he is a professor of virology at the Fox Chase Cancer Center in Philadelphia, with over 30 years of experience and that he is currently researching the use of CRISPR-Cas9 for targeting hepatitis B virus. (*See* Seeger Decl., Ex. 2454, ¶ 3.) Dr. Seeger's *curriculum vitae* reports that he has published scientific articles regarding CRISPR-Cas9, has received funding for research involving hepatitis B virus and nuclease design. and is a reviewer for several scientific journals. (*See* Curriculum Vitae Christoph Seeger, Ph.D., Ex. 2402.) ToolGen does not dispute Dr. Seeger's qualifications. We find that Dr. Seeger is qualified to testify to what one of ordinary skill in the art would have understood regarding the subject matter of this proceeding.

SaCas9, out of the more than 600 identified bacterial Cas9 orthologs, in CRISPR-Cas9 systems in eukaryotic cells. (*See* Broad Motion 3, Paper 73, 10:6–21, citing Declaration of Technical Expert Christoph Seeger ("Seeger Decl."), Ex. 2454, ¶¶ 228–48.) Broad argues that the small size of SaCas9 would not have provided a reason for an ordinarily skilled artisan to have chosen it because other orthologs, such as *Streptococcus pyogenes* were more efficient and other small Cas orthologs did not have improved efficiency. (*See* Broad Motion 3, Paper 73, 11:5–21, citing Seeger Decl., Ex. 2454, ¶¶ 238–44.)

As Broad notes, we considered these arguments in the '115 Interference and determined that Broad had failed to show that SaCas9 would not have been an obvious choice of Cas9 ortholog because it was known to be a model for studying CRISPR systems by August 2011. (*See* Broad Motion 3, Paper 73, 12:9–17; *see* Decision on Motions in '115 Interference, Paper 877, 56:10–15.) Specifically, Sapranauskas, which reports to have been published on-line 3 August 2011, 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, Exs. 1311/2215, 9276 (citations omitted).) (*See* ToolGen Opp. 3, Paper 274, 8:25–9:4.) Broad characterizes this teaching as a "passing reference," and argues that Sapranauskas "cites for this proposition to other scientists who had never reported any success in using SaCas9 systems in eukaryotes," wherein "research from Sapranauskas and others establishes that there was little to no predictability as to which Cas9 orthologs could be used in systems that would be effective in eukaryotes." (Broad Motion 3, Paper 73, 12:11–14, citing Seeger Decl., Ex. 2454,

¶ 231; Broad Reply 3, Paper 337, 6:22–7:5.) According to Broad, the teachings of Sapranauskas would not provide any motivation to try the SaCas9 ortholog in eukaryotic cells. (*See id.* 12:14–15.) Broad's arguments do not persuade us that the plain language of Sapranauskas would not have been a reason for one of ordinary skill in the art to have at least tried SaCas9 in a eukaryotic system.

> 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). Broad fails to meet this burden. Under the facts before us, Sapranauska highlights four Cas9 ortholog model systems, which would be a small enough number to have been obvious to try under the guidance of *KSR*.

Broad argues that using SaCas9 in a CRISPR-Cas9 system produced unexpected results, specifically "indels *in vivo* with efficiencies comparable to those achieved using SpCas9 ortholog, in stark contrast to the poorer performance of other Cas9 orthologs, such as StCas9." (Broad Motion 3, Paper 73, 12:21–22, citing Seeger Decl., Ex. 2454, ¶ 245.) We are not persuaded by the evidence Broad cites, specifically 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, StCas9, which happens to also be small. (*See* Seeger Decl., Ex. 2454, ¶ 245.) But Dr. Seeger does not direct us to evidence that StCas9 is inefficient because of its small size or that those of ordinary skill would have considered all small Cas9 proteins to be similarly inefficient. (*See* ToolGen Opp. 3, Paper 274, 15:1–9.) 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.

Broad argues further that the commercial success of using SaCas9 systems is objective evidence of non-obviousness. (*See* Broad Motion 3, Paper 73, 13:7–17, citing Seeger Decl., Ex. 2454, ¶ 246.) In his supporting testimony, Dr. Seeger refers to a clinical trial that reportedly uses SaCas9 and cites to Exhibits 2517, 2686, and 2687. (*See* Seeger Decl., Ex. 2454, ¶ 246.) We are not persuaded by this evidence because, where it is cited to argue for the commercial success of vector delivery, the evidence cites only a single clinical study with two patients. Furthermore, as ToolGen argues, Broad does not distinguish the asserted contribution of vector delivery from the asserted contribution of using SaCas9 to this alleged commercial success. (*See* ToolGen Opp. 3, Paper 274, 15:14–18.) Even if the conduct of a clinical trial, as compared to sales, was a demonstration of commercial success, we agree with ToolGen that the evidence cited by Broad does not demonstrate commercial success.

After considering all of the evidence the parties cite, we are not persuaded that one of ordinary skill in the art would have considered Broad's involved claims limited to SaCas9 to be non-obvious over the subject matter of Count 1 treated as

prior art. Accordingly, we are not persuaded that the claims Broad cites should be designated as not corresponding to Count 1.

