Filed on behalf of Senior Party ToolGen, Inc. Paper No. _____

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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,

Junior Party,

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,

v.

TOOLGEN, INC.

Senior Party.

Application 14/685,510

Patent Interference No. 106,126 (DK)

TOOLGEN OPPOSITION 1
(opposing motion to substitute Proposed Count 2)

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Senior Party ToolGen, Inc. requests that the Board dismiss or deny Broad's Motion 1 seeking to substitute Proposed Count 2 for Count 1. Broad's request would broaden the count to include dual-molecule RNA and rests on Broad's allegation that Count 1 improperly limits its ability to rely on its best proofs, which, according to Broad, "are based on Dr. Feng Zhang's use of dual-molecule RNA systems." Broad Motion 1 ("Mot.") 1:21–23.

At the outset, Broad's motion should be dismissed because it fails to demonstrate—*in fact, it never even argues*—that dual-molecule RNA and single-molecule RNA are the same patentable invention. That is a prerequisite for substitution, and it is absent here.

Alternatively, the motion should be denied because Proposed Count 2 does not properly define the common *claimed* subject matter—*all* of ToolGen's involved claims are limited to single-molecule RNA. And Broad's description of its "best proofs" is insufficient as a matter of law—neither ToolGen nor the Board can determine whether Proposed Count 2 is necessary based on the information or arguments provided.

Appendix 1 is a List of Exhibits Cited. Appendix 2 is the Statement of Material Facts.

I. THE BOARD SHOULD NOT ADOPT PROPOSED COUNT 2

A. Broad Fails To Demonstrate That Dual-Molecule And Single-Molecule RNA Are The Same Patentable Invention

On page 5, line 9 to page 7, line 8 of its motion, Broad argues that dual- and single-molecule RNA configurations "are analogous approaches to the RNA component in a CRISPR-Cas9 system." Mot. 5:9–7:8. The response is that Broad does not argue that dual- and single-molecule RNA configurations, as used in CRISPR-Cas9 systems in eukaryotes, are the same patentable invention, as would be required to adopt Broad's Proposed Count 2.

Broad's Proposed Count 2 retains claim 85 of ToolGen's '510 application (which is limited to sgRNA), but replaces Broad's half of the count with claim 1 of its '710 application, which

"encompasses both dual- and single-molecule RNA configurations." Mot. 3:15–4:15; F39. Broad's motion is doomed at the threshold, however. Broad fails to address—let alone demonstrate—whether dual-molecule and single-molecule RNA configurations are the same patentable invention, such that they could be properly included in the same count. The cases that Broad cites to support its request to broaden the count (Mot. 18), make clear that, in those cases, the additional subject matter added was the same patentable invention. *Grose et al. v. Plank et al.*, 15 U.S.P.Q.2d (BNA) 1338, 1342, (B.P.A.I. March 23, 1990); *Kondo et al. v. Martel et al.*, 220 U.S.P.Q. (BNA) 47, 49 (B.P.A.I. May 2, 1983). Broad has failed to make that showing here.

As a general matter, it is axiomatic that a count cannot "be broadened to such an extent as to include another, separately patentable invention." *Theeuwes v. Bogentoft*, 2 U.S.P.Q.2D (BNA) 1378, 1379 (Comm'r Pat. & Trademarks December 11, 1986); *see also, e.g.*, *Lee v. McIntyre*, 55 USPQ2d 1137, 1142 (B.P.A.I. 2000). To prove entitlement to a broadened count, Broad would have had to have demonstrated that single-molecule and dual-molecule RNA embodiments are the same patentable invention. 37 C.F.R. § 41.121(b); SO ¶121.3 ("a movant bears a burden to establish its right to any substantive relief requested in the motion."). Broad has failed to do so here.

Broad's motion is bereft of any showing that a dual-molecule system would have been *prima facie* obvious over a single-molecule system. *Spine v. Biedermann Motech GmbH*, 684 F. Supp. 2d 68, 89 (D.D.C. 2010). Under the standard *Graham* framework for determining obviousness, which applies to interferences, Broad bears the burden of establishing, *inter alia,* (1) the scope and content of the relevant prior art, (2) any difference between the dual molecule system and the single molecule system, and (3) the level of skill in the art. *Graham v. John Deere Co*., 383 U.S. 1, 17 (1966).

Broad's Motion does not address whether dual-molecule configurations are obvious over single-molecule configurations, much less the *Graham* factors. Indeed, it compares dual- and single-molecule RNA configurations only in the Background section, where it states only that the two configurations are "*highly analogous*." Mot. 6:10–11 (emphasis added). But "highly analogous" does not suffice to show that single- and dual molecule RNA configurations are the same invention. Worse, Broad's "highly analogous" contention is supported not with expert testimony, but with only lawyer argument and whisper-thin evidence: (1) a handful of articles that do not relate to or even mention CRISPR-Cas9; and (2) the inadmissible testimony of two CVC fact witnesses in the 115 interference. Neither category of evidence aids Broad's cause one bit.

First, Broad's expert, Dr. Seeger, never even mentions any of the publications Broad cites in support of its comparison (Ex. 2643, Ex. 2684, Ex. 2645, Ex. 2646), and it is well-settled that unsupported attorney argument is not evidence, nor is it sufficient to demonstrate obviousness. *Invitrogen Corp. v. Clontech Labs., Inc*., 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony."); *Elbit Sys. of Am., LLC v. Thales Visionix, Inc*., 881 F.3d 1354, 1359 (Fed. Cir. 2018); *In re Gorniak*, No. 90-1510, 1991 U.S. App. LEXIS 2741, at *3 (Fed. Cir. Feb. 20, 1991). Without Dr. Seeger's support, Broad is left with the testimony of two CVC fact witnesses from the 115 interference—Krzyzstof Chylinski and Martin Jinek. Mot. 6:20–7:8. Putting aside that their testimony is inadmissible hearsay, those witnesses stated only that dual-molecule- and single-molecule-based systems are "closely related" or "informative." *Id*. This is scarcely any different than Broad's lawyers' "highly analogous" claim. Neither witness even came close to suggesting that dual- and single-molecule RNA configurations are the same patentable invention. Broad's conclusory assertions are therefore entitled to no weight.

Second, none of Broad's cited Exhibits—2643, 2684, 2645, and 2646—relate to or even mention CRISPR-Cas9, and Broad has made no showing that a POSA would have been motivated to review those references in the context of CRISPR-Cas9. Ex. 1420, ¶¶30–34; F40. Nor does Broad provide argument or explanation of any kind regarding the content of those references, or how, or why, the teachings in those references might demonstrate that single- and dual-molecule RNA systems are the same patentable invention. Ex. 1420, ¶¶30–34; F41.

In sum, Broad's unsupported statements fail to demonstrate that single-molecule RNA and dual-molecule RNA configurations are the same patentable invention. Moreover, Broad cannot attempt to make that showing for the first time in its reply. *Nau v. Ohuchida*, Int. No. 104,258, Paper 57, at *4 (B.P.A.I. 1999) (precedential) ("The Trial Section does not deem it fair to an opponent when a party 'gets its licks in' for the first time at the reply stage after the opponent can no longer submit evidence and/or argument.").

For at least these reasons, the Board should dismiss or deny Broad's Motion.

B. Proposed Count 2 Should Be Rejected Because It Is Broader Than What Defines The Parties' Common Claimed Subject Matter

On page 21, line 8 to page 23, line 6 of its motion, Broad argues that its Proposed Count 2 reflects the full scope of the interfering subject matter. Mot. 21:8–23:6. The response is that Proposed Count 2 is broader than the parties' common claimed invention, and it therefore does not properly define the common claimed subject matter. Ex. 1420, ¶¶37–50; F42. Count 1, on the other hand, which is limited to a single-molecule RNA configuration, properly defines the common claimed subject matter. It is the parties' "common subject matter claimed" that gives rise to an interference. *Beech Aircraft Corp. v. Edo Corp*., 990 F.2d 1237, 1248–49; *Louis v. Okada*, 59 U.S.P.Q.2d 1073, 2001 WL 775529 at*4 (B.P.A.I. 2001) (precedential) ("It is the parties' *claimed* invention which gives rise to an interference under 35 U.S.C. § 135(a).") (emphasis added). Here,

ToolGen's involved claims are not generic or directed to dual-molecule RNA; the claims are *limited to a single-molecule RNA configuration*, and Broad has not argued otherwise. Paper 1 (Declaration of Interference), 12–13; F43. Broad admits this, stating: "ToolGen originally claimed … both dual- and single-molecule RNA configurations of CRISPR-Cas9 *before amending to only the single-molecule approach currently claimed in their involved patent application.*" Mot. 22:12–15 (emphasis added). Broad's "Charts Showing Alignment of ToolGen's Independent Claims With Proposed Count 2," set forth in Appendix D of its motion, confirm that ToolGen's claims are limited to single-molecule configurations. Simply put, dual-molecule RNA is not common claimed subject matter and should not be included in the count. The only common claimed subject matter is single-molecule RNA. Paper 1, Declaration of Interference, 12–13; F44.

Given that ToolGen's involved claims are limited to a single-molecule RNA configuration, on page 2, lines 21-23 and page 11, lines 11-19 of its motion, Broad, in an attempt to cure that flaw in its argument, contends that "ToolGen has likewise asserted claims directed to the eukaryotic invention with a generic RNA configuration and has [other] such claims pending." The response is that that argument is equally unavailing. It is irrelevant that ToolGen's application "initially included claims to both dual- and/or single-molecule RNA configuration" or that ToolGen is "continuing to prosecute non-limited claims in pending applications." Mot. 15–16. The only claims that matter are those involved in this interference. *See generally Louis*, 2001 WL 775529 at *4.

For at least these reasons, Broad's Motion should be dismissed or denied.

C. Broad's Alleged "Best Proofs" Do Not Justify The Substitution Of Count 1 With Proposed Count 2

On page 19, line 1 to page 20, line 8 of its motion, Broad argues that "Count 1 improperly limits its ability to rely on its best proofs." Mot. 19:1–20:8. The response is that Broad does not

identify its best proofs sufficiently such that ToolGen or the Board could determine whether substitution of Count 2 for Count 1 is appropriate. Ex. 1420, ¶¶37–50; F45. Moreover, Broad's proposed count improperly adds and removes elements of the current count. Ex. 1420, ¶¶35–36; F46.

The Board should change the scope of the count "only i[f] there is a compelling reason to do so." *See Regents of Univ. of Cal. v. Broad Inst*., Interference 106,115, Decision on Motions, Paper 877, *33 (P.T.A.B. Sept. 10, 2020) (Ex. 2121); s*ee Louis*, 2001 WL 775529 at *4. "Arguments that a moving party's best or earliest proofs are outside the scope of the existing count are ordinarily not compelling by themselves." Ex. 2121, *Regents of Univ. of Cal. v. Broad Inst*., Interference 106,115, Decision on Motion, Paper 877, *33 (P.T.A.B. Sept. 10, 2020); F47. Indeed, "a preliminary motion to broaden out the count on the basis that a party's best or earliest proofs are outside of the current count (1) should make a proffer of the party's best proofs, (2) show that such best proofs indeed lie outside of the scope of the current count, and (3) further show that the proposed new count is not excessively broad with respect to what the party needs for its best proofs." *Louis*, 2001 WL 775529 at *4. As discussed below, Broad has not satisfied any of the three requirements set forth in *Louis*.

