Filed on behalf of: **Junior Party, Broad** 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,

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.

SIGMA-ALDRICH CO., LLC,

Application 15/456,204,

Senior Party.

Patent Interference No. 106,133 (DK)
(Technology Center 1600)

BROAD REPLY 3

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

I. PRECISE RELIEF REQUESTED

Junior Party, The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College (collectively, "Broad"), requests that if the PTAB denies Motion 1 and the Interference continues with Count 1, the PTAB grant Broad Motion 3 to designate certain Broad claims as not corresponding to Count 1.

II. DESCRIPTION OF APPENDICES

Appendix 1 is a list of Exhibits. Appendix 2 is a Statement of Material Facts.

III. REPLY ARGUMENT

Broad's claims currently designated as corresponding to Count 1 are drawn to several inventions patentably distinct from the subject matter of Count 1. As set forth in Broad's Motion 3, the separately patentable inventions fall into five broad categories:

Category A: SaCas9;

Category B: Chimeric Cas9;

Category C: Cas9 having two or more NLSs;

Category D: Cas9 fused to protein domains; and

Category E: Generic RNA without donor template integration.

In its Opposition, Sigma agrees that the claims in the Categories A-D should be designated as not corresponding to Count 1. Opp. 3 at 9:13-11:28. With respect to Category E, Sigma agrees that claims in certain sub-categories should be de-designated, but argues that the remaining claims in Category E should remain designated. *Id*. at 9:4-11:25. As discussed below, the PTAB should designate as not corresponding to Count 1 not only the claims agreed to by Sigma, but also the claims that Sigma disputes. Moreover, Sigma's concessions are equally applicable to designation of claims if Broad's Motion 1 is granted and Proposed Count 3 is substituted.

A. The PTAB Should De-Designate Broad's Involved Claims That Sigma Agrees Do Not Correspond To Count 1

Sigma agrees that claims in Categories A-D should be designated as not corresponding to Count 1. Opp. 3 at 9:13-11:28. Accordingly, as set forth in Broad's Motion 3 and based on Sigma's agreement, those claims should be de-designated as shown in the chart below.

With respect to Category E—claims directed to generic RNA without reciting donor template integration—Sigma agrees that certain of these claims do not correspond to Count 1. Specifically, Sigma concedes the following three subcategories of claims in Category E do not correspond to Count 1: "(i) > 1 targeting RNA (aka 'multiplexing'); (ii) one or more mutation(s) in the Cas9 RuvC/HNH domain(s); and (iii) a nickase for a creating a 'nick' or a single stranded break in the target DNA." Opp. 3 at fn. 3. For the purposes of this Interference, based on Sigma's concession regarding these three sub-categories, the following Category E claims should also be designated as not corresponding to Count 1: claims 1-30 of U.S. Pat. No. 8,697,359 ("356 patent"); claims 2-3, 6, 12-13, 16, 22-23, and 26 of U.S. Pat. No. 8,945,839 ("839 patent"); claims 2, 5-6, and 39 of U.S. Pat. No. 9,840,713 ("713 patent"); and claim 5 of U.S. Application 14/704,551 ("551 application"). *See* Sigma Claim Correspondence Table, column "FN 3."

Based on Sigma's concessions, the following claims should be de-designated:

Patent	Claims Currently Designated	Claims That Should Be Designated As Not Corresponding To Count 1
8,865,406	1-30	ALL
8,871,445	1-30	ALL
8,889,356	1-30	1-30
8,889,418	1-28	ALL
8,895,308	1-30	ALL
8,932,814	1-30	ALL
8,945,839	1-28	2-3, 6, 12-13, 16, 22-23, 26
8,993,233	1-43	ALL
8,999,641	1-28	ALL
9,840,713	1-41	2, 5-6, 18-19, 25, 29-30, 36, 39
14/704,551	2, 4-18	9-11
15/330,876	1, 16-21, 30-40	ALL

B. The Remaining Claims In Category E Should Also Be Designated As Not Corresponding To Count 1

Sigma contests the de-designation of the remaining claims in Category E. Broad's response is that its claims that are both generic as to RNA and not limited to Donor Template Integration are neither within the Broad half of Count 1 (which requires sgRNA) nor the Sigma half of Count 1 (which requires Donor Template Integration). Mot. 3 at 3-6, 20-33; *see* Ex. 2464 (Seeger Decl.) ¶¶ 248-51. Sigma's arguments in opposition fail for multiple reasons.

1. Sigma Does Not Address Broad's Actual Argument: Designating Any Category E Claims As Corresponding To Count 1 Is Inequitable

At 1:6-8 and 3:12-5:4, Sigma argues that Broad has failed to show that its generic RNA claims should be de-designated under a one-way obviousness test. Opp. 3 at 1:6-8, 3:12-5:4. This argument ignores the explicit basis of Broad's motion: that the one-way obviousness test should not be applied here. It is not a *per se* rule that the one-way test must rigidly be applied in all situations; rather, if, as is the case here, the one-way test would end up with an inequitable outcome, it should not be used. Ex. 2305, Rules of Practice Before the Board of Patent Appeals and Interferences, 69 FR 49960-01, at *49994 (Comment 186/Answer).