D. Two or More NLSs

Broad argues that claims[6] requiring the use of two or more nuclear localization signals ("NLSs") do not correspond to Count 1. (*See* Broad Motion 3, Paper 73, 15:6–18:19.) Broad cites, for example to claim 1 of the involved Broad patent 8,871,445, which recites "wherein the CRISPR-Cas system comprises two or more nuclear localization signals (NLSs)." (*Id.*, citing patent 8,871,445, Ex. 2029, claim 1.) Broad argues that there is no teaching or suggestion in either Count 1 or the prior art to use two or more NLSs in a CRISPR-Cas9 system in a eukaryotic cell. (*See* Broad Motion 3, Paper 73, 16:13–15, citing Seeger Decl., Ex. 2454, ¶¶ 258–78.)

Broad argued and we decided the same issue in the prior '115 Interference. (*See* '115 Interference, Decision on Motions, Paper 877, 62:7–67:2.) Specifically, we determined that Broad had not shown that its claims requiring two or more NLSs were improperly designated as corresponding to the count in that interference. (*See id.*) As explained above, the count in the '115 Interference included the same Broad claim that makes up part of current Count 1 – claim 18 of Broad patent 8,697,359. (*See id.*; *see* '115 Interference, Declaration, Paper 1, 12.)

[6] Broad asserts that claims 1–30 of patent 8,871,445; claims 1–30 of patent 8,932,814; claim 7 of patent 8,993,233, claims 9–11 of application 14/704,551, and claim 34 of application 15/330,876 should be designated as not corresponding to Count 1 under this ground. (*See* Broad Motion 3, Paper 73, 15:10–14.)

Thus, we previously determined that Broad failed to persuasively show that a CRISPR-Cas9 system using two or more NLSs would not have been obvious over the subject matter of claim 18 of Broad patent 8,697,359.

ToolGen does not argue the doctrine of issue preclusion prevents Broad from relitigating the issue of correspondence of claims requiring two or more NLSs in the current interference, but ToolGen does argue that Broad's arguments and the evidence cited are the same it presented in the '115 Interference. (*See* ToolGen Opp. 3, Paper 274, 19:5–7.) Even if Broad is not precluded from arguing that its claims limited to two or more NLSs do not correspond to Count 1, Broad fails to persuade us it is entitled to relief. We briefly review Broad's arguments below.

Broad argues that there is no evidence that using an arrangement of two or more NLSs in a CRISPR-Cas9 system would be functional because "functional domains," such as NLSs, may be buried or shielded during protein folding. (Broad Motion 3, Paper 73, 17:14–18:5, citing Seeger Decl., Ex. 2454, ¶¶ 271–76.) Broad argues that for this reason there would also be no expectation of success. (*See id.*) Broad exemplifies "functional domains" as two or more NLSs, not one NLS. (*See* Broad Motion 3, Paper 73, 17:19–23.) We note that the ToolGen part of Count 1 recites a Cas9 protein that "comprises a nuclear localization signal." (*See* ToolGen Opp. 3, Paper 337, 23:23:25–26; Declaration, Paper 1, 12.) Thus, a Cas9 protein with at least one NLS is taken as prior art for our inquiry of claim correspondence. In light of the subject matter recited in Count 1, Broad must provide sufficient evidence that one of ordinary skill in the art would not have considered it

reasonably predictable to successfully use two or more NLSs, even though the use of Cas9 with one NLS was known in the prior art.

Broad cites to the testimony of Dr. Seeger to support its argument. (*See* Broad Motion 3, Paper 73, 16:13–15, citing Seeger Decl., Ex. 2454, ¶¶ 258–78.) Dr. Seeger testifies that "neither Count 1 nor Proposed Count 2 contains any limitation or disclosure of use of an NLS to localize Cas9 to the nucleus of a eukaryotic cell." (Seeger Decl., Ex. 2454, ¶ 263.) Dr. Seeger testifies further:

> The POSA seeking to attempt use of any NLS with a CRISPR-Cas9 system would face numerous uncertainties, unknowns, and potential design options. The POSA would not have the benefit of any literature addressing use of an NLS on a Cas9 protein and would have to address selection of an NLS, the number of NLSs to use, and the position or configuration of the NLS. . . . The POSA would know that CRISPR-Cas9 systems may fail in eukaryotic cells for many reasons including for example protein folding issues, complex formation issues, and RNA degradation issues. Given a negative result, it would be difficult for the POSA to determine whether one of these fundamental issues was at play or whether further variation of the NLS selection, number, or position could address the negative result.

(Seeger Decl., Ex. 2454, ¶ 265.) Because the ToolGen part of Count 1 recites a Cas9 protein that "comprises a nuclear localization signal," it is assumed that one of ordinary skill would have considered using one NLS on a Cas9 to be in the prior art. (Declaration, Paper 1, 12.) Without the understanding that this subject matter is taken to be in the prior art, Dr. Seeger's testimony is not helpful for our analysis.

Broad also cites to several references to support its argument regarding a lack of reasonable expectation of success, but does not explain how the teachings would have indicated two or more NLSs to be unpredictable when it was known

that Cas9 as a fusion protein with one NLS was known to be functional. (*See* Broad Motion 3, Paper 73, 17:14–18:5, citing Seeger Decl., Ex. 2454, ¶¶ 271–76; Turner,[7] Ex. 2264; Brothers,[8] Ex. 2263; Fieck,[9] Ex. 2258.) Given that the prior art teaches that in at least one system "[n]uclear localization was always improved by . . . reiterating the [nuclear localization] signal . . . ," we are not persuaded of the non-obviousness of using two or more NLSs when one is already known to be operable. (Fischer-Fantuzzi,[10] Ex. 1324, 5496; *see* ToolGen Opp. 3, Paper 274, 19:22–20:9.)