1. Broad's proffer of its "best proofs" does not provide ToolGen or the Board with sufficient information to support its request for relief

On page 7, lines 16–19 of its motion, Broad contends that its best proofs demonstrate actual "reductions to practice" using dual-molecule RNA CRISPR-Cas9 systems. Mot. 7:16–19. The response is that Broad's proffer must—but does not—describe its best proofs in sufficient detail such that: (1) ToolGen may decide whether and how to oppose, and (2) the Board can evaluate the respective positions of the parties. S*ee Byrn v. Aronhime*, Int. No. 105,384, Paper 64, at 11

(B.P.A.I. Sept. 20, 2006). Broad, which bears the burden of supporting its motion with "appropriate evidence," fails on both scores. *See* 37 C.F.R. § 41.208(b).

Broad's motion provides scant information regarding the very few proofs it presents, and Broad's own expert did not opine on the underlying data such that ToolGen and the Board could evaluate Broad's proofs to determine whether Proposed Count 2 is necessary. Ex. 1420, ¶¶37-49; F48.

(a) Broad's alleged 2011 proofs

Broad first alleges on page 7, lines 16–19 that Dr. Zhang performed experiments in 2011 including "reductions to practice with CRISPR-Cas9 systems using tracrRNA and crRNA that were ***not*** fused or covalently linked but were still hybridized as an RNA duplex in the cutting complex with Cas9." Mot. 7:16–19 (emphasis in original). The response is that Broad offers no evidence of any such experiments upon which ToolGen or the Board can evaluate. Ex. 1420, ¶¶37–40; F49. Broad submits no testimony from Dr. Zhang or other scientists, and Dr. Seeger expressly does ***not*** rely on any such testimony. Ex. 2454, ¶185; F50. Broad alleges without fact witness or expert support that Zhang studied Deltcheva 2011 (Ex. 2214) and understood that "during the maturation process, the crRNA hybridized with [the tracrRNA] and those RNA components remained hybridized in the cutting complex." Mot. 7:19-22. The response is that Zhang did not so testify in this matter and regardless, Deltcheva recognized such hybridization not for DNA cleavage, but for maturing pre-crRNA repeats. Ex. 2214; Ex. 1420, ¶43; F51. Moreover, the emails Broad cites (Mot. 7:22–23) show that Dr. Zhang had at best a research plan as late as October 2011, in which he was still trying various RNA combinations. Ex. 2710 ("It's worthwhile to try dsRNA . . . I don't think transfecting crRNA alone will work."); F52. He was not, as Broad alleges, successful, nor does Broad offer any evidence that he was.

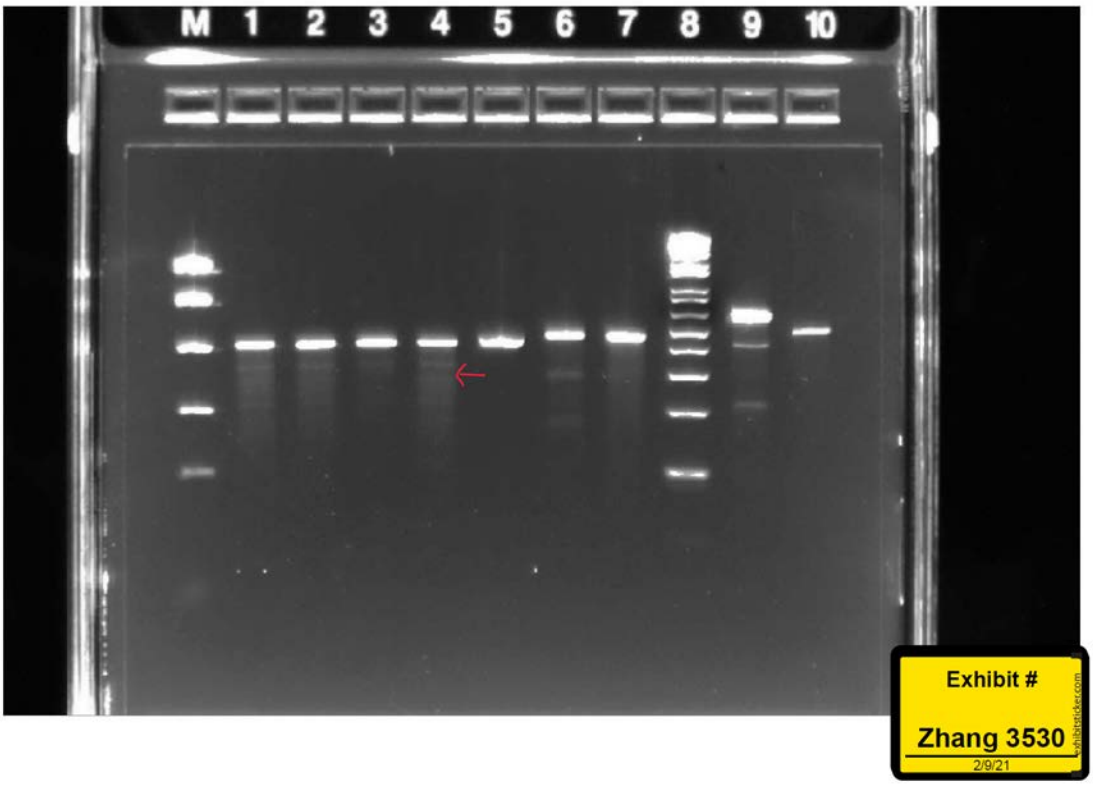
Broad alleges that Exhibits 2526, 2708 and 2530, evidencing Dr. Feng Zhang's 2011 experiments, demonstrate reductions to practice with CRISPR-Cas9 systems using dual-molecule RNA. Mot. 7:3–13. The response is that Broad's proffered exhibits do not provide adequate information to evaluate Broad's claim, nor do they possibly disclose all limitations of Proposed Count 2. Ex. 1420, ¶¶37–38, 40.

Broad claims that Exhibit 2526 is a "file dated April 5, 2011 [showing] that Dr. Zhang had completed a vector design" that "[w]hen expressed … would have a dual-molecule RNA configuration, not a single-molecule RNA configuration." Mot. 8:3–8. Dr. Seeger's declaration adds that Dr. Zhang's vector design was "intended to be expressed in the eukaryotic cell." Ex. 2454, ¶191. The response is that Exhibit 2526 does not provide adequate information to evaluate Broad's assertion or Dr. Seeger's conclusion. Ex. 1420, ¶37. As an initial matter, neither Dr. Zhang, nor any witness with personal knowledge, provide any explanation of the file's contents. F53. The file itself is undated, and there is no indication that the file was ever dated April 5, 2011. Ex. 2526; Ex. 1420, ¶37; F54. Moreover, on its face, the exhibit does not illustrate any component of a vector or its design that might be used for introduction or expression of CRISPR components in a eukaryotic cell; it provides only a genetic map and sequence of a CRISPR system in a bacterium, specifically, in *Streptococcus thermophilum*. Ex. 2526; Ex. 1420, ¶37; F55. Exhibit 2526 does not support Broad's prediction that "[w]hen expressed, this system would have a dual-molecule RNA configuration." Ex. 2526; Ex. 1420, ¶37; F56.

Next, at page 8, lines 9–11, Broad cites to an email purportedly from Dr. Zhang that Broad says shows that Dr. Zhang "ordered a vector to express tracrRNA and pre-crRNA array." Mot. 8:9–11. The response is that Exhibit 2708 shows a DNA sequence, but provides no annotation of the functional elements, coding sequence(s) or purpose of the sequence or any description of any

planned experiments. Ex. 2708; Ex. 1420, ¶38; F57. Dr. Seeger opines that, "when expressed and matured, this system would have had a dual-molecule RNA configuration." Mot. 8:10–11, Ex. 2454 ¶¶ 192–93. But Dr. Seeger did not consider any experiments using this vector. Ex. 2454 ¶ 192–93; F58. Rather, his opinion as to the intended or actual use is based on assumptions provided to him. Ex. 2454 ¶ 192–93. Plainly, such testimony is not helpful to the Board.

As evidence of whether the vector that Dr. Zhang allegedly ordered was ever used, Broad cites only Exhibit 2530. Mot. 8:12–13. The response is that Exhibit 2530 provides no such correlation and is effectively devoid of any useful information. Ex. 1420, ¶40; F59. Misnumbered Ex. 3530, but filed as Ex. 2530, the exhibit is reproduced here in its entirety:



That is, Exhibit 2530 is an unlabeled, uncorrelated and unexplained image of what may be an electrophoresis gel, that cannot serve as any basis for Broad's contention that "[t]his system was

used to target, cleave, and edit an endogenous 'NTF3' genomic target in eukaryotic cells in October-November 2011," as Broad suggests to the Board. Mot. 8:12–13; Ex. 1420, ¶40; F59.

In addition to containing no information correlating it to Broad's other exhibits, on its face, Ex. 2530 provides no useful information. Ex. 1420, ¶40; F59. A POSA would have expected certain identifying features to be present in a gel image, such as labeling, captioning, or a description that would allow a POSA to infer the nature of the experiment or results being illustrated. Ex. 2530; Ex. 1420, ¶40; F60. All are absent in Ex. 2530, which also lacks the typical indications of molecular masses or sizes of bands, the standard molecular weight ladder, any indication of the components or approach used to generate the elements observed in each lane, and any indication of the identity of any of the bands on the gel. Ex. 2530; Ex. 1420, ¶40; F61.

Taken as a whole, Broad's Exhibits 2526, 2708 and 2530 do not provide the Board adequate information to assess whether Broad's alleged proofs require an expanded count. Ex. 1420, ¶47. Moreover, even with every benefit of the doubt, Broad's exhibits are insufficient to demonstrate that every element of Proposed Count 2, including that "the DNA molecule is cleaved or edited in the eukaryotic cell" is satisfied. Ex. 1420, ¶47; *See* SO ¶158.2.1. ("Explanation of tests or data must come in the form of an affidavit, preferably accompanied by citation to relevant pages of standard texts (which should be filed as exhibits). In addition to providing the explanation required in Bd. R. 158(b), the proponent of the test evidence should provide any other information it believes would assist the Board in understanding the significance of the test or the data.").

(b) 2012 NIH Grant Application (Exhibit 2051)

Next, Broad makes the unsupported statement that, "[i]n view of the success of his experiments"—a premise for which there is no evidence in Broad's motion—"Dr. Zhang followed up with a January 12, 2012 NIH grant application based on dual-molecule RNA CRISPR systems engineered for use in eukaryotic cells." Mot. 8:14–16. Citing to Ex. 2051 at page 9, lines 1–5,

Broad argues that the system shown in Figure 4B of the application "would provide a dual molecule tracrRNA:crRNA duplex after processing" and "would not include a single molecule RNA as part of the active cutting complex." Mot. 9:1–5. The response is that the NIH grant application provided in Exhibit 2051 does not provide sufficient information to evaluate whether an embodiment of the proposed count was reduced to practice. Ex. 1420, ¶41-44.