As Broad explained in Motion 3—and as Sigma does not dispute—Broad's generic/non-limited RNA claims (along with the properly designated sgRNA claims) are currently at risk in this Interference, but Broad's proofs on *dual-molecule* RNA systems *without* a donor template (Broad's best and earliest proofs) are excluded by Count 1. Ex. 2464 (Seeger Decl.) ¶¶ 151-66; MF 51. If the Interference proceeds to priority phase with Count 1, Sigma will no doubt argue that Broad cannot rely on dual-molecule RNA proofs because Broad's half of Count 1 is limited to sgRNA—but that is nonsensical unless the genus and species are separately patentable inventions. Sigma will also likely argue that Broad cannot rely on those same proofs for Sigma's half of Count 1 because they do not involve Donor Template Integration or "only one NLS." *Id.*; Sigma Mot. 1.

Accordingly, Broad's earliest and best proofs are not within either half of Count 1; however, unfairly and inequitably, claims of that same scope are designated as corresponding to Count 1.

Broad should not be excluded from using its earliest dual-molecule proofs for Count 1 while simultaneously putting at risk claims with the same scope. If that situation holds, then Broad could be denied its Category E claims solely because Count 1 imports separate specific limitations (sgRNA; Donor Template Integration) that are not part of the fundamental breakthrough of getting the CRISPR-Cas9 system to work in eukaryotic cells—an invention that Broad invented first.

Moreover, as discussed at length in Motion 3, and unaddressed in Sigma's Opposition, designating Broad's Category E claims as not corresponding to Count 1 is consistent with the Federal Circuit's decision in *Eli Lilly & Co. v. Board of Regents of University of Washington*, 334 F. 3d 1264, 1268 (Fed. Cir. 2003), which found that the PTAB had the discretion to adopt a two-way test to prevent "the proliferation of unnecessary, wasteful interference proceedings concluding that both parties are entitled to patents in situations in which the claimed inventions do not define the same patentable invention, but merely overlap in scope." *Id*. Consistent with *Eli Lilly*, the development of certain working species (the sgRNA system; integration of donor templates) should not be dispositive on priority to generic claims where another working species within that genus (dual-molecule without donor template integration) was invented first but cannot be relied upon to show priority due to the wording of the count.

Sigma does not address Broad's arguments on these points at all—rather, it sets up a strawman argument that Broad never made about compliance with the one-way obviousness test. Broad's showing that the Category E claims should be designated as not corresponding to Count 1 is thus uncontested on the bases for Broad's motion: that the one-way obviousness test should not be applied here as it would lead to an unjust and unfair result.

Sigma's argument at 5:26-6:19 should also be dismissed. There, Sigma argues that Broad's position is "facially inconsistent" with its position in Broad Motion 2 that dual-RNA and sgRNA claims should be designated to Proposed Count 3, which, unlike Count 1, is generic as to RNA. Opp. 3 at 5:26-6:19. The response is that there is no such inconsistency. Broad showed in Motion 3 that its generic claims do not correspond to Count 1 and that showing was not based on the one-way obviousness test. Thus, Broad's showing that its dual- and sgRNA claims correspond to Proposed Count 3 that is generic as to RNA is not inconsistent.

If this Interference continues with Count 1, in the interests of fairness and justice, Broad's "generic" non-limited RNA claims that do not require Donor Template Integration should be designated as not corresponding to Count 1.

2. Sigma Does Not Address Broad's Arguments That "Guide RNA" Includes Both Single- And Dual-Molecule RNA Systems

At 7:1-9:8, Sigma notes that "Sigma concurs with the Board's detailed decision" in the 115 Interference regarding the construction of "guide RNA" and block quotes a substantial portion of that decision. Opp. 3 at 7:1-9:8. Sigma offers no evidence or any argument on these points, aside from its concurrence with the PTAB's decision. In Motion 3, however, Broad addressed the proper construction of "guide RNA" at length (Mot. 3 at 4-5, 22-28), including arguments and evidence not previously part of the record in the 115 Interference, such as the use of the "guide RNA" in Sigma's P1 application (Ex. 1524), as evidence of its plain and ordinary meaning at the time. Sigma has failed to contest Broad's showing here, including not making any response to the new evidence that was not of record in the 115 Interference. Broad demonstrated that "guide RNA" had a plain and ordinary meaning encompassing both dual- and sgRNA at the relevant time, and that Broad did not act as its own lexicographer redefining the term in Zhang B1.