Broad cites further to evidence from the '115 Interference that another group working on use of CRISPR-Cas9 systems in eukaryotic cells was not able to determine an NLS configuration that successfully achieved eukaryotic CRISPR-Cas9 activity. (*See* Broad Motion 3, Paper 73, 18:6–15, citing e-mails dated 2012, Exs. 2704, 2705.) Even if this evidence is not hearsay, given Dr. Seeger's testimony, we are not persuaded it is persuasive. Dr. Seeger testifies that at the

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[7] Turner et al., "Carboxyl-terminal Vesicular Stomatitis Virus G Protein-tagged Intestinal Na-dependent Glucose Cotransporter (SGLT1)," J. BIOL. CHEM., 271:7738–44 (1996) (Ex. 2264.)

[8] Brothers, et al., "Unexpected Effects of Epitope and Chimeric Tags on Gonadotropin-Releasing Hormone Receptors: Implications for Understanding the Molecular Etiology of Hypogonadotropic Hypogonadism," J. CLIN. ENDO. & MET., 88:6107–12 (2003f (Ex. 2263).

[9] Fieck et al., "Modifications of the E. coli Lac repressor for expression eukaryotic cells: effects of nuclear signal sequences on protein activity and nuclear accumulation," NUCL. ACIDS RES., 20:1785–91 (1992) (Ex. 2258).

[10] Fischer-Fantuzzi and Vasco, "Cell-dependent efficiency of reiterated nuclear signals in a mutant simian virus 40 oncoprotein targeted to the nucleus," MOL. CELL. BIOL., 8:5495–5503 (1988) (Ex. 1324).

time of the e-mails, in 2012 before it was known that a CRISPR-Cas9 system would work at all in eukaryotic cells, one of ordinary skill in the art

> would know that CRISPR-Cas9 systems may fail in eukaryotic cells for many reasons including for example protein folding issues, complex formation issues, and RNA degradation issues. Given a negative result, it would be difficult for the POSA to determine whether one of these fundamental issues was at play or whether further variation of the NLS selection, number, or position could address the negative result.

(Seeger Decl., Ex. 2454, ¶ 265.) Thus, the correspondence Broad cites does not necessarily indicate the unpredictability of NLSs in a system known to be operable in a eukaryotic cell.

Broad argues further that even if there had been some teaching or suggestion to use two or more NLSs in the prior art, the Broad inventors demonstrated that doing so resulted in significantly greater co-localization of CRISPR Cas9 components in the nucleus of a eukaryotic cell than could be expected. (*See* Broad Motion 3, Paper 73, 16:16–18.) Specifically, Broad cites to experiments in a priority application, discussed by Dr. Seeger as producing surprising results, wherein

> a single NLS on the C-terminal end of SpRNase III (but not the N terminus) was sufficient to target that protein to the nucleus, a version of SpCas9 with an NLS attached at each end exhibited a very high degree of nuclear localization, and was more efficient than versions with a single NLS.

(Seeger Decl., Ex. 2454, ¶ 267, citing appl. 61/736,527, Ex. 2001, ¶ 170.) Because these results are not a comparison between Cas9 with two or more NLSs and Cas9

with a single NLS, but rather a comparison of different proteins, we are not persuaded that the evidence is a comparison with the closest prior art. *In re Merchant,* 575 F.2d 865, 869 (CCPA 1978) (comparative tests to show non-obviousness must compare the claimed invention to the closest prior art). Furthermore, Broad does not explain why these results would have been unexpected, given that prior art such as Fischer-Fantuzzi (Ex. 1324) taught that multiple NLSs could increase localization to the nucleus.

Broad fails to meet its burden of presenting sufficient evidence to show that one of ordinary skill in the art would have considered the claims Broad highlights as being limited to two or more NLSs to be non-obvious over the subject matter of Count 1 treated as prior art. Accordingly, we are not persuaded that the claims Broad cites should be designated as not corresponding to Count 1.

E. Vector Delivery

Broad argues that claims[11] "limited to the use of vectors for delivery and expression of the RNA components" do not correspond to Count 1. (*See* Broad Motion 3, Paper 73, 5:9–9:6.) Broad cites, for example to claim 1 of the involved

[11] Broad provides Appendix C to Motion 3, which it asserts includes the following claims that should be designated as not corresponding to Count 1 under this ground: claims 1–14 of patent 8,867,359; claims 1–29 of patent 8,771,945; claims 1–25 of patent 8,795,965; claims 1–23 of patent 8,865,406; claims 1–25 of patent 8,871,445; claims 1–23 of patent 8,889,356; claims 25–28 of patent 8,889,418; claims 1–24, 29 of patent 8,895,308; claims 1–24 of patent 8,932,814; claims 1–20 of patent 8,945,839; claims 1–43 of patent 8,993,233; claims 1–21 of patent 8,999,641; claims 1–14, 37, and 40–41 of patent 9,840,713; claims 2 and 4–18 of application 14/704,551, and claims 1, 16–21, and 30–40 of application 15/330,876. (*See* Broad Motion 3, Paper 73, 5:11–13.)