First, the application does not provide any preliminary data indicating that the illustrated construct had been tested, nor that a POSA would reasonably expect the construct to generate a functional CRISPR-Cas9 complex if it were tested. Ex. 1420, ¶41; F62. There is no explanation regarding how the individual tracrRNA and guide RNA components would be expected to function when embedded in surrounding self-spliced introns. Ex. 1420, ¶42; F63. To the contrary, as Dr. Stoddard explains, a POSA would not expect the construct shown in Figure 4B to yield an appropriate stoichiometric balance of protein and RNA molecules for generation of active CRISPR-Cas9 complex. Ex. 1420, ¶42; F64.

Dr. Seeger provides no evidence or testimony to the contrary. Indeed, he does not testify as to whether the system had been tested or that he reviewed any experimental data at all. Ex. 1109, 230:16-20. 204:14-22; F65, F66. Consistently, when asked during his deposition in the 115 interference "whether the construct shown in Figure 4 of the NIH application produced a functional CRISPR-Cas9 system," he testified that he had "no opinion on data." Ex. 1109, 230:16–20; F65. He further testified that he had not inquired whether the experiments proposed in the NIH grant application were even conducted. *Id*. at 204:14–22; F66.

Broad does not offer any such construct used in mammalian cells or in any other experiment, and the "design" offered in the NIH grant application was pure conjecture that was not reduced to practice. *See generally* Ex. 2051; Ex. 1420, ¶41; F67. Indeed, according to the

NIH application, "the development of the CRISPR system for modifying mammalian genomes" was not to begin until "year 2"—i.e., September 2013 – August 2014). Ex. 2051 at 3; F68.

Second, contrary to Broad's assertions, Figure 4B illustrates a significant lack of understanding of the molecular basis for CRISPR-Cas9 function. Ex. 1420, ¶¶41,43. According to Figure 4B, "[t]he crRNAs direct enzymes from the Cas Gene Module to cleave the target DNA at specific sequences." Ex. 2051, Fig. 4B; Ex. 1420, ¶43. The tracrRNA element, however, merely "facilitate[s] the processing of guide RNAs, and the guide RNA array." Ex. 2051, Fig. 4B; Ex. 1420, ¶43; F69. Indeed, at the time (and as reflected in Figure 4B), Deltcheva *et al.* (Ex. 1203) taught that the tracrRNA simply directed the maturation of another non-coding RNA (Pre-crRNA) to yield the active species (crRNAs), which (at the time) occurred by an unknown process. Ex. 1420, ¶43; *See* Ex 1203; F70. It was not known that the tracrRNA was part of the guide RNA, only that it was necessary to mature the active crRNAs, and Figure 4B does not reflect any advanced understanding of that concept. Ex. 1420, ¶43; F71. Indeed, given the state of the art at the time, Figure 4B suggests that Dr. Zhang was unaware that a dual complex (tracrRNA:crRNAs) was in fact the dual-guide component of the CRISPR-Cas9 system. Ex. 1420, ¶¶41, 43; F72.

Given the lack of details in the proofs, neither ToolGen nor the Board can determine whether substitution of Proposed Count 2 for Count 1 is needed. Broad's NIH grant application, alone or in conjunction with Broad's Exhibits 2526, 2708 and 2530, still does not disclose every element of Proposed Count 2, including that "the guide sequence directs the Cas9 to the target sequence, whereby the DNA molecule is cleaved or edited in the eukaryotic cell." Mot. 4:13–14.

(c) April 2012 Reporter Experiment

Next, citing to Exhibit 2533 at page 9, lines 6–8, Broad asserts that "Dr. Zhang continued to develop this system throughout early 2012, where, among other things, he tested in April 2012 a human-codon-optimized version of a construct to express SpCas9 in his dual-molecule RNA

system in a eukaryotic cell." Mot. 9:6–8; Ex. 1420, ¶45. The response is that Broad provides no explanation or fact witness or expert testimony regarding what is shown in Exhibit 2533, which on its face purports to show an SpCsn1 sequence that Dr. Zhang allegedly ordered (based on Exhibit 2734). Exhibit 2533 provides no annotation of the functional elements of the sequence, the coding sequence(s) or purpose of the DNA sequence shown, and no indication of how it might be incorporated in any particular vector or used for the purpose of testing CRISPR-Cas9 in a eukaryotic cell. Ex. 1420, ¶45; F73. And Dr. Seeger did not cite to or opine on Ex. 2533. Given the lack of details in the proofs, Exhibit 2533 does not provide sufficient information to determine whether substitution of Count 2 for Count 1 is needed based on Broad's "proofs." Ex. 1420, ¶45. Moreover, at the time, there is no indication that Dr. Zhang had become aware that the tracrRNA was part of the guide RNA. Ex. 1420, ¶45; F74.

Citing to Exhibits 2535–36 at page 9, lines 9–13, Broad further argues that "[t]his test further confirmed his successful use of his CRISPR-Cas9 system for function in a eukaryotic cell by using a frame-shift CRISPR reporter that, when cleaved by the dual-molecule RNA CRISPR-Cas9 system, shifted a green fluorescent protein into frame, providing a green color read out indicating success." Mot. 9:9–13; Ex. 1420, ¶46. The response is that, in a manner consistent with all of Broad's "best proofs," Exhibits 2535 and 2536 are insufficient to support its representation, much less to prove anything. Ex. 1420, ¶46. The exhibits are missing any identifying features, labeling, captioning, or description that would allow a POSA to infer the nature of the experiment or the results being illustrated. Ex. 1420, ¶46; F75. There is no indication or description of the components or approach used to generate the images shown, nor any details of the form of microscopy employed. Ex. 1420, ¶46; F76. And once again, Dr. Seeger did not consider or cite to these exhibits in his declaration. F77. Instead of evaluating and analyzing the underlying data,

Dr. Seeger merely parroted his assumptions—from what he was told by counsel—about the system's purpose. Ex. 2454, ¶197. *See* SO 158.1.1 ("Each affidavit expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based. Bd.R. 152; Fed. R. Evid. 705. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.").

Broad's proofs, purportedly illustrating its April 2012 reporter experiment, alone or in conjunction with the exhibits previously described, still do not disclose every element of Proposed Count 2, including that "the guide sequence directs the Cas9 to the target sequence, whereby the DNA molecule is cleaved or edited in the eukaryotic cell." Mot. 4, lines 13–14; Ex. 1420, ¶47.

(d) Single-molecule RNA

On page 9, lines 14–16, Broad argues that "[i]t was only after Dr. Zhang had already engineered and tested dual-molecule RNA CRISPR-Cas9 systems in eukaryotic cells that, on June 26, 2012, he conceived of and by July 20, 2012 actually reduced to practice a single-molecule RNA system using a GAAA linker." Mot. 9:14–16. To support its conclusory statement, Broad cites to nineteen exhibits without providing any argument, explanation or comment from Dr. Seeger. *Id.* at 9:14–10:6. The response is that the exhibits do not demonstrate that (1) Broad reduced to practice dual-molecule RNA, (2) that any purported reduction to practice occurred prior to allegedly reducing to practice a single-molecule RNA system, or (3) that Dr. Zhang actually reduced to practice a single-molecule RNA system by July 20, 2012.

(e) Cong 2013

Finally, on page 10, lines, 7–11, Broad argues that Cong 2013 (Ex. 2201) "describes experiments that involved expressing tracrRNA and pre-crRNA separately—a dual-molecule RNA system" along with "eukaryotic single molecule RNA work." Mot. 10:7–11; Ex. 1420, ¶49. The response is that Cong 2013 is of no consequence here. Cong 2013 does not indicate that dual-

molecule experiments were performed prior to single-molecule RNA experiments. Ex. 1420, ¶49; F78. Cong 2013 does not disclose the dates for its experiments, and a POSA would not infer a chronological order of those experiments based on Cong 2013. Ex. 1420, ¶49; F79.

* * *

In summary, Broad has not met its burden of supporting its motion with "appropriate evidence." 37 C.F.R. § 41.208(b). Broad fails to provide sufficient information to evaluate whether its "best proofs" merit expansion of the count. *Byrn v. Aronhime,* Int. No. 105,384, Paper 64, at 11 (B.P.A.I. Sept. 20, 2006). The proofs that Broad relies upon do not even suggest, let alone prove, that Broad conducted dual-guide experiments before it conducted any single-guide experiments, or that it reduced to practice every element of the proposed count. For these reasons, the Board should deny or dismiss Broad's Motion.

2. Broad's own admissions demonstrate that its best proofs encompassed a single-molecule RNA system and thus do not lie outside of the scope of the current count

Broad has failed to offer appropriate and sufficient evidence to establish that Count 1, a single-guide count, excludes its purported best proofs. *See Genentech, Inc. v. Zymogenetics, Inc*., Int. No. 105,664, Paper 131 at 13–15 (B.P.A.I. Jan. 26, 2010) (denying motion to change scope of the count for failure of movant to establish that its best proofs could not be relied upon under the present count). Broad's own admissions show that all of the systems described in its best proofs encompassed a single-molecule RNA configuration, and thus redefining the count to include dual-molecule RNA configurations is unnecessary because Broad's proofs do not "lie outside of the scope of the current count." *Louis*, 2001 WL 775529 at *4.

On page 8, lines 10–13, Broad argues that "Dr. Zhang ordered a vector to express tracrRNA and pre-crRNA array" that "[w]hen expressed and matured … would also have had a dual-

molecule RNA configuration." Mot. 8:10–13. Pointing to Ex. 2530, Broad argued that, "[t]his system was used to target, cleave, and edit an endogenous 'NTF3' genomic target." Mot. 8:12–13. On page 9, lines 4–5 of its motion, Broad further argues that Figure 4B in the NIH grant application illustrates a system that would ***not include*** a single-molecule RNA. Mot. 9:4–5. The response is that Broad's arguments are contrary to the inventor declaration that Broad submitted during prosecution to obtain single-molecule RNA claims. During prosecution of Application 14/704,551, Dr. Zhang, in his December 21, 2015 declaration, identified the same Figure 4B as evidence of his "appreciation that ***a single RNA*** can be used as a guide in the CRISPR-Cas system, including as shown by the RNA used in the experiment of the below figure entitled 'CRISPR NTF3 Surveyor . . . .'" Ex. 1110, ¶ 19 (emphasis added); F80. Broad cannot reconcile its current position with the statement of this declaration, and should not be permitted to do so in its reply.

In fact, Broad should be estopped from now making representations contrary to those it previously made to this agency. Broad submitted Dr. Zhang's statement during prosecution of the '551 application for the purpose of antedating prior art and establishing that Broad had possession of a chimeric RNA or fused RNA [single-molecule RNA] vector system. Ex. 1111 (Supplemental Response); F81. This statement allowed Broad to obtain claims directed to single-molecule subject matter (i.e., its claims in the '551 application reciting "chimeric RNA"). Ex. 1112 (Notice of Allowance); F82. Indeed, the Office expressly referenced the declaration of Dr. Zhang in the Statement of Reasons for Allowance, demonstrating that it was among the "reasons why the application was allowed." Ex. 1112 at 4; *See* MPEP § 1302.14.I (9th ed. Rev. 7, Nov. 2015); F83. Broad cannot now re-characterize its proofs as limited to dual-molecule RNAs that "would not include a single molecule RNA as part of the active cutting complex." Mot. 9:4–5.