3. Sigma Improperly Incorporates Non-Responsive Arguments Regarding Donor Template From Its Opposition 1

At footnote 1 of its Opposition 3, Sigma improperly incorporates by reference arguments from its Opposition 1. Opp. 3 at fn. 1. Sigma's incorporation by reference directly violates Standing Order ¶ 106.2, which states that "[i]ncorporation by reference and combined papers are prohibited…. Incorporation of arguments by reference amounts to a self-help increase in the length of the brief and a pointless imposition on the Board's time." As this sole footnote appears to be the only potential basis for Sigma's contention that claims that recite what Sigma terms "cleavage plus altering gene expression" should correspond to Count 1, that argument should be deemed waived and Broad's argument that these claims do not correspond should be deemed uncontested. *See* Standing Order ¶ 106.2 (citing *DeSilva v. DiLeonardi*, 181 F.3d 865, 866-67 (7th Cir. 1999) (refusing to consider arguments incorporated by reference)).

Indeed, Sigma's incorporation by reference of its Opposition 1 arguments highlights a particular problem with Sigma's extensive use of incorporation by reference throughout its oppositions. It is unclear how (and even whether) Sigma thinks its incorporated arguments in Opposition 1 are relevant to the question of designating the claims "cleavage plus altering gene expression" to Count 1. Sigma's Opposition 3 incorporates Opposition 1 by reference on the question of correspondence, so Sigma's Opposition 3 does not address the question presented by Motion 3. Nowhere in either Opposition 1 or 3 does Sigma contend that non-sgRNA claims, to what it terms "cleavage plus altering gene expression," correspond to Count 1, or that it would be equitable to keep such claims designated as corresponding to Count 1. And Sigma also does not argue in either opposition that such claims are obvious over Donor Template Integration. It is thus unclear exactly what argument Sigma is incorporating or how Broad should respond.

Another problem with Sigma's use of incorporation by reference here is that it hides

Sigma's actual position and muddies the issues. For instance, the premise of Sigma's Motion 1 is, in part, that Zhang B1's disclosure of Donor Template Integration working examples does not disclose possession of what Sigma terms "cleavage plus altering gene expression." Sigma may perceive tension between that position and its apparent (but unarticulated) Motion 3 position that claims, to what it terms "cleavage plus altering gene expression," are rendered obvious by Sigma's half of the count, which recites Donor Template Integration, but does not specifically refer to alteration of expression. While obviousness is not sufficient to show possession, to explain its apparent position that "cleavage plus altering gene expression" is rendered obvious by Donor Template Integration, Sigma would need to concede many if not most of the facts sufficient to show Broad's possession of Count 1 here—i.e., that a POSA understood that a system capable of Donor Template Integration is also capable of altering gene expression. By improperly incorporating arguments by reference, Sigma hopes to avoid spotlighting the issue.

The PTAB's rule against incorporation by reference thus has special applicability here, and Sigma's argument regarding de-designation of claims that recite what Sigma terms "cleavage plus altering gene expression" should be deemed waived and Broad's Motion 3 granted in its entirety.

4. The Record Contradicts Sigma's Arguments In Opposition 1 Seeking To Explain Away Its Statements Regarding Separate Patentability

Even if considered, Sigma's arguments in Opposition 1 do not explain away its prior statements regarding the separate patentability of Donor Template Integration subject matter. These statements continue to support Broad's argument that Broad's claims that do not require Donor Template Integration do not correspond to Sigma's half of Count 1.

In particular, Sigma has argued during prosecution that claims that do not recite integration of a donor template do not correspond to a count that includes such a requirement, even if they recite other forms of cleavage and editing/repair. Ex. 2074 (October 13, 2020 Suggestion of

Interference) at 7. Sigma has also repeatedly argued that Donor Template Integration and other forms of cleavage and repair were separately patentable inventions, and that a POSA would not have reasonably expected success in integrating a donor template even if the art showed recognition of successful cleavage and repair in a eukaryotic cell. Ex. 2074 (April 9, 2018 Petition) at 9, 24-25; Ex. 2074 (April 29, 2019 Applicant Remarks) at 19 (citing Ex. 2465 (April 29, 2019 Cannon Decl.) ¶¶ 97-98). Accordingly, based on Sigma's statements, Broad's claims that require neither sgRNA nor Donor Template Integration do not correspond to either half of Count 1.

At 13:25-17:33 and 20:7-23:19 of Opposition 1, Sigma contends that its prosecution arguments were limited to distinguishing over "cleavage only" subject matter and accuses Broad of "fabricat[ing] a non-existent argument by Sigma." Opp. 1 at 13:25-17:33, 20:7-23:19. In particular, Sigma argues that it has never characterized claims "to cleavage ***plus*** a further demonstrable genomic engineering result" as separately patentable from Donor Template Integration. Opp. 1 at 14:21-15:2 (emphasis in original).