Broad '359 patent, which provides for components "a) a first regulatory element" linked to nucleotide encoding sequence a CRISPR-Cas system guide RNA and "b) a second regulatory element" linked to a nucleotide sequence encoding a Type-II Cas9 protein, "wherein components a) and b) are located on same or different vectors of the system . . . ." (Broad Motion 3, Paper 73, 5:11–29, citing '359 patent, Ex. 2011, claim 1.)

Broad argues that there is no teaching or suggestion in Count 1, or in the prior art, directing one of ordinary skill to "vector-delivered RNA for use in eukaryotic cells" and that in 2012 one of ordinary skill would not have had a reasonable expectation of success doing so. (*See* Broad Motion 3, Paper 73, 6:13–15.) Broad cites to the testimony of Dr. Seeger, in support of its arguments. (*See id.*, citing Seeger Decl., Ex. 2454, ¶¶ 212–27.) Broad argues further that "[t]here is no prior art that delivered CRISPR-Cas9 systems to eukaryotic cells at all and so, of course, there is none directed to vector delivery of the RNA." (Broad Motion 3, Paper 73, 6:13–17.)

We agree with Broad's framing of the issue as whether there would have been a teaching or suggestion to use vectors to deliver CRISPR-Cas9 RNA for use in eukaryotic cells because we agree that Count 1 does not specify the means of delivery to a eukaryotic cell. But, we disagree that correspondence of claims to Count 1 is determined by whether it would have been obvious that CRISPR-Cas9 system would work in eukaryotic cells at all because this element is provided in Count 1 – the acknowledged prior art. Thus, Broad's argument that "[v]ectors were not 'common' for delivery of CRISPR-Cas9 to eukaryotic cells in December 2012 – indeed, there had been no published reports of the use of

CRISPR-Cas9 in eukaryotic cells at all," does not address the relevant issue presented by Broad's motion. (*See* Broad Reply 3, Paper 337, 4:22–5:1.)

Similarly, Broad's reliance on the unpredictable nature of delivery of CRISPR-Cas9 to eukaryotic cells as determined in *Regents of Univ. of Cal. V. Broad Institute, Inc.*, 903 F.3d 1286, 1294 (Fed. Cir. 2018), is not relevant to the issue of whether Broad's claims correspond to Count 1 because the ability to deliver CRISPR-Cas9 components is assumed in Count 1. (*See* Broad Reply 3, Paper 337, 3:22–5:6.) Rather Broad's request for relief to designate certain claims as not corresponding to Count 1 requires us to determine only whether one of ordinary skill in the art would not have considered it obvious to use vectors to deliver CRISPR-Cas9 RNA components to a eukaryotic cell as opposed to any other means of delivery. (*See* Broad Motion 3, Paper 73, 5:11–12.)

Broad argues that delivery of the RNA components of a CRISPR-Cas9 system can be accomplished in multiple ways and that it has been characterized as the "most difficult barrier" to *in vivo* use. (*See* Broad Motion 3, Paper 73, 6:13–7:2, citing Lino,[12] Ex. 2648, abstract.) Broad identifies delivery of already translated RNA as a means of delivery, in particles, or by microinjection or transfection. (*See* Broad Motion 3, Paper 73,. at 7:12–17.) According to Broad, many ways of delivering RNA components to a eukaryotic cell performed poorly or failed with CRISPR-Cas9 systems, such as using "extraordinarily high amounts of already-translated" RNA to cells previously transfected with Cas9. (*See* Broad

[12] Lino et al., "Delivering CRISPR: a review of the challenges and approaches," DRUG DELIVERY, 25: 1234–57 (2018) (Ex. 2648).

Motion 3, Paper 73,. at 7:3–11.) Broad concludes that "[t]he prior art does not teach or suggest the use of, or provide reasons to select from that list, a vector for delivery of the RNA." (*Id.* at 7:17–18.)

We note that Broad argues that "the order of providing elements may be an important feature to getting the CRISPR/Cas9 system to work in eukaryotic cells." (*Id.* at 6:22–7:23, quoting 28 October 2016 Interview Summary in ToolGen application 14/685,568, Ex. 2069; *see* Broad Reply 3, Paper 337, 4:4–7.) This particular argument is unpersuasive because Broad does not explain how the order of providing elements is a feature of the vector delivery recited in claims Broad asserts should not correspond to Count 1.