Broad's current position is therefore judicially estopped by its prior statements that allowed it to obtain single-molecule RNA claims. *Zedner v. United States*, 547 U.S. 489, 504 (2006) ("[W]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position . . . ."). Judicial estoppel applies to agency adjudications just as it does to court adjudications. *See Trustees in Bankr. of N. Am. Rubber Thread Co. v. United States*, 593 F.3d 1346, 1354 (Fed. Cir. 2010) ("Judicial estoppel applies just as much when one of the tribunals is an administrative agency as it does when both tribunals are courts."). All the relevant factors here compel a finding of judicial estoppel: (1) Broad's current position is inconsistent with its prior position; (2) Broad obtained allowance of claims to single-guide RNA in part as a result of submitting Dr. Zhang's declaration; and (3) Broad would derive an unfair advantage if permitted to argue inconsistently here, to ToolGen's detriment (e.g., ToolGen's single molecule claims would run the risk of being dominated by a generic RNA claim). *New Hampshire v. Maine*, 532 U.S. 742, 750–51 (2001).

Accordingly, the NIH Grant Proposal, and the systems described therein that Broad "continued to develop thereafter" do not demonstrate that Broad has earlier proofs that "lie outside of the scope of the count." *Louis*, 2001 WL 775529 at *4. And to the extent Broad seeks to rely on Dr. Zhang's declaration in its reply to bolster its barebones proofs proffered in Motion 1, the Board should not entertain those improper arguments because: (1) Dr. Zhang's declaration demonstrates that those proofs encompass single-molecule RNA configurations and are thus within the scope of Count 1, and (2) Broad bears the burden of supporting its motion with "appropriate evidence" and cannot make that showing for the first time in its reply. 37 C.F.R. § 41.208(b); *Nau v. Ohuchida*, Int. No. 104,258, Paper 57, at 4 (B.P.A.I. 1999) (precedential).

3. Broad's Proposed Count 2 is excessively broad with respect to what Broad allegedly needs for its best proofs, and would eliminate significant limitations of the current count

Even the proofs, for which Broad only offers hints, show that Broad's proposed count is excessively broad in comparison to any such proofs. At the same time, Broad's proposed count also would improperly eliminate significant elements of Count 1.

(a) Broad's Proposed Count 2 is excessively broad

On page 21, line 8 to page 23, line 6, Broad argues that Proposed Count 2 reflects the full scope of the interfering subject matter. Mot. 21:8–23:6. The response is that Broad's Proposed Count 2 is excessively broad with respect to what it requires for its best proofs. Broad's half of the proposed count ('710 application, claim 1) recites that "the guide sequence directs the Cas9 to the target sequence, whereby the DNA molecule is cleaved ***or edited*** in the eukaryotic cell." Mot. 2. DNA "editing," however, is broader than DNA "cleavage," as it includes results other than cleavage, such as epigenetic DNA modifications. Ex. 1420, ¶¶35–36; F84. Notably, current Count 1 is limited to DNA "cleavage." F85.

As discussed in Section I.C.1. above, to the extent Broad argues "proofs" regarding an alleged reduction to practice of Proposed Count 2, those proofs are limited to purported DNA cleavage—not DNA ***editing*** more broadly. Ex. 1420, ¶¶35-36. While Broad's lawyers characterize Dr. Zhang's 2011 experiments as attempting to "***target, cleave, and edit*** an endogenous 'NTF3' genomic target," Mot. 8, the documents themselves, even as reimagined by Dr. Seeger, do not claim to "edit" the genomic target. And Dr. Seeger does not state otherwise. He clarified that the system "was intended to ***target and cleave***" the genomic target. Ex. 2454, ¶192; F86. Indeed, a POSA would have understood that editing of genomic DNA to be broader than targeting or cleaving genomic DNA. Ex. 1420, ¶35; F87.

Likewise, with respect to the NIH grant application that allegedly describes a dual-molecule RNA CRISPR-Cas9 system, Dr. Seeger described the disclosed system as one "that ***cleaves*** the target DNA." Ex. 2454, ¶196; F88. And with regard to the April 2012 experiments, Broad indicated that the shift in green fluorescent protein was attributed to "***cleav[age]***" of the CRISPR reporter. Mot. 9; F89. Even in its best light, Broad's proffered evidence is limited to cleaving DNA and does not support the inclusion of "editing" of DNA, as contained in Broad's proposed claim. Accordingly, Broad has not shown that its Proposed Count is not excessively broad with respect to what Broad needs for its best proofs. *Louis*, 2001 WL 775529 at *4. For this reason, the Board should reject Broad's Proposed Count.

(b) Broad's Proposed Count 2 eliminates significant limitations of the current count

At the same time, and without any explanation, Broad argues for a proposed count that also ***eliminates*** significant elements of the current count, including the limitation that "***expression of at least one gene product is altered***." Mot. 13–14. The response is that none of Broad's proffered best proofs, to the extent understood, even comes close to demonstrating that expression of a gene product was altered, which explains Broad's deletion of the limitation. Ex. 1420, ¶¶36, 48; F90. Eliminating the alteration limitation unnecessarily changes the scope of the count and for this additional reason, the Board should deny or dismiss Broad's Motion. Broad offers no legal basis, and there is none, for its unexplained deletion of this limitation of Count 1. For this additional reason, Broad's Proposed Count is improper.

D. Count 1 Does Not Unjustly Put At Risk Broad's Entitlement To Generic RNA Claims.

On page 20, line 12 to page 21, line 7, Broad argues that the current count unjustly puts at risk Broad's entitlement to generic RNA claim now and in the future. The response is, contrary to

Broad's complaints, the risk to "Broad's entitlement to current and future claims to the genus (eukaryotic CRISPR)" is not unjust. Mot. 20:12–21:7. Losing a generic claim is simply the legal consequence of losing a count encompassed within the generic claim. "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). As Broad acknowledges, "a losing party is barred on the merits from seeking a claim that would have been anticipated or rendered obvious by the subject matter of the lost count." MPEP § 2308.03 (9th ed. Rev. 7, Nov. 2015). And as the Board aptly noted in the '115 Interference, "[i]f Broad's generic claims are anticipated or rendered obvious by CRISPR-Cas9 with a single-molecule RNA configuration, Broad is not entitled to the claims under the principles of estoppel if it loses on priority to Count 1. Broad's burden is to show that its claims are not anticipated or rendered obvious by Count 1." Ex. 2121 (Interference 106,115, Decision on Motion, Paper 877, *51 (P.T.A.B. Sept. 10, 2020)). The party prevailing on a single-molecule RNA count should not have that invention dominated by a generic RNA claim of the losing party. Thus, Broad's "unfairness" argument rings hollow.

Moreover, there is no injustice here, given that Broad could have pursued other remedies. Broad could have filed a motion requesting ToolGen add applications or claims directed to generic or dual-molecule RNA to be designated as corresponding to current Count 1, but it did not do so. SO ¶¶203.2, 208.5. Accordingly, maintaining Count 1 does not unjustly risk Broad's entitlement to generic claims.

II. EVEN IF SINGLE-MOLECULE RNA CLAIMS ARE SEPARATELY PATENTABLE INVENTIONS FROM DUAL-MOLECULE RNA CLAIMS, GENERIC RNA CLAIMS SHOULD BE DESIGNATED AS CORRESPONDING

TO COUNT 1

On page 23, lines 10–18, Broad argues that "[i]f 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," "[t]he 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." Mot. 23:10–18. The response is that either outcome would be erroneous.

A determination that single-molecule RNA eukaryotic CRISPR systems are separately patentable from dual-molecule RNA systems is fatal to Proposed Count 2, because a count cannot include two separately patentable inventions. *See* Section I.A. above. If the Board determines the inventions are separately patentable, the generic RNA claims should remain as corresponding to Count 1, contrary to what Broad suggests. Mot. 23. To determine whether a claim corresponds to a count, the subject matter of the count is assumed to be prior art to the party. If the count would have anticipated the claim or rendered the claim obvious, then the claim corresponds to the count. *See* 37 CFR 41.207(b)(2). Here, a generic claim covering both single and dual-molecule RNA configurations would be anticipated by the species Count 1, which is assumed to be prior art, and which is limited to single-molecule RNA. Thus, the generic claim corresponds to Count 1. *See* MPEP § 2301.03 (9th ed. Rev. 7, Nov. 2015), Interfering Subject Matter, Example 1.

Broad made this same argument during a previous interference and lost—and properly so. The argument has not improved with age or repetition. In the 115 Interference, this Board held: "If Broad's generic claims are anticipated or rendered obvious by CRISPR-Cas9 with a single-molecule RNA configuration, Broad is not entitled to the claims under the principles of estoppel if it loses on priority to Count 1. Broad's burden is to show that its claims are not anticipated or

rendered obvious by Count 1." Ex. 2121, *Regents of Univ. of Cal. v. Broad Inst*., Interference 106,115, Decision on Motion, Paper 877, *51 (P.T.A.B. Sept. 10, 2020). This Board further stated: "Given that Broad appears to consider the single molecule RNA configuration to be the same patentable invention as a generic configuration, it is not clear that Broad could argue that a count reciting a single-molecule RNA configuration CRISPR-Cas9 system would not at least render obvious a claim reciting a generic RNA configuration." *Id*. at 52. Here, just like in the 115 Interference, Broad does not set forth any argument that the subject matter of its generic claims would not be anticipated or rendered obvious by the single-molecule RNA configuration CRISPR-Cas9 system recited in Count 1. Mot. 23:10–18; F91. For this reason, Broad has once again "failed to meet its burden of showing that these claims were not properly designated as corresponding to Count 1." *Id*.

III. BROAD DOES NOT SHOW PATENTABILITY OF DUAL-MOLECULE RNA OVER THE PRIOR ART

It is well-settled that a count should not encompass prior art; otherwise, a "priority proof" might simply be a replication of another's work. *Univ. of S. Cal., v. Depuy Spine, Inc*., 473 F. App'x 893, 895 (Fed. Cir. 2012), citing Board Decision (Dec. 23, 2009). Thus, a party seeking to substitute a count must show that the new count is patentable over the prior art. 37 C.F.R. § 41.208(c)(2). On page 27, line 20 to page 29, line 16 of its motion, Broad argues that its proposed claim is patentable over the prior art. Mot. 27:20–29:16. The response is that while Broad makes this bare assertion, it does not cite "testimony from a knowledgeable witness certifying that there is no known prior art that would have overcome the differences." SO ¶208.1.

Broad rests on the argument that "the patentability of the eukaryotic subject matter of Proposed Count 2 is confirmed by the findings of the PTAB in the 048 Interference as affirmed by the Federal Circuit." Mot. 28:4–5. The response is that the Board's finding in that case is

inapposite here—the scope of Broad's Proposed Count 2 is different from the scope of the count at issue in the now dissolved '048 proceeding. Broad's Proposed Count 2 is a generic count, where in the '048 Interference, the Count, and the representative claims, were limited to single-guide RNA—it was not a generic count. *See* Ex. 2011 (claim 1 of the '359 patent reciting a "guide" RNA); Ex. 2061 (claim 165 of UC's involved '859 application reciting a single molecule DNA-targeting RNA); F92. *See also* Ex. 2121, *Regents of Univ. of Cal. v. Broad Inst*., Interference 106,115, Decision on Motion, Paper 877, *32 (P.T.A.B. Sept. 10, 2020) (finding that "guide RNA" is limited to a single-molecule RNA configuration: "Our review of the parties' arguments leads us to the conclusion that Broad's use of the term "guide RNA" in its involved claims is not a generic term, but is limited to a single-molecule RNA configuration of the guide sequence and tracrmate, which together make the crRNA, and the tracrRNA sequences."); *id*. at *37 (stating that claim 1 of the 359 is limited to single molecule RNA). In the 048 Interference, looking at a count limited to sgRNA, the Board simply held that CRISPR-Cas9 systems "in eukaryotic cells would not have been obvious over the invention of CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro…." Ex. 2110, *Broad Inst. v. Regents of Univ. of Cal.*, Interference 106,048, Decision on Motion, Paper 893, *2 (P.T.A.B. Feb. 15, 2017); F93. The Board did not speak to whether generic claims encompassing both single and dual-molecule RNA would have been obvious over the use of single-guide RNA in a eukaryotic cell, and Broad made no showing in that case that a generic count is patentable over single molecule RNA. F94.