The response is that, during prosecution, Sigma distinguished its Donor Template Integration claims from art that disclosed more than "cleavage only"—*i.e.*, the subject matter that Sigma distinguished included what Sigma now calls "a further demonstrable genomic engineering result." For instance, ToolGen's Kim P1 application does not purport be limited to "cleavage only"; rather, as Sigma itself stated during prosecution, Kim's alleged disclosure included cleavage repaired by "small insertions and deletions (indels) around the target sequence via error-prone non-homologous end-joining (NHEJ)." Ex. 2073 (April 17, 2017 Supp. Response) at 14. This is not "cleavage only." Yet Sigma nonetheless distinguished its claims over ToolGen's Kim P1 application by relying on its donor template limitation. Ex. 2073 (April 17, 2017 Supp. Response) at 18 (arguing Kim P1 "fails to disclose, suggest, or contemplate using a Cas9/RNA complex to

integrate an exogenous sequence at a target site…") (emphasis in original). Sigma's present argument that it never characterized subject matter that has a "further demonstratable genomic engineering result" as separately patentable from Donor Template Integration is inconsistent with its arguments used to secure allowance of its claims.

Similarly, Sigma erroneously asserts that in its filings provoking 132 Interference, it "has consistently—and only—distinguished Sigma's ***cleavage plus integration*** claims with CVC's ***cleavage only*** claims." Opp. 1 at 15:6-9 (emphasis in original). But during prosecution of its 204 application, Sigma suggested an interference against CVC with a count reciting Donor Template Integration. At that time, it argued that only claims that were directed to "methods of integrating a donor polynucleotide sequence into the chromosomal sequence of a eukaryotic cell" corresponded to the count. Ex. 2074 (October 13, 2020 Suggestion of an Interference) at 7-8.

Finally, Sigma told the PTAB that it is "properly not a party" to Broad's interferences with CVC and ToolGen "because all of Sigma's involved claims are directed solely to the patentably distinct 'cleavage plus integration' technological advance in the art." Ex. 2124 (132 Sigma Mot. 1) at 4:14-23. At 20:7-23:19 of Opposition 1, Sigma now tries to explain away this statement by claiming that those interferences should properly be treated as limited to "cleavage only" because Sigma alleges that CVC, ToolGen, and Broad have all "strategically chosen to limit their respective priority contests to ***cleavage only*** in a eukaryotic cell." Opp. 1 at 20:7-23:19 (emphasis in original). Sigma mischaracterizes the record in those cases, including claiming that CVC did not, in the 115 Interference, challenge Broad's priority evidence. Sigma's arguments are contradicted by the plain language of the counts in the other Broad interferences—all of which include Claim 18, the current Broad half of Count 1, which requires cleavage whereby "expression of the at least one gene product is altered." The count of those interferences defines the interfering

subject matter, and Sigma unequivocally has based its arguments, including in its Motion 1 here, on its assertion that Broad's Claim 18 is to a "further demonstratable genomic engineering result," not cleavage only. Sigma Mot. 1. Sigma's representation that is it not "properly a party" to such interferences cannot now be re-characterized to avoid the effect of those prior arguments.

Sigma thus repeatedly argued that Donor Template Integration and other forms of cleavage and repair were separately patentable inventions in securing its claims. Accordingly, Broad's claims that require neither sgRNA nor Donor Template Integration should be designated as not corresponding to Count 1.

IV. CONCLUSION

For the foregoing reasons and for the reasons set forth in Broad's Motion 3, Broad respectfully requests that the PTAB grant Broad Motion 3.

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Respectfully submitted,

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APPENDIX A: LIST OF EXHIBITS CITED

Ex.	Description
Ex. 1524	Sigma P1
Ex. 2073	Excerpts of U.S. Patent Application 15/188,911, Chen et al., dated June 21, 2016
Ex. 2074	Excerpts of U.S. Patent Application 15/456,204, Chen et al., dated March 10, 2017
Ex. 2124	Paper 482, Sigma Motion 1 (to Substitute Proposed Count 2 for Count 1), Interference 106,132, November 19, 2021.
Ex. 2305	Rules of Practice Before the Board of Patent Appeals and Interferences, 69 Fed. Reg. 49960-01.
Ex. 2464	Declaration of Christoph Seeger, executed December 3, 2021.
Ex. 2465	Declaration of Paula M. Cannon, Ph.D., Application No. 15/456,204 Prosecution History, dated April 29, 2019.

APPENDIX B: STATEMENT OF MATERIAL FACTS

BROAD STATEMENT OF MATERIAL FACTS AND SIGMA RESPONSES

1. Count 1 is an "or" count drawn to (Broad half, Broad US Patent 8,697,359, claim 18) a eukaryotic CRISPR-Cas9 system comprising Cas9 and RNA that comprises a guide sequence fused to a tracr sequence that targets and hybridizes to a DNA target sequence in a eukaryotic cell (Ex. 2011, 359 patent, claim 18), or (Sigma half, Sigma application 15/456,204 ("the 204 application"), claim 31) a method for using a CRISPR-Cas9 system in a eukaryotic cell to create a double-stranded break in target DNA and integrate a donor template. Paper 12 at 13.

Response: Denied

2. The CRISPR-Cas9 system of the Sigma half of Count 1 requires integration of a donor template; the Broad half of Count 1 requires sgRNA but does not require integration of a donor template. *Id*.