ToolGen opposes Broad's argument by arguing that the use of plasmid vectors was well known in the art and widely employed for introducing DNA sequences encoding RNA molecules into eukaryotic cells. (*See* Broad Motion 3, Paper 73, 2:13–3:2.) According to ToolGen, those of ordinary skill in the art would have been motivated to use them and would have had a reasonable expectation of success doing so. (*See id.*) ToolGen cites to prior art available more than a decade before the parties' priority dates that teaches methods of introducing RNA molecules into cultured cells using vectors. (*See* ToolGen Opp. 3, Paper 274, 3:20–4:22, citing Stoddard Decl., Ex. 1420, ¶¶ 143.) ToolGen cites to publications, for example Paul,[13] which is entitled "Effective expression of small interfering RNA in human cells," and teaches that an "expression cassette"

[13] Paul et al., "Effective expression of small interfering RNA in human cells," NATURE BIOTECH., 29:505–08 (2002) (Ex. 1248).

allows for widespread transcription in human cell types, "suggest[ing] that this mode of siRNA delivery could be useful for suppressing expression of a wide range of genes." (Paul, Ex. 1248, abstract; *see* ToolGen Opp. 3, Paper 274, 3:20–22.) ToolGen also cites to Sambrook,[14] published in 2001, for its discussion of using vectors to transfer DNA into eukaryotic cells (*see* Ex. 1243, 28, 30), to Ichim,[15] published in 2004, reviewing the advantages of expressing siRNA from a plasmid to allow for higher expression and more control (*see* Ex. 1309, 1229), and to Paddison,[16] published in 2002, discussing the expression of shRNA *in vivo* from RNA polymerase promoters on vectors (*see* Ex. 1310, 956). (*See* ToolGen Opp. 3, Paper 274, 3:25–4:22.) ToolGen relies on Dr. Stoddard's testimony to argue that vectors were well known to provide the advantage of continuous and sustained RNA expression and chemical stability in eukaryotic cells. (*See* ToolGen Opp. 3, Paper 274, 5:1–3, citing Stoddard Decl., Ex. 1420, ¶ 144.)

ToolGen cites further to the discussion by the Federal Circuit in 2003 of RNA insertion in eukaryotic cells using vectors, referring to a specification that presumably was filed years earlier. (*See* ToolGen Opp. 3, Paper 274, 3:22–25, citing *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094, 1100 (Fed. Cir. 2003) ("Specifically, the patent proceeds to explain in section 5.2 that '[i]n order to express a biologically active α–Gal A, the coding sequence for the

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[14] Sambrook and Russell, Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press (2001) (Ex. 1243).
[15] Ichim et al., "RNA Interference: A Potent Tool for Gene-Specific Therapeutics," AM. J. TRANSPLANTATION, 4:1227–36 (2004) (Ex. 1309).
[16] Paddison et al., "Short Hairpin RNAs (shRNAs) Induce Sequence-Specific Silencing in Mammalian Cells," GENES & DEV., 16:948–58 (2002) (Ex. 1310).

enzyme, . . . is inserted into an appropriate eukaryotic expression vector, i.e. a vector which contains the necessary elements for transcription and translation of the *inserted coding sequence* in appropriate eukaryotic host cells.'"). ToolGen argues that this case demonstrates how "widely employed" vectors were for introducing RNA into eukaryotic cells, even before the parties' priority dates. (ToolGen Opp. 3, Paper 274, 3:22–24.)

Broad counters that ToolGen's position on the obviousness of using vector delivery in a CRISPR-Cas9 system encompassed in Count 1 is contradicted by ToolGen's expert. Specifically, ToolGen cites to Dr. Stoddard's cross-examination testimony that "[t]he issue of plasmids being an undesirable or suboptimal delivery vehicle was definitely being recognized by investigators and [persons of ordinary skill in the art] right around then, including in my own lab." (Stoddard Depo., Ex. 2459, 186:16–19; *see* Broad Reply 3, Paper 337, 2:9–13.) Dr. Stoddard's testimony is in response to questions about Kim,[17] a publication discussing the limitations of "off-target effects and unwanted integration of DNA segments derived from plasmids encoding Cas9 and guide RNA at both on-target and off-target sites in the genome." (Kim, Ex. 2647, abstract; *see* Stoddard Depo., Ex. 2459, 184:16–185:22.) Kim teaches that delivery of purified recombinant Cas9 protein and guide RNA into cultured cells is preferable. (*See* Kim, Ex. 2647, abstract.)

[17] Kim et al., "Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins," GENOME RESEARCH, 24:1012–19 (2014 (Ex. 2647).

We are not persuaded that Dr. Stoddard's testimony supports Broad's argument that using vectors for delivery of CRISPR-Cas9 RNA would not have been obvious over the subject matter of Count 1. Although Dr. Stoddard echoes Kim's teachings about the undesirability of using vectors to introduce RNA and Cas9 protein for a CRISPR-Cas9 system, both Dr. Stoddard and the disclosures of Kim indicate this technique had been performed and was known to those of ordinary skill, at least by 2014. Kim, the reference about which Dr. Stoddard testified, states:

> To express Cas9 and guide RNA in cultured cells in vitro, typically, plasmids that encode them are transfected via lipofection or electroporation. Unfortunately, use of plasmids is often limited by random integration of all or part of the plasmid DNA into the host genome, a process known as stable transfection.

(Kim, Ex. 2647, 1012.) Thus, Kim supports ToolGen's argument that using vectors for delivery and expression of CRSIPR-Cas9 RNA components was known, indicating further that it had been done, and therefore that vector delivery would have been obvious to those of ordinary skill in the art. The issue is not whether vector delivery was the most dersirable option, but whether it would have been suggested by the prior art and therefore obvious over Count 1. Even if better alternatives are taught, the inferior alternative is still available for obviousness analysis. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Neither Dr. Stoddard nor Kim demonstrates that delivery of RNA via a vector was known to prevent all CRISPR-Cas9 activity in eukaryotic cells, only that it was less desirable than other methods.