IV. CLAIM CORRESPONDENCE

On page 30, lines 1–6, Broad argues that five sets of Broad's involved claims that currently correspond to Count 1 do not correspond to Proposed Count 2 (nor Count 1 as argued in Broad Motion 3). Mot. 30:1–6. According to Broad, these claims include limitations directed to "(A) use of vectors for RNA expression; (B) use of a selected Cas9—*Staphylococcus aureus* Cas9; (C)

chimeric Cas9; (D) use of two or more nuclear localization signals (NLSs); and/or (E) 6 Cas9 fused to specified protein domains." *Id.* The response is that, as is the case in its Motion 3, Broad has failed to meet its burden to show that Proposed Count 2 would not have anticipated or rendered obvious the claims at issue. 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R. §§ 41.121(b), 41.208(b); *Schaenzer v. Knight*, No. 105,058, 2003 WL 22521270, at *2 (B.P.A.I. 2003) (The Board's "initial designation of claim correspondence . . . is presumed correct unless shown otherwise by the moving party.").

A. Broad's Claims Requiring the Use of Vectors for RNA Expression Correspond to Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)

On page 30, lines 13–15 of Broad's Motion 1, Broad argues that "there is no teaching or suggestion in Proposed Count 2 or in the prior art directing a POSA to vector-delivered RNA for use in eukaryotic cells, nor was there a reasonable expectation of success in so doing." Mot. 30:13–15. The response is that as of the priority date—December 12, 2012—the use of vectors, *e.g.*, plasmid vectors, was well known and widely employed for introducing DNA sequences encoding RNA molecules into eukaryotic cells. Ex. 1420, ¶¶143–145; F95. Broad avoids this fact by narrowing the scope of inquiry to the delivery of RNA *in CRISPR-Cas9 systems*. Mot. 30:15–17 (*citing* Ex. 2454, ¶ 215). Given that Count 1 and Proposed Count 2, and their disclosures that CRISPR-Cas9 functions in eukaryotic cells, are assumed prior art, Broad does not dispute that the use of vectors was well-known or that a POSA would have been motivated to combine the well-known use of vectors and the CRISPR-Cas9 system in Proposed Count 2. Ex. 1420, ¶¶143–145; F96.

Broad further argues that Dr. Zhang's vector delivery systems have been "extremely successful." Mot. 30:21–31:2. But Broad does not prove significant success, citing to a single study performed by Dr. Zhang's own company and a list of plasmids requested from a solitary

supplier, a single clinical study, and the purported "recent[] use[] in two patients." Mot. 30:20–31:2; Ex. 2454, ¶¶ 225–27; Exs. 2502–2505. Regardless, Broad does not, as it must, prove—or even argue—any nexus between the purported commercial success and the alleged patentable feature. For example, Broad does not attribute even a single sale of the Zhang vector systems to the use of vectors for RNA expression in CRISPR-Cas9. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) ("[T]o be accorded substantial weight in the obviousness analysis, the evidence of secondary considerations must have a 'nexus' to the claims, *i.e.*, there must be a legally and factually sufficient connection between the evidence and the patented invention." (internal citation omitted)). Broad has not met its burden and the Board should not de-designate the vector claims if it adopts Proposed Count 2.

B. Broad's Claims Requiring *Staphylococcus Aureus* Cas9 Protein (SaCas9) Correspond To Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)

Recycling its losing arguments and testimony from the 115 interference, on page 31, lines 3–8, Broad argues that "proposed Count 2 does not recite any particular ortholog of Cas9 protein" and "Broad determined that using Cas9 from *Streptococcus aureus* in CRISPR-Cas9 system … in a eukaryotic cell provides a surprising combination of benefits not taught or suggested by the prior art." Mot. 31:3–8. The response is that given the assumption of the proposed count as prior art a POSA would have been motivated to use SaCas9 in the eukaryotic CRISPR-Cas system of Proposed Count 2 with a reasonable expectation of success, and Broad has failed to show otherwise. SaCas9 was known in the art to be a small Cas9 protein, and, because of its small size, a POSA would have been motivated to use it in the eukaryotic CRISPR-Cas system of Proposed Count 2, particularly for human therapeutics, *e.g.*, with Adeno-associated virus vectors. Ex. 1420, ¶¶82–98. Accordingly, the Board should reject Broad's argument that the vector claims do not correspond to Proposed Count 2.

C. Broad's Claims Requiring a Chimeric Cas9 Correspond to Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)

On page 31, lines 9–13, Broad argues that "nothing in Proposed Count 2 or in the prior art teaches, suggests, or provides motivation to a POSA to design a chimeric Cas9 that is comprised of two fragments from difference organisms"—the claimed invention of Broad's 418 patent. Mot. 31:9–13. The response is that a POSA would have been motivated to use a chimeric Cas9 protein in the eukaryotic CRISPR-Cas system of Proposed Count 2 with a reasonable expectation of success, and Broad has failed to show otherwise.

As of the priority date, the use of chimeric proteins was both well-known and widely employed. Ex. 1420, ¶148; F97. Broad's argument ignores the vast array of prior-art references disclosing the use and numerous benefits of chimeric proteins. More than a decade before the October 2012 priority date, it was well known to design chimeric proteins in both prokaryotic and eukaryotic cells. Ex. 1317 (Hamamoto 1992), Abstract; Ex. 1318 (Matsui 1987), Abstract; Ex. 1420, ¶148; F98. Relevant here, several naturally occurring chimeric variants of Cas proteins were well known in the art. Ex. 1207 (Makarova 2011), Abstract; Ex. 1420, ¶148; F99. Among other reasons, a POSA would have been motivated to design a chimeric Cas9 protein because of the known ability to alter the functions of the wild-type Cas9 protein. Ex. 1420, ¶148; F100. PAM sequences, for example, were known to differ between Cas proteins, and thus a POSA would have been motivated to design a chimeric Cas protein to modify target PAM sequences. Ex. 1207, 467 (third column, last full paragraph); Ex. 1420, ¶148; F101. Such a modification would have been routine for a POSA as of the priority date. *Id.* Thus, a POSA would have been motivated to design a chimeric Cas9 protein with a reasonable expectation of successfully creating a chimeric Cas9 to function in the eukaryotic CRISPR system of Proposed 2. Ex. 1420, ¶148; F102.

Furthermore, Broad has failed to establish any objective indicia of non-obviousness. Broad cites to its own patent specification as evidence that chimeric Cas9 has "unexpected benefits" compared to wild-type Cas9. Mot. 31:13–16 (*citing* Ex. 2454, Seeger Decl. ¶¶ 249–57 (*citing* Ex. 2060, 83:45-52)). However, it is well settled that "conclusory statements in a patent's specification cannot constitute evidence of unexpected results in the absence of factual support." *Sud-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1009 (Fed. Cir. 2009). U.S. Patent No. 8,889,418 ("the '418 patent") provides no data or testing results to support Broad's argument, Ex. 2060, 83:45–52; F103, and Broad cites none. Nor does Broad provide any "surprising" or "unexpected" results over the assumed prior art proposed count, relying instead on benefits that a POSA would have expected to achieve using a chimeric Cas9 protein. Ex. 1420, ¶149, ¶153. Accordingly, Broad has failed to meet its burden.

D. Broad's Claims Requiring Two or More Nuclear Localization Sequences (NLS) Correspond to Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)

Again repeating its unsuccessful 115 interference arguments and evidence, on page 31, lines 17–21, Broad argues that Proposed Count 2 does not recite the use of two or more NLSs, which Broad determined "unexpectedly… resulted in CRISPR-Cas9 systems with significantly improved localization to the nucleus." Mot. 31:17–21. The response is that NLSs were well known and a POSA, armed with the assumed prior art Proposed Count 2 that recites a system with an NLS (a fact which Broad misses, Mot. at 31; MF35), would have been motivated to use two or more NLSs in the eukaryotic CRISPR-Cas system of Proposed Count 2 with a reasonable expectation of success, Ex. 1420, ¶113–140, and Broad has failed to show otherwise.

Before the priority date, POSAs routinely used NLSs to localize prokaryotic and eukaryotic proteins, with different sequence and three-dimensional structure, to the nucleus. Ex. 1420, ¶¶113–114; F105. POSAs also routinely attached two or more NLSs to proteins to increase nuclear

localization while maintaining protein function. Ex. 1420, ¶115; F105. Thus, a POSA would have had a reasonable expectation of successfully attaching two or more NLSs to Cas9. Ex. 1420, ¶¶130–140; F106. For example, Jinek 2012 (Ex. 2202) attached a four-amino-acid tag to a Cas9 while retaining function, thereby providing further reasonable expectation for successfully attaching two or more NLSs. Ex. 1420, ¶¶131–133; F107. Even the references that Dr. Seeger cites in paragraph 277 of his declaration show that the nuclear localization of a protein increases when additional NLSs are attached to the protein. Ex. 2262 (Park 2002), 31427–28; Ex. 2267 (Lyssenko 2007), 597–98; Ex. 2268, 847; Ex. 1420, ¶¶121–127. Broad's NLS claims would have been obvious over Proposed Count 2, and Broad has failed to meet its burden to show otherwise.

E. Broad's Claims Limited to a Cas9 Fused to Specified Protein Domains or Including Heterologous Domains Correspond to Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)

On page 31, line 23 to page 32, line 2, Broad argues that "there is no teaching or suggestion in Proposed Count 2, or the prior art, directing a POSA to modify the naturally occurring Cas9 protein sequences." Mot. 31:23–32:2. The response is that a POSA would have been motivated to fuse the Cas9 protein to specified protein domains in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2 with a reasonable expectation of success, and Broad has not shown otherwise.

The ToolGen half of Proposed Count 2 recites "wherein the Cas9 polypeptide comprises a nuclear localization signal[.]" Paper 1, Declaration of Interference, 12; Mot. 3. That is, Proposed Count 2 recites a Cas9 protein having at least one NLS attached thereto. As of the priority date, a POSA would have understood that an NLS attached to a Cas9 protein would be a fusion protein. Ex. 1420, ¶151; F108. Furthermore, Broad fails to acknowledge the vast array of prior-art references disclosing the use and numerous benefits of fusing proteins. Ex. 1420, ¶152. Contrary

to Broad's assertion, as of the priority date—indeed more than a decade before, it was well known in the art to fuse proteins to specified protein domains. Ex. 1327 (Brizzard and Chubet 1997), Abstract; Ex. 1328 (Hollenbaugh and Aruffo 2002), Abstract; Ex. 1329, (Margolin 2000), Abstract, Margolin; Ex. 1420, ¶152; F109. In fact, generating protein fusions had been used for decades before the priority date as a method of purifying proteins and fusing green fluorescent protein (GFP) to proteins was also used as method of detecting protein localization in prokaryotic and eukaryotic cells. Ex. 1329; Ex. 1420, ¶152; F110. Thus, Broad has failed to meet its burden under § 41.208(b).