Response: Denied

3. In the 132 Interference, Sigma submitted expert testimony that the following would not have been obvious to a POSITA as of early December 2012 in view of Sigma's proposed count in the 132 Interference: "a Cas9 protein that includes a Protein Transduction Domain ('PTD')"; "one or more mutation(s) in the Cas9 RuvC/HNH domain(s)"; and "chimeric Cas9 protein." Ex. 2124 (132 Sigma Mot. 1) at 27:11-28:2; Ex. 2465 (132 Cannon Decl.) ¶ 35.

Response: Admitted

4. Count 1 does not recite any particular ortholog of Cas9 protein, including SaCas9. Paper 1 at 12-13; Broad Motion 1 at 4.

Response: Admitted

5. There is no teaching or suggestion in Count 1 or the prior art to use SaCas9 in CRISPR-Cas9 systems in eukaryotic cells. *See* Ex. 2464 (Seeger Decl.) ¶¶ 177-96.

Response: Lack sufficient information to admit or deny

6. CRISPR-Cas9 systems using SaCas9 possess a combination of small size and high efficacy in eukaryotes. Ex. 2017, 406 patent, 83:1-25-84:1-23; Ex. 2464 (Seeger Decl.) ¶ 193.

Response: Denied

7. Small size and high efficacy in eukaryotes render CRISPR-SaCas9 systems advantageous for use in eukaryotic cell-based applications where vector delivery using the highly versatile adeno-associated virus (AAV) is favored because AAV vectors are space-constrained. Ex. 2464 (Seeger Decl.) ¶¶ 193, 245; Ex. 2017, 406 patent, 83:1-25-84:1-23.

Response: Denied

8. As of 2012, SpCas9 was the most commonly studied Cas9 ortholog. Ex. 2464 (Seeger Decl.) ¶ 177; Ex. 2215.

Response: Lack sufficient information to admit or deny

9. As of 2012, more than 600 bacterial Cas9 orthologs that had been identified. Ex. 2226, Ran 2015; Ex. 2464 (Seeger Decl.) ¶ 181.

Response: Lack sufficient information to admit or deny

10. As of 2012, there was nothing in the art pointing the POSA to use SaCas9 in eukaryotic cells including nothing pointing to SaCas9 out of the many known "small" Cas9 orthologs that are similar in size to, or smaller than, SaCas9. Ex. 2464 (Seeger Decl.) ¶¶ 185-93.

Response: Lack sufficient information to admit or deny

11. SpCas9 is larger than SaCas9. *Id*. ¶¶ 178-92.

Response: Admitted

12. During prosecution of the 204 application, Sigma argued that many aspects of the eukaryotic CRISPR-Cas9 system, including those associated with the Cas9 protein, were

unpredictable. *See, e.g.*, Ex. 2074 (April 29, 2019 Applicant Remarks) at 19, 27-28; Ex. 2466 (October 17, 2017 Urnov Decl.) ¶¶ 15-17.

Response: Admitted

13. Broad determined that using an CRISPR-SaCas9 system 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. 2464 (Seeger Decl.) ¶¶ 193-94.

Response: Denied

14. SaCas9 is used for more therapeutic applications than any other Cas9 ortholog. *Id*. ¶ 194; *see* Ex. 2017, 406 Patent at 83:25-84:23; Exs. 2687, 2517, 2686.

Response: Denied

15. All claims of Broad's 418 patent (Ex. 2060) require that the Cas9 is not taken from a single organism but rather is a chimeric Cas9 that includes two fragments from different Cas9. Ex. 2060 at 83:45-52; Ex. 2464 (Seeger Decl.) ¶¶ 197-202.

Response: Denied

16. Count 1 and the prior art do not teach, suggest, or provide motivation to a POSA to design a chimeric Cas9 that is comprised of two fragments from different organisms. Ex. 2464 (Seeger Decl.) ¶¶ 197-202; Paper 1 at 12-13; Broad Motion 1 at 4.

Response: Lack sufficient information to admit or deny

17. Ex. 2060, 418 patent at 4:21-25 recites "[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."

Response: Admitted

18. The 418 patent (Ex. 2060 at 83:45-52) recites benefits of a chimeric Cas9. *See also*

Ex. 2464 (Seeger Decl.) ¶¶ 201-07.

Response: Admitted

19. The Sigma half of Count 1 specifically recites that the Cas9 has "only one NLS," while the Broad half of Count 1 does not indicate anything about the Cas9 with regard to NLSs. Paper 1 at 12-13.

Response: Admitted

20. Neither Count 1 nor the prior art provides any teaching or suggestion to use two or more NLSs in a CRISPR-Cas system in a eukaryotic cell, nor was there a reasonable expectation of success in using two or more NLSs. Ex. 2464 (Seeger Decl.) ¶¶ 209-32.