Broad attempts to support its arguments further by citing to other testimony by Dr. Stoddard that delivery of "SpCas9" with AAV vectors was "possible under certain conditions," but also "problematic." (Stoddard Depo., Ex. 2459, 139:5–10.) This testimony also fails to persuade us that the claims Broad highlights do not correspond to Count 1 because the testimony is directed to the specifics of SpCas9 and the AAV vector. (*See* Stoddard Depo., Ex. 2459, 136:12–19.) Dr. Stoddard qualifies his testimony, explaining "the context of this relative to AAV, which is being stripped from the question. And packaging of AAV is a -- for the purpose of gene modification and editing is a very complex process that requires much more than just a nuclease." (*Id.*) Broad does not explain how this testimony would have indicated one of ordinary skill in the art would not have considered it obvious to use *any* vector for RNA expression in a CRISPR-Cas9 system, particularly when other types of vector delivery was known to be useful in other systems.

Broad argues that "ToolGen offers no reason why a [person of ordinary skill in the art] would select an 'undesirable or suboptimal delivery vehicle' from a wide range of choices, particularly for use in the challenging and unpredictable eukaryotic cell environment." (Broad Reply 3, Paper 337, 3:6–8.) But it is not ToolGen's burden to show that Broad's highlighted claims would have been obvious over the subject matter of Count 1. Rather it is Broad's burden to show the claims it wishes to be designated as not correspond to the count are not obvious from Count 1. In other words, it was Broad's burden to show why one of ordinary skill in the art would not have had sufficient reason to at least try, with a reasonable expectation of a successful outcome, to use vectors for delivery of

CRISPR-Cas9 RNA components, when there were a limited number of known routes of delivery according to Lino (DNA plasmids, translated mRNA, and ribonucleoprotein complexes; *see* Ex. 2648, 1241) and plasmid vectors had been successfully used to express RNA in eukaryotic cells for years prior to either party's benefit date. The Supreme Court explained that the presence of "a finite number of identified, predictable solutions" can give a person of ordinary skill "good reason to pursue the known options within his or her technical grasp" and if this leads to the anticipated success can indicate that the "combination was obvious to try" and obvious under § 103. *See KSR*, 550 U.S. at 421. Broad failed to meet its burden.

Broad cites to *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), to argue where there are a number of prior art choices, the art must provide some reason to select one in order to find obviousness. (*See* Broad Motion 3, Paper 73, 7:18–21; Broad Reply 3, Paper 337, 3:12–19.) We are not persuaded that the facts of *Ortho-McNeil* are so alike to those present in this case so as to compel the same result. In *Ortho-McNeil*, the Federal Circuit determined that the case did not present "the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Ortho-McNeil,* 520 F.3d at 1364. In contrast, the facts before us now are that there are a small number of choices of means of delivering CRISPR-Cas9 RNA components (three) and a large number of teachings that vectors can be used to express RNA in eukaryotic cells. Thus, we are not persuaded by the decision in *Ortho-McNeil*.

Broad argues further that the use of vectors for delivery of CRISPR-Cas9

RNAs produces unexpected results and commercial success indicating that the highlighted claims would not have been obvious over Count 1. (*See* Broad Motion 3, Paper 73, 8:7–9:3.) Broad asserts that the "eukaryotic vector-based CRISPR-Cas9 system developed by Dr. Zhang is one of the most requested CRISPR vectors of all time from Addgene." (Broad Motion 3, Paper 73, 8:9–11.) Broad does not direct us to evidence of a comparison between vector delivery and any other type of delivery of CRISPR-Cas9 RNA components. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991). Broad cites to Exhibits 2502–2505, but does not explain their significance. (*See* Broad Motion 3, Paper 73, 8:8–11.) These exhibits appear to show the availability of CRISPR-Cas9 vectors, but we do not readily discern any comparative information about how often they had been requested.

Similarly, Broad cites to Dr. Seeger's testimony, but he refers only to a product reportedly used in clinical trials, without further explanation to how it compares to any other delivery system. (*See* Broad Motion 3, Paper 73, 8:7–14, citing Seeger Decl., Ex. 2454, ¶¶ 225–227.) Broad fails to persuade us that vector delivery produces results that would have been unexpected to one of ordinary skill in the art, given the subject matter of Count 1 treated as prior art.

Broad also argues that "CRISPR-Cas9 systems with vector-delivered RNA have shown commercial success," citing to Dr. Seeger's declaration and Exhibits 2517, 2686, and 2687, which refer to the use of gene-editing to treat vision loss. (Broad Motion 3, Paper 73, 8:15–16.) As ToolGen argues, this

evidence is insufficient because it cites only a single clinical study with two patients. (*See* ToolGen Opp. 3, Paper 274, 7:8–10.) ToolGen argues further that this evidence is not commensurate in scope with claims limiting the CRISPR-Cas9 system to vector delivery because Dr. Seeger testifies that other features, specifically the use of SaCas9, provided for the commercial success. (*See* ToolGen Opp. 3, Paper 274, 7:11–15, citing Seeger Decl., Ex. 2454, ¶ 246.) Even if the conduct of a clinical trial, as compared to sales, was a demonstration of commercial success, we agree with ToolGen that the evidence cited by Broad does not demonstrate commercial success.