V. CONCLUSION

For the foregoing reasons, the Board should dismiss or deny Broad's request to substitute Count 1 with Proposed Count 2.

Respectfully submitted,

Dated: August 6, 2021

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APPENDIX 1: LIST OF EXHIBITS CITED

Ex. No.	Description
1109	Deposition Transcript of Christoph Seeger, Ph.D., Regents of University of California v. The Broad Institute, Interference No. 106, 115, December 6, 2019
1110	Declaration of Feng Zhang, Ph.D., December 21, 2015, U.S. Application 14/704,551 to Feng Zhang
1111	Supplemental Response to Office Action, January 5, 2016, U.S. Application 14,704,551 to Feng Zhang
1112	Notice of Allowance, February 24, 2016, U.S. Application 14/704,551 to Feng Zhang
1203	Deltcheva *et al.*, CRISPR RNA Maturation by *Trans*-Encoded Small RNA and Host Factor RNase III, *Nature*, 471, 602–07 (2011), with Supplementary Information.
1207	Makarova *et al.*, Evolution and Classification of the CRISPR-Cas Systems, *Nature Review Microbiology*, 9, 467–77 (2011).
1317	Hamamoto *et al.*, Analysis of functional domains of endoglucanases from *Clostridium cellulovorans* by gene cloning, nucleotide sequencing and chimeric protein construction, *Mol. Gen. Genet.*, 231, 471–479 (1992).
1318	Matsui *et al.*, Production of chimeric protein coded by the fused viral H-*ras* and human N-*ras* genes in *Escherichia coli*, *Gene*, 52, 215–223 (1987).
1319	Rebar *et al.*, Induction of angiogenesis in a mouse model using engineered transcription factors, *Nature Medicine*, 8(12), 1427–1432 (2002)
1320	Cermak *et al.*, Efficient design and assembly of custom TALEN and other TAL effector-based constructs for DNA targeting, *Nucleic Acids Research*, 39(12), e82, 1–11 (2011).
1321	Reiss *et al.*, RecA protein stimulates homologous recombination in plants, *Proc. Natl. Acad. Sci. USA*, 94, 3094–3098 (1996).
1322	Los *et al.*, Halotag™ Technology: Cell Imagining and Protein Analysis, *Cell Notes*, 14, 1–11 (2006).
1323	Dai *et al.*, The Transcription Factors GATA4 and dHAND Physically Interact to Synergistically Activate Cardiac Gene Expression through a p300-dependent Mechanism, *J. Biol. Chem.*, 277(27), 24390–24398 (2002).

Ex. No.	Description
1324	Fischer-Fantuzzi and Vesco, Cell-dependent efficiency of reiterated nuclear signals in a mutant simian virus 40 oncoprotein targeted to the nucleus, *Mol. Cell. Biol.*, 8(12), 5495–5503 (1988).
1325	Planey *et al.*, Inhibition of Glucocorticoid-induced Apoptosis in 697 Pre-B Lymphocytes by the Mineralocorticoid Receptor N-terminal Domain, *J. Biol. Chem.*, 277(44), 42188–42196 (2002).
1326	Ran, CRISPR/Cas9: Tools and Applications for Eukaryotic Genome Editing, *NABC Report*, 26, 69–82 (2014).
1327	Brizzard and Chubet, Epitope Tagging of Recombinant Proteins, *Current Protocols in Neuroscience*, 5.8.1–5.8.10 (1997).
1328	Hollenbaugh and Aruffo, Construction of Immunoglobulin Fusion Proteins, *Current Protocols in Immunology*, 10.19A.1–10.19A.11 (2002).
1329	Margolin, Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells, *Methods*, 20, 62–72 (2000).
1420	August 6, 2021 Declaration of Barry Stoddard, Ph.D.
2051	U.S. Patent Application No. 14/704,551, Ex. 22 to Sanjana Declaration ("NIH application")
2060	U.S. Patent No. 8,889,418 issued on November 18, 2014, to Feng Zhang, et al. ("the 418 Patent")
2121	Paper 877, Declaration of Interference, Interference 106,015, September 10, 2020.
2201	Cong et al., Multiplex Genome Engineering Using CRISPR/Cas Systems, 339(6121) SCIENCE 819-823 (2013) with Supplemental Material.
2202	Jinek et al., A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity, 337(6096) SCIENCE 816-821 (2012) with Supplemental Material
2214	Deltcheva et al., CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III, 471 NATURE 602-607 (2011) with Supplementary Materials
2262	In-Hyun Park, et al., Regulation of Ribosomal S6 Kinase 2 by Mammalian Targetof Rapamycin, J. Biol. Chem. 277(35): 31423–31429 (2002) (Ex. 1035)

Ex. No.	Description
2267	Lyssenko, N.N. et al., Cognate putative nuclear localization signal effects strong nuclear localization of a GFP reporter and facilitates gene expression studies in Caenorhabditis elegans, BioTechniques 43(5):596-600 (November 2007) (Ex. 1593)
2268	Luo, M. et al., Multiple Nuclear Localization Sequences Allow Modulation of 5-Lipoxygenase Nuclear Import, Traffic 5: 847-854 (2004) (Ex. 1589)
2454	Declaration of Christoph Seeger, executed May 28, 2021.
2503	https://www.broadinstitute.org/research-highlights-crispr (accessed on October 8, 2019).
2526	Sequence Streptococcus thermophilus LMD9 CRISPR1 region
2530	Gel image of the surveyor assay for the NTF3 72 hour time point
2533	March 1, 2012 Evernote Record
2535	Image 293F_AAV1GFP_a.pdf
2536	Image 293F_AAV1GFP_b.pdf
2643	Plavec et al., Solution structure of a let-7 miRNA:lin-41 mRNA complex from C. elegans, 36 Nucleic Acids Research 2330-2337 (2008)
2645	Siolas et al., Synthetic shRNAs as potent RNAi triggers, 23 Nature Biotech. 227 (2005)
2646	Ke et al., Crystallization of RNA and RNA-protein complexes, 34 Methods 408 (2004)
2684	Ma, J-B., et al., Structural basis for overhang-specific small interfering RNA recognition by the PAZ domain, Nature, 429:318-322 (2004)
2708	Email from Feng Zhang to Mike Shao, dated August 7, 2011, with 11 page attachment, 12 pages total

Ex. No.	Description
2710	Email from Feng Zhang to Shuailiang Lin, dated October 24, 2011, 1 page
2734	Email from order_confirmation@lifetech.com to Feng Zhang, dated March 5, 2012, with 4 page attachment, 5 pages total

APPENDIX 2: STATEMENT OF MATERIAL FACTS

Junior Party's Alleged Facts 1-38 and Senior Party's Answers

1. Count 1 is limited to only single-molecule RNA. Paper 1 at 12-13.

Response: Admitted.

2. Proposed Count 2 substitutes the Broad half of the current "or" count with allowed claim 1 of the 710 application that encompasses both dual-molecule and single-molecule RNA.

Response: Admitted.

3. Dual-molecule and single-molecule RNA approaches with CRISPR-Cas9 systems are highly analogous in eukaryotic cells. Ex. 2214 at Fig. 1b; Ex. 2201 at Fig. 2B, Fig. S1 and legend; Ex. 2643, at Fig. 1 and p. 2330; Ex. 2456 ¶¶ 139-140; Ex. 2457 ¶¶ 45, 116, 237.

Response: Denied.

4. Broad's earliest work on CRISPR-Cas9 systems in eukaryotic cells date to 2011 and involved dual-molecule RNA experiments. Ex. 2454, Seeger Decl. ¶¶ 184-199; Exs. 2526, 2708, 2530, 2716, 2051 at 74 and Fig. 4B, 2533, 2734, 2535-36.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

5. From 2011 and prior to June 2012, Dr. Feng Zhang designed several CRISPR13-Cas9 systems for gene editing in eukaryotic cells in 2011 and 2012. *Id.*

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

6. A file dated April 5, 2011 (Ex. 2526) shows that Dr. Zhang had completed a vector design, with a separate tracrRNA component, to express Cas9, crRNA, and tracrRNA in a eukaryotic cell. Ex. 2526.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

7. In August 2011, Dr. Zhang ordered a vector to express tracrRNA and pre-crRNA array that when expressed and matured, would also have had a dual-molecule RNA configuration. Ex. 2708; Ex. 2454, Seeger Decl. ¶¶ 192-193.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

8. The system Dr. Zhang ordered in August 2011 was used to target, cleave, and edit an endogenous "NTF3" genomic target in eukaryotic cells in October-November 2011. Ex. 2530.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

9. Dr. Zhang filed a January 12, 2012 NIH grant application based on dual-molecule RNA CRISPR systems engineered for use in eukaryotic cells. Ex. 2454, Seeger Decl. ¶¶ 194-196; Ex. 2716.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

10. In April 2012, Dr. Zhang tested a human-codon-optimized version of a construct to express SpCas9 in his dual-molecule RNA system in a eukaryotic cell. Exs. 2533, 2734, 2535-36; *see also* Ex. 2454, Seeger Decl. ¶¶ 197-199.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

11. It was only after Dr. Zhang had already engineered and tested dual-molecule RNA CRISPR-Cas9 systems in eukaryotic cells that, on June 26, 2012, he conceived of and by July 20,

2012 actually reduced to practice a single-molecule RNA system using a GAAA linker. *See, e.g.* Exs. 2751, 2770-73, 2563, 2581-82, 2922, 2566, 2582, 2784, 2830, 2780, 2781-82, 2775, 2777, 2565, 2582, 2829, 2842.

Response: ToolGen does not have sufficient information and accordingly is unable to admit or deny the fact.

12. Broad's 713 patent (Ex. 2043), includes claims, including claims 15-26 and 28-41, that are not limited to single-molecule RNA and do not contain the term "guide RNA," but which are still designated as corresponding to Count 1. *See* Ex. 2454, Seeger Decl. ¶¶ 150-151.

Response: Denied.

13. Independent claim 1 and dependent claims 2-24 of Broad's 418 patent (Ex. 2060) do not recite any RNA component, and thus are not limited to use of a single-molecule RNA format. *See* Ex. 2454, Seeger Decl. ¶¶ 152-154.

Response: Denied.

14. Claim 1 of U.S. Application No. 15/160,710 and claim 74 of U.S. Application No. 15/430,260 recite two RNA components without any limitation on their RNA configuration. Ex. 2063, 2065; *see also* Ex. 2454, Seeger Decl. ¶¶ 155-160; Ex. 2063 (Part 4 at PDF page 230, 253); Ex. 2065 (Part 36 at 248).

Response: Denied.