Response: Lack sufficient information to admit or deny

21. During prosecution of the 204 application, Sigma submitted expert testimony from Dr. Cannon that modifications to the Cas9 protein such as adding an NLS could "affect Cas9 protein folding and the final protein structure" such that it "could interfere with Cas9 function; for instance, by interfering with a binding site or catalytic domain." Ex. 2465 (April 29, 2019 Cannon Decl.) ¶¶ 59-60.

Response: Admitted

22. During prosecution of the 204 application, Sigma argued that "[b]ecause a protein's function is inextricably linked to its folded structure, proper folding after (or during) translation is crucial" and that misfolded proteins would be subject to degradation in the eukaryotic environment. Ex. 2074 (April 29, 2019 Applicant Remarks) at 30.

Response: Admitted

23. During prosecution of the 204 application, Sigma argued that "when a protein is expressed as a fusion, such as with an NLS or epitope or chimeric tag, there are unexpected results,

further confirming that there was no reasonable expectation of success as to a eukaryotic CRISPR-Cas9 system wherein the Cas9 includes one or more NLSs." Ex. 2074 (April 29, 2019 Applicant Remarks) at 27 (citing Ex. 2465 (April 29, 2019 Cannon Decl.) ¶¶ 76-77).

Response: Admitted

24. 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. 2464 (Seeger Decl.) ¶¶ 202-21; Ex. 2001, Zhang B1, Figure 1B; Ex. 2201, Cong 2013, Figure 1A; Ex. 2793.

Response: Lack sufficient information to admit or deny

25. A POSA would have understood that adding amino acids to a protein such as Cas9 could alter its folding affecting its structure and function in ways that were not predictable. Ex. 2464 (Seeger Decl.) ¶¶ 216-17, 222-28; Ex. 2258 at 1785-1790; Exs. 2263-2265; Ex. 2465 (April 29, 2019 Cannon Decl.) ¶¶ 59-60 (one could not "predict with any reasonable certainty whether ***any*** functional domain... will be properly exposed when expressed as a fusion with Cas9"); *id.* ¶¶ 59-60.

Response: Admitted

26. Count 1 does not recite that the Cas9 is fused to specified protein domains. Paper 1 at 12-13; Broad Motion 1 at 4.

Response: Admitted

27. There is no teaching or suggestion in Count 1 or the prior art to modify the naturally occurring Cas9 to include protein domains. Ex. 2464 (Seeger Decl.) ¶¶ 233-40.

Response: Lack sufficient information to admit or deny

28. 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; Ex. 2464, ¶ 239.

Response: Admitted

29. Broad's 713 patent (Ex. 2043), includes claims, including claims 15-26 and 2841, that are not limited to single-molecule RNA and do not contain the term "guide RNA." *See* Ex. 2464 (Seeger Decl.) ¶¶ 114-18.

Response: Denied

30. Independent claim 1 and dependent claims 2-24 of Broad's 418 patent (Ex. 2060) do not recite any RNA component. *See* Ex. 2464 (Seeger Decl.) ¶¶ 116-17.

Response: Admitted

31. The 308 patent, claim 1 describes a method using CRISPR-Cas system having "guide RNA" that hybridizes to the target sequence and claim 6 covers the "method of claim 1, wherein the guide RNA comprises a guide sequence and a tracr sequence." Ex. 2013.

Response: Denied

32. The 616 patent, claim 1 describes a CRISPR-Cas system having a "guide RNA" polynucleotide sequence comprising a guide sequence, a tracr mate sequence, and a tracr sequence, claim 2 covers the "composition of claim 1, wherein the modified guide RNA comprises a chimeric guide sequence and a tracr sequence," and claim 5 covers the "composition of claim 1, wherein the modification comprises fusing the tracr mate sequence and the tracr sequence through an artificial loop." Ex. 2014.

Response: Denied

In the 965 patent (Ex. 2012), none of the dependent claims include limitations that the components of the guide RNA be fused or bound to one another in a chimeric manner.

Response: Denied

33. The Broad patents disclose preferred embodiments that are dual-molecule RNA systems. Ex. 2011, 359 patent at 43:49-53, 44:5-8; Ex. 2464 (Seeger Decl.) ¶¶ 138-41.

Response: Denied

34. Sigma's 204 specification explains that "[i]n some embodiments, the guide RNA comprises a single molecule..." and "[i]n other embodiments, the guide RNA can comprise two separate molecules." Ex. 2074 (204 specification) at [0077].

Response: Admitted

35. Sigma's 204 application, claim 31 uses the generic term "guide RNA," while dependent claims 33 and 34 specify that the "guide RNA is a single molecule" and "the guide RNA is two molecules" respectively. Paper 12 at 2.

Response: Admitted

36. 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. 2068, ¶¶ [168]-[170]; Ex. 2067, ToolGen PCT, ¶¶ [0168]-[0169]; Ex. 2062, 510 application, ¶¶ [0094]-[0095].

Response: Denied

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

Response: Denied

38. In the original claims of the ToolGen PCT application and the 510 application, the inventors included claims 3 and 4, which respectively limited that "guide RNA" to a dualRNA (a dual molecule RNA) and a "single-chain" guide RNA (a single molecule RNA). *Id*.