After considering all of the evidence the parties cite, we are not persuaded that one of ordinary skill in the art would have considered Broad's involved claims limited to vector delivery to be non-obvious over the subject matter of Count 1 treated as prior art. Accordingly, we are not persuaded that the claims Broad cites should be designated as not corresponding to Count 1.

F. Chimeric Cas9

Broad argues that claims 1–28 of involved patent 8,889,418 ("the '418 patent") are limited to using a Cas9 protein that is a chimeric enzyme in a CRISPR-Cas9 system and do not correspond to Count 1. (*See* Broad Motion 3, Paper 73, 13:18–15:5.) Broad cites, for example to claim 1 of the '418 patent, which provides for an enzyme that is "a Cas9 protein that is a chimeric CRISPR enzyme in that it comprises a first fragment and a second fragment, wherein each of the first and second fragments is from a different Cas9 protein . . . ." (*Id.* at 13:22–14:8, citing the '418 patent, Ex. 2060, claim 1.) Broad argues that there is no teaching or suggestion in either Count 1 or the prior art to use a chimeric Cas9

protein in a CRISPR-Cas9 system in eukaryotic cells. (*See* Broad Motion 3, Paper 73, 14:17–19, citing Seeger Decl., Ex. 2454, ¶¶ 249–57.)

In support of its argument, Broad cites to the specification of the '418 patent, which reports that "[t]hese chimeric Cas9 proteins may have a higher specificity or a higher efficiency than the original specificity or efficiency of either of the individual Cas9 enzymes from which the chimeric protein was generated." ('418 patent, Ex. 2060, 4:21–25; *see* Broad Motion 3, Paper 73, 14:19–22.) Broad cites further to reportedly unexpected results identified in the '418 patent, including reduced toxicity, improved expression in eukaryotic cells, etc. (*See* Broad Motion 3, Paper 73, 14:22–15:1, citing '418 patent, Ex. 2060. 83:45–52.) But no further explanation of why these results would have been unexpected, given the teachings of the prior art, is provided.

Broad also cites to Dr. Seeger's testimony, but he states only that nothing in either the count or the prior art disclosed or taught any benefits of using a chimeric Cas9. (*See* Seeger Decl., Ex. 2060, ¶¶ 249–57.) The testimony to which Broad cites does not further explain what was known in the prior art regarding chimeric Cas9 proteins. The only discussion Dr. Seeger provides is about a reference published in 2019 (Ex. 2683), but it is not clear how this reference indicates non-obviousness of the highlighted claims over Count 1. Accordingly, we give Dr. Seeger's testimony little weight. *See Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003) ("[W]hat the Board consistently did was accord little weight to broad conclusory statements that it determined were unsupported by corroborating references. It is within the discretion of the trier of fact to give each item of evidence such weight as it feels appropriate.").

In the absence of evidence why claims reciting chimeric Cas9 proteins would have not have been obvious over the subject matter of Count 1, we are not persuaded by Broad's arguments. "Argument of counsel cannot take the place of evidence lacking in the record." *Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977).

G. Fusions with Protein Domains or Heterologous Domains

Broad argues that its claims[18] requiring Cas9 to be fused to a specified protein domain or including heterologous domains should be designated as not corresponding to Count 1. (*See* Broad Motion 3, Paper 73, 18:20–20:17.) Broad cites, for example to claim 1 of the involved Broad patent 8,999,641, which recites "a nucleotide sequence encoding a fusion of a Type-II Cas9 protein and one or more protein domains," as well as a "Cas9 protein compris[ing] one or more mutations in a catalytic domain." (Broad Motion 3, Paper 73, 19:2–24, citing patent 8,999,641, Ex. 2047, claim 1.) Claim 1 of the involved Broad patent 8,999,641 provides for many "protein domains," including epitope tags, reporters, and domains having different activities, including transcription activation, transcription repression, etc. (*See* patent 8,999,641, Ex. 2047, claim 1.)

Broad argues that there is no teaching or suggestion in either Count 1 or the prior art "directing a POSA to modify the naturally occurring Cas9 protein sequences as set forth in these claims." (*See* Broad Motion 3, Paper 73, 20:1–3,

[18] Broad argues that claims 1–43 of patent 8,993,233 (Ex. 2024), claims 1–28 of patent 8,999,641 (Ex. 2047), claims 18–19, 25, 29, 30, and 36 of patent 7139,840, (Ex. 2043) and claim 21 of application 876 (Ex. 2064) should be designated as not corresponding to Count 1. (*See* Broad Motion 3, Paper 73, 18:24–19:2.)

citing Seeger Decl., Ex. 2454, ¶¶ 279–84.) Dr. Seeger testifies:

> the prior art did not address functional eukaryotic CRISPR-Cas9 systems at all and so there are no disclosures of improvements to such systems. And, the POSA would have been hesitant to mutate the Cas9 or fuse it to protein domains as it would have been expected that such engineering of the Cas9 could affect its ability to function at all, especially in a eukaryotic cell.

(Seeger Decl., Ex. 2454, ¶ 282.) Dr. Seeger's testimony refers only to protein domains on Cas9, not to "protein domains" in general. Neither Dr. Seeger nor Broad cites to other evidence regarding what was taught or suggested by the prior art.