15. Broad's eukaryotic CRISPR patent issued as the 359 patent on April 15, 2014, and the independent claims are not limited as to the configuration of the "guide RNA" recited therein, and since issuance, Broad has been awarded other patents with claims being non-limited regarding RNA configuration. Ex. 2011; Paper 14 at 3-67; Ex. 2454, Seeger Decl. ¶¶ 147-83.

Response: Denied.

16. On April 13, 2015, ToolGen filed the 510 application as a continuation 1 of PCT application PCT/KR2013/009488 (the "ToolGen PCT") (Ex. 2067), which had been filed on October 23, 2013, and claiming priority to provisional patent applications dating back to October 23, 2012. Ex. 2062, 510 application; Ex. 2067, ToolGen PCT.

Response: Admitted.

17. ToolGen's patent applications explicitly define "guide RNA" to encompass both dual- and single-molecule RNA configurations:

> In the present invention, the guide RNA may consist of two RNA, i.e., CRISPR RNA (crRNA) and transactivating crRNA (tracrRNA) or be a single-chain RNA (sgRNA) produced by fusion of an essential portion of crRNA and tracrRNA.

Ex. 2067, ToolGen PCT ¶¶ [0168]-[0169]; Ex. 2062, 510 application ¶¶ [0094]-[0095].

Response: Admitted to the extent the quoted language appears in Ex. 2067 and Ex. 2062; otherwise, denied.

18. In the original claims of the ToolGen PCT application and the 510 application as filed, the inventors then included claims reciting "guide RNA," without any restriction as to RNA configuration. Ex. 2067, ToolGen PCT; Ex. 2062, 510 application original claims.

Response: Denied.

19. ToolGen is continuing to prosecute claims without any restriction as to RNA configuration in pending applications within the same patent family as the 510 application, such as claim 58 from U.S. Patent Application No. 17/004,355 ("'355 patent") (Ex. 2066).

Response: Denied.

20. Zhang B1 was continuously disclosed or incorporated by reference in its entirety through each chain of the patents and patent applications involved in this Interference. Exs. 2015, 2012, 2029, 2016, 2037, 2022, 2014, and 2043; Exs 2017, 2060, 2013, 2047, 2064, 2063, 2065.

Response: Admitted.

21. Each of the involved patents and patent applications, as well as each intervening applications incorporates Zhang B1 by reference in its entirety. *Id.*

Response: Admitted.

22. The 945, 965, 445, 356, 814, 839, 616, 359, and 713 patents (Exs. 2015, 2012, 2029, 2016, 2037, 2022, 2014, 2011, and 2043), and the 551 application (Ex. 2051) all contain an explicit disclosure of Zhang B1 Example 1.

Response: Denied.

23. Broad's 233, 406, 418, 308, and 641 Patents and the 876, 260, and 710 applications (Exs. 2024, 2017, 2060, 2013, 2047, 2064, 2063, 2065) incorporate Zhang B1 by reference.

Response: Admitted.

24. Each involved patent, patent application, and intervening application of this Interference: (1) shares a common inventor, Dr. Zhang, (2) was filed timely in accordance with § 120, and (3) contains a specific reference to Zhang B1 (claiming priority to Zhang B1, and to any intervening applications, as well as incorporating Zhang B1 and any intervening applications by reference).

Response: Admitted.

25. The involved patents and patent applications (and the 710 and 260 applications) are all entitled to the benefit of the priority date of Zhang B1, December 12, 2012.

Response: Denied.

26. Substituting broader Proposed Count 2 for narrower Count 1 would not have any effect on ToolGen's earliest benefit date.

Response: Denied.

27. None of the art prior to December 12, 2012, alone or in combination, anticipates or renders obvious the subject matter of Proposed Count 2.

Response: Denied.

28. All of the claims that are proposed to correspond to Proposed Count 2 (*see* Section G.1) have been allowed over the art of record, except for the indication of the need for an interference for ToolGen's claims to be allowed over Broad's and/or CVC's claims.

Response: Admitted.

29. There are many ways that the RNA components of the system can be delivered to a eukaryotic cell, many of which performed poorly or failed outright. See Ex. 2454, Seeger Decl. ¶¶ 212-227.

Response: The statement is too vague to be admitted or denied, therefore, ToolGen is unable to admit or deny this fact.

30. ToolGen's priority application (Kim P1) discloses for delivery to the eukaryotic cell only a sequential process that includes adding extraordinarily high amounts of already translated RNA to cells previously transfected with Cas9. *Id.* ¶¶ 219-222; Ex. 2071.

Response: Denied.

31. Dr. Zhang's vector systems are among the most requested vectors 1 by researchers in the field and Broad licensee Editas Medicine is conducting a clinical trial using CRISPR-Cas9 systems that include vector delivery to human patients. *Id.* ¶¶ 225-227.

Response: Admitted, but only to the extent the clinical trial involves two patients; otherwise, denied.

32. Proposed Count 2 does not recite any particular ortholog of Cas9 protein, including SaCas9.

Response: Admitted.

33. Broad determined that using Cas9 from *Streptococcus aureus* in a CRISPR-Cas9 system

for DNA cleavage or editing or for modulating transcription in a eukaryotic cell provides a surprising combination of benefits not taught or suggested by the prior art, namely high efficiency and small size. *See* Ex. 2454, Seeger Decl. ¶¶ 228-248.

Response: Denied.

34. All claims of Broad's 418 patent (Ex. 2060) are directed to the improvement in which the Cas9 is not taken from a single organism but rather is a chimeric Cas9 that includes two fragments from different Cas9, which has unexpected benefits. *Id*. at 83:45-52; Ex. 2454, Seeger Decl. ¶¶ 249-257.

Response: Admitted to the extent the Broad Ex. 2060 Claim 1 is directed to a chimeric Cas9 that includes two fragments from different Cas9; otherwise denied.

35. Proposed Count 2 does not recite two or more NLSs.

Response: Denied.

36. Broad determined that, unexpectedly, the use of two or more NLSs resulted in CRISPR-Cas9 systems with significantly improved localization to the nucleus, as compared to systems lacking two or more NLSs. *See generally* Ex. 2454, Seeger Decl. ¶¶ 258-278.

Response: Denied.

37. There is no teaching or suggestion in Proposed Count 2, or the prior art, directing a POSA to modify the naturally occurring Cas9 protein sequences. Ex. 2454, Seeger Decl. ¶¶ 279-287.

Response: Denied.

38. The 233 patent notes that there is a benefit to fusing functional domains to Cas9, as doing so can "to turn the Cas9/gRNA CRISPR system into a generalized DNA binding system [which] can execute functions beyond DNA cleavage." Ex. 2024, at 73:22-37.

Response: Admitted to the extent the quoted language appears in Ex 2024; otherwise, denied.

ToolGen's Additional Material Facts 39–110

39. Proposed Count 2 replaces Broad's half of the current count with claim 1 of Broad's '710 application, which "encompasses both dual- and single-molecule RNA configurations." Mot. 3:15–4:15.

40. None of Broad's cited Exhibits—2643, 2684, 2645, and 2646—relate to or even mention CRISPR-Cas9, and Broad has made no showing that a POSA would have been motivated to review those references in the context of CRISPR-Cas9. Ex. 1420, ¶¶30–34.

41. Nor does Broad provide argument or explanation of any kind regarding the content of those references, or how, or why, the teachings in those references might demonstrate that single- and dual-molecule RNA systems are the same patentable invention. Ex. 1420, ¶¶30–34.

42. Proposed Count 2 is broader than the parties' common claimed invention, and it therefore does not properly define the common claimed subject matter. Ex. 1420, ¶¶37–50.

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.

44. In this interference (106, 126), the only common claimed subject matter is single-molecule RNA. Paper 1 (Declaration of Interference), 12–13.

45. Broad does not identify its best proofs sufficiently such that ToolGen or the Board could determine whether substitution of Count 2 for Count 1 is appropriate. Ex. 1420, ¶¶37–50.

46. Broad's proposed count improperly adds and removes elements of the current count. Ex. 1420, ¶¶35–36.

47. In 106,115 interference, the Board stated that "Arguments that a moving party's best or

earliest proofs are outside the scope of the existing count are ordinarily not compelling by themselves." Ex. 2121, *Regents of Univ. of Cal. v. Broad Inst*., Interference 106,115, Decision on Motion, Paper 877, *33 (P.T.A.B. Sept. 10, 2020).

48. Broad's own expert did not opine on the underlying data such that ToolGen and the Board could evaluate Broad's proofs to determine whether Proposed Count 2 is necessary. Ex. 1420, ¶¶37–49.

49. Broad offers no evidence of the experiments Dr. Zhang allegedly performed in 2011 including reductions to practice with CRISPR-Cas9 systems using tracrRNA and crRNA that were ***not*** fused or covalently linked but were still hybridized as an RNA duplex in the cutting complex with Cas9. Ex. 1420, ¶¶37–40.

50. Broad submits no testimony from Dr. Zhang or other scientists, and Dr. Seeger expressly does not rely on any such testimony. Ex. 2454, ¶185.

51. Deltcheva recognized hybridization of crRNA with tracrRNA not for DNA cleavage, but for maturing pre-crRNA repeats. Ex. 2214; Ex. 1420, ¶43.

52. As late as October 2011, Dr. Zhang had only a research plan in which he was still trying various RNA combinations and not reductions to practice of CRISPR-Cas9 systems using tracrRNA and crRNA that were ***not*** fused or covalently linked but were still hybridized as an RNA duplex in the cutting complex with Cas9. Ex. 2710 ("It's worthwhile to try dsRNA . . . I don't think transfecting crRNA alone will work.").

53. Neither Dr. Zhang, nor any witness with personal knowledge, provides any explanation of the contents of the file contained in Exhibit 2526. Ex. 2526.

54. The file of Exhibit 2526 itself is undated, and there is no indication that the file was ever dated April 5, 2011. Ex. 2526; Ex. 1420, ¶37.

55. On its face, Exhibit 2526 does not illustrate any component of a vector or its design that might be used for introduction or expression of CRISPR components in a eukaryotic cell; it provides only a genetic map and sequence of a CRISPR system in a bacterium, specifically, in *Streptococcus thermophilum*. Ex. 2526; Ex. 1420, ¶37.

56. Exhibit 2526 does not support Broad's prediction that "[w]hen expressed, this system would have a dual-molecule RNA configuration." Ex. 2526; Ex. 1420, ¶37.

57. Exhibit 2708 shows a DNA sequence, but provides no annotation of the functional elements, coding sequence(s) or purpose of the sequence or any description of any planned experiments. Ex. 2708; Ex. 1420, ¶38.

58. Dr. Seeger did not consider any experiments using the vector in Exhibit 2708. Ex. 2454 ¶ 192–93.

59. Exhibit 2530 is an unlabeled, uncorrelated and unexplained image of what may be an electrophoresis gel, that cannot serve as any basis for Broad's contention that "[t]his system was used to target, cleave, and edit an endogenous "NTF3" genomic target in eukaryotic cells in October-November 2011." Ex. 2530; Ex. 1420, ¶40.

60. A POSA would have expected certain identifying features to be present in a gel image, such as labeling, captioning, or a description that would allow a POSA to infer the nature of the experiment or results being illustrated. Ex. 2530; Ex. 1420, ¶40.

61. Ex. 2530 also lacks the typical indications of molecular masses or sizes of bands, the standard molecular weight ladder, any indication of the components or approach used to generate the elements observed in each lane, and any indication of the identity of any of the bands on the gel. Ex. 2530; Ex. 1420, ¶40.