Response: Denied

39. In the disclosures from Ex. 2067 and 2062 referenced in MFs 36 and 37, ToolGen used the term "guide RNA" consistent with Jinek 2012's use of the term to include both sgRNA and dualRNA.

Response: Denied

40. Jinek 2012 states: "In this ternary complex, the dual tracrRNA:crRNA structure acts as guide RNA that directs the endonuclease Cas9 to the cognate target DNA." Ex. 2202, Jinek 2012, at Figure S1 description.

Response: Admitted

Sigma moved to change the count in the 132 Interference. Ex. 2124. **Response: Admitted**

41. In the 132 Interference, the current count is an "or" count directed on one hand (the Sigma half) to Donor Template Integration, and on the other hand (the CVC half), to Non-Template activity. *Id*.

Response: Denied

42. Sigma stated in Motion 1 in the 132 Interference that "using a CRISPR-Cas9 system in a eukaryotic cell to cleave DNA and thereafter to integrate a donor polynucleotide into that cleaved DNA via HDR is patentably distinct from (not obvious in view of) simply using a CRISPR-Cas9 system in a eukaryotic cell to cleave DNA." *Id*. at 5:3-7.

Response: Admitted

43. Sigma stated in Motion 1 in the 132 Interference that "in early December 2012 a POSITA would not have had a reasonable expectation that such a process in a CRISPR-Cas9 system would be successful in eukaryotic cells." *Id*. at 6:23-29.

Response: Admitted

44. In Motion 1 in the 132 Interference, Sigma identified Donor Template Integration claims as the only involved claims corresponding to 132 Interference Proposed Count 2. *Id*. at 27:1-8.

Response: Denied

45. In Motion 1 in the 132 Interference, Sigma stated that there are three interferences pending before the PTAB directed to Non-Template CRISPR-Cas9 activity in a eukaryotic cell, but that "Sigma is ***properly*** not a party to those pending 'cleavage only' interferences because all of Sigma's involved claims are directed solely to the patentably distinct 'cleavage plus integration' technological advance in the art." *Id*. at 4:14-23.

Response: Denied

46. Sigma has argued that integration of a donor template via a CRISPR-Cas9 system in a eukaryotic cell is a distinct invention from cleavage and repair of DNA by other means. *See, e.g.*, Ex. 2074 (October 13, 2020 Applicant Remarks) at 8-9.

Response: Denied

47. In October 2020, Sigma filed a suggestion of Interference during prosecution of the 204 application for CVC's 680 application, proposing a Count that required integration of a donor template. Ex. 2074 (October 13, 2020 Suggestion of an Interference).

Response: Denied

48. Sigma argued that only claims from CVC's applications that expressly recite

donor template integration would correspond to its proposed Count. *Id*.

Response: Denied

49. Broad's best proofs include dual-molecule RNA systems without a donor polynucleotide. Ex. 2464 (Seeger Decl.) ¶¶ 20, 151-66.

Response: Lack sufficient information to admit or deny

SIGMA MATERIAL FACTS & BROAD RESPONSES

50. In Broad Motion 3, with respect to Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/chimeric RNA and dgRNA), Broad does not cite the one-way obviousness analysis for evaluating whether those claims correspond to Count 1. Broad Mot. 3.

Response: Denied, Broad noted the one-way test and showed it did not apply here.

51. In Broad Motion 3, with respect to Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/chimeric RNA and dgRNA), Broad does not apply the one-way obviousness analysis for evaluating whether those claims correspond to Count 1. *Id.*

Response: Admitted, Broad's argument was not based on the one way test.

52. In Broad Motion 3, with respect to Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/chimeric RNA and dgRNA), Broad does not assert that those claims would have been obvious in view of Count 1. *Id.*

Response: Admitted.

53. In Broad Motion 3, with respect to Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/chimeric RNA and dgRNA)**,** Broad does not address how the prior art teachings—particularly those of Jinek (2012)—would have impacted the obviousness inquiry for a POSITA in December 2012. *Id.*

Response: Admitted.

54. In Broad Motion 3, with respect to Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/chimeric RNA and dgRNA), Broad does not address Broad's arguments in Broad Motion 2, which seeks to involve Broad's generic RNA claim (Claim 52), dgRNA claim (Claim 53), and sgRNA claim (Claim 54) in this interference. *Id.*

Response: Admitted as such was not relevant to Broad's proofs.

55. With respect to Broad's claims reciting "guide RNA", the Board's decision in the *CVC v. Broad* interference (No. 106,115) determined that those Broad claims are properly construed to be limited to sgRNA/chimeric RNA claims. Ex. 1528.

Response: Admitted that the decision addressed the claim construction issue, but on a different factual record than is present here.

56. The Board's conclusions in in the *CVC v. Broad* interference (Int'f No. 106,115) regarding Broad's "guide RNA" claim recitals apply equally here. Ex. 1518 ¶¶ 39-41.