In contrast, ToolGen argues that there is a "vast array of prior-art references disclosing the use and numerous benefits of fusing proteins." (*See* ToolGen Opp. 3, Paper 274, 24:9–10.) ToolGen cites to examples of generating protein fusions at least a decade before the parties' priority date, including Brizzard[19] (Ex. 1327), with is entitled "Epitope Tagging of Recombinant Proteins," Hollengbaugh[20] (Ex. 1328), which is entitled "Construction of Immunoglobulin Fusion Proteins," and Margolin[21] (Ex. 1329), which is entitled "Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells." (*See* ToolGen Opp. 3, Paper 274, 24:10–13.) ToolGen argues further that the ToolGen

[19] Brizzard and Chubet, "Epitope Tagging of Recombinant Proteins," CURRENT PROTOCOLS IN NEUROSCIENCE, 5.8.1–5.8.10 (1997) (Ex. 1327).
[20] Hollenbaugh and Aruffo, "Construction of Immunoglobulin Fusion Proteins," CURRENT PROTOCOLS IN IMMUNOLOGY, 10.19A.1–10.19A.11 (2002) (Ex. 1328).
[21] Margolin, "Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells," METHODS, 20:62–72 (2000) (Ex. 1329).

portion of Count 1 recites a Cas9 protein with a nuclear localization signal, which one of ordinary skill in the art would have understood to be a fusion protein. (*See* ToolGen Opp. 3, Paper 274, 23:23–24:3, *see* Stoddard Decl., Ex. 1420, ¶ 151.)

Even if the prior art did not specifically address modifying Cas9, as Broad argues, neither Broad nor Dr. Seeger cites to evidence persuading us that the prior art would not have suggested modifying Cas9 by adding a functional domain. (*See* Broad Reply 3, Paper 337, 15:10–12.) First, Broad fails to address the fusion of an NLS to Cas9 in the ToolGen portion of Count 1, which is treated as prior art in our inquiry here. Second, Broad fails to explain why the prior art, such as that cited by ToolGen, would have been understood to be inapplicable to Cas9 by those of ordinary skill in the art.

Broad argues that ToolGen has not identified any teaching or suggestion in Count 1 or the prior art directing one of ordinary skill in the art to modify naturally occurring Cas9 protein, but it is Broad's burden to show why such modification would have been non-obvious over the prior art, particularly when ToolGen has identified seemingly relevant art. (*See* Broad Reply 3, Paper 337, 15:21–23.)

Broad fails to persuade us that one of ordinary skill in the art would have considered the claims Broad highlights as being limited to specific protein domains or as including heterologous domains to be non-obvious over the subject matter of Count 1 treated as prior art. Accordingly, we are not persuaded that the claims Broad cites should be designated as not corresponding to Count 1.

H. Conclusion

Because Broad fails to persuade us that any claims should be designated as not corresponding to Count 1, we deny Broad Motion 3.

V. ToolGen Motion 1

ToolGen filed Motion 1, seeking to be accorded benefit of provisional application 61/837,481, which was filed 20 June 2013, or benefit of international application PCT/KR2013/009488, which was filed 23 October 6 2013. (*See* ToolGen Motion 1, Paper 31.)

As ToolGen acknowledges, benefit of the filing date, 23 October 2012, of provisional application 61/717,324, was accorded to ToolGen upon declaration of the interference. (*See* Declaration, Paper 1, 16.) Thus, ToolGen was accorded an earlier filing date than either of the dates it asserts in Motion 1. Broad did not file a motion to change this benefit.[22] (*See* Broad Opp. 1, Paper 269, 1:8–9.)

[22] We note that Broad filed two versions of its Opposition 1: a version under seal (Paper 268) and a redacted version (Paper 269). Broad was not authorized to file either a version under seal or a redacted version. Broad also argues that ToolGen's Motion 1 need not be decided because it is "irrelevant at this time" because ToolGen's accorded benefit date had not been challenged. (*See* Broad Opp. 1, Paper 269, 1:9–11.) Apparently, ToolGen agrees. (*See* ToolGen Reply 1, Paper 334, 1:3–4 ("Motion 1 argues that ToolGen is entitled to the benefit of its P3 or PCT application if the Board grants a Broad motion attacking ToolGen's P1. Broad has not so moved (or otherwise attacked) ToolGen's P1. Thus, the sole contingency has not been met.").) Broad should have requested a conference call to discuss the filing of an opposition to avoid an unathorized filing and both parties should have contacted the Board to avoid a waste of the parties' and the Board's resources.

Accordingly, we dismiss ToolGen Motion 1 as being moot.

VI. ToolGen Miscellaneous Motion to Exclude Evidence

ToolGen filed a miscellaneous motion to exclude evidence relied upon by Broad. (*See* Paper 349.) Because we deny Broad Motion 1 and Motion 3 even if we consider the exhibits highlighted by ToolGen, we need not determine if they were admissible.

Accordingly, we dismiss ToolGen Miscellaneous Motion 1 as being moot.

VII. Conclusion

We deny Broad Motion 1 and Motion 3.

We dismiss as moot Broad Motion 2 and ToolGen Motion 1, as well as ToolGen Miscellaneous Motion 1.

Information regarding a priority phase will be entered separately.

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