62. The NIH grant application provided in Exhibit 2051 does not provide any preliminary data

indicating that the illustrated construct had been tested, nor that a POSA would reasonably expect the construct to generate a functional CRISPR-Cas9 complex if it were tested. Ex. 1420, ¶41.

63. The NIH grant application provided in Exhibit 2051 does not provide explanation regarding how the individual tracrRNA and guide RNA components would be expected to function when embedded in surrounding self-spliced introns. Ex. 1420, ¶42; Exhibit 2051.

64. A POSA would not expect the construct shown in Figure 4B in the NIH Grant Application to yield an appropriate stoichiometric balance of protein and RNA molecules for generation of active CRISPR-Cas9 complex. Ex. 1420, ¶42; Exhibit 2051.

65. In the 106, 115 interference, when asked "whether the construct shown in Figure 4 of the NIH application produced a functional CRISPR-Cas9 system," Dr. Seeger testified that he had "no opinion on data." Ex. 1109, 230:16–20.

66. In the 106,115 interference, Dr. Seeger testified he had not inquired whether the experiments proposed in the NIH grant application were even conducted. Ex. 1109, 230:16-20. 204:14–22.

67. The NIH grant application provided in Exhibit 2051 did not offer any such construct used in mammalian cells or in any other experiment, and the "design" offered in the NIH grant application was pure conjecture that was not reduced to practice. Ex. 2051; Ex. 1420, ¶ 41.

68. The NIH grant application provided in Exhibit 2051 stated development of the CRISPR system for modifying mammalian genomes was not to begin until "year 2" "—i.e., September 2013 – August 201. Ex. 2051 at 3.

69. Figure 4B of the NIH grant application states that the tracrRNA element, however, merely "facilitate[s] the processing of guide RNAs, and the guide RNA array." Ex. 2051, Fig. 4B; Ex. 1420, ¶43.

70. During the time period of the NIH grant application, Deltcheva 2011 taught that the tracrRNA simply directed the maturation of another non-coding RNA (Pre-crRNA) to yield the active species (crRNAs), which (at the time) occurred by an unknown process. Ex. 1420, ¶43; *see* Ex 1203.

71. During the time period of the NIH grant application, it was not known in the art that the tracrRNA was part of the guide RNA only that it was necessary to mature the active crRNAs, and Figure 4B does not reflect any advanced understanding of that concept. Ex. 1420, ¶43.

72. Figure 4B of the NIH grant application suggests that Dr. Zhang was unaware that a dual complex (tracrRNA:crRNAs) was in fact the dual-guide component of the CRISPR-Cas9 system. Ex. 1420, ¶¶41, 43.

73. Exhibit 2533 provides no annotation of the functional elements of the sequence, the coding sequence(s) or purpose of the DNA sequence shown, and no indication of how it might be incorporated in any particular vector or used for the purpose of testing CRISPR-Cas9 in a eukaryotic cell. Ex. 1420, ¶45.

74. At the time, there is no indication that Dr. Zhang had become aware that the tracrRNA was part of the guide RNA. Ex. 1420, ¶45.

75. Exhibits 2535 and 2536 are missing any identifying features, labeling, captioning, or description that would allow a POSA to infer the nature of the experiment or the results being illustrated. Ex. 1420, ¶46.

76. Exhibits 2535 and 2536 have no indication or description of the components or approach used to generate the images shown, nor any details of the form of microscopy employed. Ex. 1420, ¶46.

77. Dr. Seeger did not consider Exhibits 2535 and 2536 in his declaration. *See generally* Ex.

2454.

78. Cong 2013 does not indicate that dual-molecule experiments were performed prior to single-molecule RNA experiments. Ex. 1420, ¶49.

79. Cong 2013 does not disclose the dates for its experiments, and a POSA would not infer a chronological order of those experiments based on Cong 2013. Ex. 1420, ¶49.

80. During prosecution of Application 14/704,551, Dr. Zhang, in his December 21, 2015 declaration, identified the same Figure 4B as evidence of his "appreciation that ***a single RNA*** can be used as a guide in the CRISPR-Cas system, including as shown by the RNA used in the experiment of the below figure entitled 'CRISPR NTF3 Surveyor . . . .'" Ex. 1110, ¶ 19 (emphasis added).

81. Broad submitted Dr. Zhang's declaration during prosecution of the '551 application for the purpose of antedating prior art and establishing that Broad had possession of a chimeric RNA or fused RNA [single-molecule RNA] vector system. Ex. 1111 (Supplemental Response).

82. Dr. Zhang's declaration allowed Broad to obtain claims directed to single-molecule subject matter (i.e., its claims in the '551 application reciting "chimeric RNA"). Ex. 1112 (Notice of Allowance).

83. The Patent Office expressly referenced the declaration of Dr. Zhang in the Statement of Reasons for Allowance, demonstrating that it was among the "reasons why the application was allowed." Ex. 1112 (Notice of Allowance).

84. DNA "editing," however, is broader than DNA "cleavage," as it includes results other than cleavage, such as epigenetic DNA modifications. Ex. 1420, ¶¶35–36.

85. Notably, current Count 1 is limited to DNA "cleavage." Paper 1 (Declaration of Interference), at 12–13.

86. Dr. Seeger, does not state the system was intended to "edit" the genomic target, he clarified that the system "was intended to ***target and cleave***" the genomic target. Ex. 2454, ¶192.

87. A POSA would have understood that editing of genomic DNA to be broader than targeting or cleaving genomic DNA. Ex. 1420, ¶35.

88. With respect to the NIH grant application that allegedly describes a dual-molecule RNA CRISPR-Cas9 system, Dr. Seeger described the disclosed system as one "that ***cleaves*** the target DNA." Ex. 2454, ¶196.

89. With regard to the April 2012 experiments, Broad indicated that the shift in green fluorescent protein was attributed to "***cleav[age]***" of the CRISPR reporter. Mot. 9.

90. None of Broad's proffered best proofs, to the extent understood, even comes close to demonstrating that expression of a gene product was altered, which explains Broad's deletion of the limitation. Ex. 1420, ¶¶36, 48.

91. Here, just like in the 115 Interference, Broad does not set forth any argument that the subject matter of its generic claims would not be anticipated or rendered obvious by the single-molecule RNA configuration CRISPR-Cas9 system recited in Count 1. Mot. 23:10–18.

92. Broad's Proposed Count 2 is a generic count, where in the '048 Interference, the Count, and the representative claims, were limited to single-guide RNA—it was not a generic count. *See* Ex. 2011 (claim 1 of the '359 patent reciting a "guide" RNA); Ex. 2061 (claim 165 of UC's involved '859 application reciting a single molecule DNA-targeting RNA); *see also* Ex. 2121, *Regents of Univ. of Cal. v. Broad Inst.,* Interference 106,115, Decision on Motion, Paper 877, *32 (P.T.A.B. Sept. 10, 2020).

93. In the 048 Interference, looking at a count limited to sgRNA, the Board simply held that CRISPR-Cas9 systems "in eukaryotic cells would not have been obvious over the invention of

CRISPR-Cas9 systems in any environment, including in prokaryotic cells or in vitro…." Ex. 2110, *Broad Inst. v. Regents of Univ. of Cal.*, Interference 106,048, Decision on Motion, Paper 893, *2 (P.T.A.B. Feb. 15, 2017).

94. In the 048 Interference, the Board did not speak to whether generic claims encompassing both single and dual-molecule RNA would have been obvious over the use of single-guide RNA in a eukaryotic cell, and Broad made no showing in that case that a generic count is patentable over single molecule RNA. Ex. 2110, *Broad Inst. v. Regents of Univ. of Cal.*, Interference 106,048, Decision on Motion, Paper 893, *2 (P.T.A.B. Feb. 15, 2017).

95. As of the priority date—December 12, 2012—the use of vectors, *e.g.*, plasmid vectors, was well known and widely employed for introducing DNA sequences encoding RNA molecules into eukaryotic cells. Ex. 1420, ¶¶143–145.

96. Broad does not dispute that the use of vectors was well-known or that a POSA would have been motivated to combine the well-known use of vectors and the CRISPR-Cas9 system in Proposed Count 2. Ex. 1420, ¶¶¶143–145.

97. As of the priority date, the use of chimeric proteins was both well-known and widely employed. Ex. 1420, ¶148.

98. More than a decade before the October 2012 priority date, it was well known to design chimeric proteins in both prokaryotic and eukaryotic cells. Ex. 1317 (Hamamoto 1992), Abstract; Ex. 1318 (Matsui 1987), Abstract; Ex. 1420, ¶148.

99. Several naturally occurring chimeric variants of Cas proteins were well known in the art. Ex. 1207 (Makarova 2011), Abstract; Ex. 1420, ¶148.

100. A POSA would have been motivated to design a chimeric Cas9 protein because of the known ability to alter the functions of the wild-type Cas9 protein. Ex. 1420, ¶148.

101. PAM sequences, for example, were known to differ between Cas proteins, and thus a POSA would have been motivated to design a chimeric Cas protein to modify target PAM sequences. Ex. 1207, 467 (third column, last full paragraph) and it would have been routine. Ex. 1420, ¶148.

102. A POSA would have been motivated to design a chimeric Cas9 protein with a reasonable expectation of successfully creating a chimeric Cas9 to function in the eukaryotic CRISPR system of Proposed 2. Ex. 1420, ¶148.

103. U.S. Patent No. 8,889,418 ("the '418 patent") provides no data or testing results to support Broad's argument, Ex. 2060, 83:45–52.

104. Before the priority date, POSAs routinely used NLSs to localize prokaryotic and eukaryotic proteins, with different sequence and three-dimensional structure, to the nucleus. Ex. 1420, ¶¶113–114.

105. Before the priority date, POSAs also routinely attached two or more NLSs to proteins to increase nuclear localization while maintaining protein function. Ex. 1420, ¶115.

106. Before the priority date, a POSA would have had a reasonable expectation of successfully attaching two or more NLSs to Cas9. Ex. 1420, ¶¶130–140.

107. Jinek 2012 (Ex. 2202) attached a four-amino-acid tag to a Cas9 while retaining function, thereby providing further reasonable expectation for successfully attaching two or more NLSs. Ex. 1420, ¶¶131–133.

108. As of the priority date, a POSA would have understood that an NLS attached to a Cas9 protein would be a fusion protein. Ex. 1420, ¶151.

109. More than a decade before the priority date, it was well known in the art to fuse proteins to specified protein domains. Ex. 1327 (Brizzard and Chubet 1997), Abstract; Ex. 1328 (Hollenbaugh and Aruffo 2002), Abstract; Ex. 1329, (Margolin 2000), Abstract, Margolin; Ex.

1420, ¶152;

110. Generating protein fusions had been used for decades before the priority date as a method of purifying proteins and fusing green fluorescent protein (GFP) to proteins was also used as method of detecting protein localization in prokaryotic and eukaryotic cells. Ex. 1329; Ex. 1420, ¶152.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **TOOLGEN OPPOSITION 1** was filed via the Interference Web Portal on August 6, 2021 by 8:00 PM EDT, and thereby served on the attorneys of record for the Junior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to agreement of the parties, service copies are being sent by email by 11:00 pm ET to counsel for Junior Party as follows:

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