Response: Denied, that decision addressed the claim construction issue, but on a different factual record than is present here.

57. All of the fourteen involved Broad patents and application involved in the *CVC v. Broad* interference (Int'f No. 106,115) are also involved in this interference. Ex. 1528.

Response: Admitted.

58. With respect to the *CVC v. Broad* interference (Int'f No. 106,115), the additional Broad patent and application involved in this interference (8,889,418 and 15/330,876) are continuations of Application 14/104,977, and thus share the same specification as involved Broad Patents 8,895,308 and 8,865,406.

Response: Admitted.

59. The claims identified in the magenta highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite Staphylococcus aureus Cas9 or SaCas9. *See* Ex. 1518 (Cannon Supp'l Decl.), Appx. C.

Response: Admitted.

60. The claims identified in the orange highlighting in Sigma's Claim Correspondence

Table (Sigma Opp'n 3 at 10) all recite chimeric Cas9. *Id*.

Response: Admitted.

61. The claims identified in the blue highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite two or more NLSs. *Id*.

Response: Admitted.

62. The claims identified in the red highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite a Cas9 protein fused to one or more protein domains. *Id*.

Response: Admitted.

63. The claims identified in the lavender highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite nickase. *Id*.

Response: Admitted.

64. The claims identified in the gold highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite either (i) more than one targeting RNA (aka "multiplexing"), and/or (ii) one or more mutation(s) in the Cas9 RuvC/HNH domain(s). *Id*.

Response: Admitted.

65. The claims identified in the yellow highlighting (but not included within parentheses) in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite "guide RNA". *Id*.

Response: Admitted.

66. The claims identified in the cyan highlighting (but not included within parentheses) in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite cleavage plus altering gene expression. *Id*.

Response: Admitted.

67. The claims identified in the mint green highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite cleavage plus insertion of a template. *Id*.

Response: Admitted.

68. The claims identified in the bright green highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite cleavage plus integration via HDR. *Id*.

Response: Admitted.

69. Of Broad's 461 involved patent claims, 340 of those claims are directed to "cleavage plus altering gene expression" (or an analogous recital). *Id*.

Response: Denied, "cleavage plus altering gene expression" is a term created by Sigma and not the actual language of the claims.

70. Of Broad's 461 involved patent claims, 42 of those claims are directed to cleavage plus insertion of a template. *Id*.

Response: Admitted the Broad has Donor Template Integration related claims, but otherwise denied, as "cleavage plus insertion of a template" is a term created by Sigma and not the actual language of the claims.

71. Of Broad's 461 involved patent claims, 8 of those claims are dependent claims directed to cleavage plus integration by HDR. *Id*.

Response: Admitted the Broad has HDR related claims, but otherwise denied, as "cleavage plus integration by HDR" is a term created by Sigma and not the actual language of the claims.

72. Claims 8, 9, 16, and 27 of Broad Patent 9,840,713 recite "a chimeric RNA" or "a guide sequence fused to the tracr sequence". Ex. 1518 (Cannon Supp'l Decl.) ¶ 43.

Response: Admitted.

73. Claims 15, 17-26, and 28-41 of Broad Patent 9,840,713 do not recite "RNA", and thus do not include a recital of generic RNA. *Id*. ¶ 44.

Response: Denied, those claims recite "guide sequence," "tracr mate sequence," and "tracr sequence" all of which are RNA and which allow for generic RNA as those claims do not limit the RNA components to either being in a chimeric RNA or in a dual molecule RNA so they do generically recite RNA.

74. Claims 1, 3-4, 7-17, 20-24, 26-28, 31-35, 37-38, 40-41 of Broad Patent 9,840,713 recite "displays a phenotype or carries DNA to display a phenotype of the genetic modification", which is analogous to altering gene expression. *Id*. ¶ 45.

Response: Admitted that the selective cropped quote is in the claims; otherwise, denied.

75. Claim 35 of Broad Application 15/330,876 recites "the vector comprises a U6 promoter operably linked to a nucleotide sequence encoding the chiRNA", which would not have been obvious in view of Count 1. *Id.* ¶ 47.

Response: Admitted that the selective cropped quote appears in claim 35; Broad accepts for purposes of this Interference Sigma's concession that the subject matter of the claim would not have been obvious in view of Count 1 without taking an affirmative position one way or another on the obviousness issue.

Broad's Additional Material Facts

76. In its Opposition, Sigma concedes in its Claim Correspondence Table in the "Sigma Does Not Contest Do Not Correspond" and "FN3" columns that the identified Broad's claims should be designated as not corresponding to Count 1. Opp. 3 at 10.

CERTIFICATE OF FILING AND SERVICE

I hereby certify that on April 26, 2022, a true and complete copy of the foregoing **BROAD OPPOSITION 3** is being filed and served by 8:00 pm ET via the Interference Web Portal (SO ¶ 105.3; Paper 27 at 11). By agreement, service copies are being sent by email by 11:00 pm ET to counsel for Senior Party as follows:

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