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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 1

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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 the PTAB grant Broad Motion 1 to change the count of this Interference to Proposed Count 3.

II. DESCRIPTION OF APPENDICES

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

III. REPLY ARGUMENT

A. Sigma Does Not Meaningfully Dispute The Multiple, Independent Reasons Set Out In Broad's Motion 1 Showing That Proposed Count 3 Should Be Substituted For Count 1

Broad showed in Motion 1 that Proposed Count 3 should be substituted for Count 1 for at least three reasons, each of which alone is sufficient to warrant adopting Proposed Count 3. Sigma does not meaningfully dispute any of these reasons and, accordingly, the PTAB should grant Broad's Motion 1 and re-declare the Interference with Proposed Count 3.

1. Sigma Does Not Meaningfully Dispute That Count 1 Does Not Describe The Interfering Subject Matter

Broad showed in its Motion 1 that Count 1 does not describe the scope of the interfering subject matter: use of a CRISPR-Cas9 system in a eukaryotic cell to target and cleave both strands of a DNA molecule, with the cleavage being repaired by integrating a donor polynucleotide sequence ("Donor Template Integration"). In its Opposition 1, Sigma does not dispute that all of its involved claims are limited to Donor Template Integration. Nor does it dispute that CRISPR-Cas9 mediated cleavage repaired via template integration was the very basis of allowability of its involved claims. Regarding Broad's claims, Sigma does not dispute that Broad has issued and allowed claims directed to Donor Template Integration and that Zhang B1 (Ex. 2001) discloses successful uses of CRISPR-Cas9 in a eukaryotic cell to perform Donor Template Integration.

Count 1 thus does not reflect the scope of the parties' commonly-claimed interfering subject matter because it is *not* limited to Donor Template Integration and, if retained, would defeat the very purpose of an interference, which is to determine "which of the competing parties was first to invent the duplicative subject matter." *Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington*, 334 F.3d 1264, 1267 (Fed. Cir. 2003). Proposed Count 3 allows for that determination—Count 1 does not. On that basis alone, Broad Motion 1 should be granted.

2. It Is Undisputed That A Count Should Not Encompass Two Distinct Inventions, And That Sigma Has Repeatedly Stated That Donor Template Integration Is A Distinct Invention

Sigma does not dispute, nor could it, that "[t]he single Count 1 in this interference should not encompass two patentably distinct inventions." Ex. 2124 (132 Sigma Mot. 1) at 1:12-13; MF 34. Nor does Sigma dispute that it contends that its half of the count in the 132 Interference with CVC (which is the same as Sigma's half of Count 1 here) is patentably distinct from CVC's half of the count (Claim 156 of U.S. Application 15/981,807) *because Sigma's half of the count requires Donor Template Integration while CVC's half does not*. Likewise, Broad's half of Count 1 here (Broad's Claim 18 of U.S. Pat. No. 8,697,359) *does not require Donor Template Integration*. Given Sigma's contention that its Claim 31 is patentably distinct from CVC's Claim 156 based on *Donor Template Integration*, Sigma cannot credibly argue that its Claim 31 is not also patentably distinct from Broad's Claim 18.

CVC's Claim 156 was half of the count in the 115 Interference (that recently concluded in a judgment in Broad's favor on priority). The very premise of the 115 Interference was that CVC's Claim 156 and Broad's Claim 18 were directed to the same invention. If Sigma's Claim 31 is, as Sigma argues, patentably distinct from CVC's Claim 156, then Claim 31 must also be patentably distinct from Broad's Claim 18 for the same reason. This Interference should not continue with a Count that encompasses, given Sigma's arguments, two patentably distinct inventions.

Given that, according to Sigma's own arguments, Donor Template Integration claims are patentably distinct over claims not requiring Donor Template Integration, it would work a tremendous injustice to Broad to proceed with Count 1. Most of Broad's claims currently designated as corresponding to Count 1 are not limited to Donor Template Integration, but rather are Non-Template claims—Sigma does not dispute this in its Opposition. *See* Mot. 1, Section IV.C; Ex. 2464 (Seeger Decl.) ¶¶ 148-50; MF 6-10. This Interference thus presents the "anomalous possibility" that Sigma can seek priority to the ***entirety*** of Count 1's scope based on only donor template proofs which, according to Sigma, are "***patentably distinct subject matter that are different inventions***." Ex. 2074 (April 9, 2018 Petition) (emphasis in original).

At 13:25-19:11 and 20:7-23:19, Sigma argues Broad has not shown that Donor Template Integration claims are separately patentable from Non-Template claims and further asserts that Sigma has never argued the separate patentability of such claims. Opp. 1 at 13:25-19:11, 20:7-23:19. The response is that Broad's motion is properly based on the substantial evidence of Sigma's clear and repeated assertions in, *inter alia*, prosecution of its involved U.S. Application 15/456,204 ("204 application") and the co-pending 132 Interference. Indeed, even in its Opposition 1, Sigma states that it "has consistently maintained that claims directed to ***cleavage plus integration via HDR*** in a eukaryotic cell are patentably distinct from claims directed to ***cleavage only***." Opp. 1 at 11:17-19 (emphasis in original).

Sigma now tries to explain away its prior statements regarding the patentable distinctness of Donor Template Integration, but those explanations cannot be squared with its prior arguments.

a. Sigma Fails To Explain Away Its Statements Regarding Patentability During Prosecution Of The 204 Application

As Broad showed in Motion 1, Sigma argued throughout prosecution of its involved 204 application that its claims were allowable *because* they are limited to Donor Template Integration

and thus separately patentable from art disclosing cleavage only or other forms of DNA repair.

At 13:25-17:33 and 20:7-23:19, 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; MF 17. 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); MF 18. 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, at 18:20-19:11, Sigma argues that Broad needed to show that its Non-Template claims are patentably distinct from Sigma's Donor Template Integration claims. Opp. 1 at 18:20-19:11. The response is that, again, Sigma's prior admissions are more than sufficient evidence to carry Broad's burden. Moreover, such a showing is not required to support a motion to change the count. *See* 37 C.F.R. §§ 41.121(a)(1)(i) and 41.208(a)(2); Standing Order ¶ 208.2. Broad addressed claim correspondence to Proposed Count 3, which requires Donor Template Integration, in Motion 1. This is all that Broad was required to address.

b. Sigma Fails In Its Attempt To Explain Away Its Statements In The 132 Interference

In an effort to limit the count in the 132 Interference to Donor Template Integration, 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; MF 33. At 20:7-23:19, 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 necessarily 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.

Accordingly, Broad's Motion 1 should be granted on the separate ground of Sigma's repeated arguments that Donor Template Integration represents a distinct invention and the law that a count should not encompass two patentably distinct inventions.

3. Sigma Does Not Dispute That Broad's Dual Molecule RNA Proofs Would Be Excluded Under Count 1, And Further Argues That Broad's sgRNA Proofs Would Also Be Excluded

As Broad showed in Motion 1, the PTAB should substitute proposed Count 3 for Count 1 for a third reason, namely because Count 1 would unfairly exclude Broad's best proofs—including dual molecule RNA experiments. Sigma does not dispute that Count 1 would exclude those dual molecule RNA experiments. Indeed, Sigma argues that Count 1 should *also* exclude Broad's sgRNA experiments that formed the basis for the Judgment of Priority in the 115 Interference in Broad's favor. Specifically, in Sigma's Motion 1, filed concurrently with Broad's Motion 1, Sigma expressly argued that Broad should *not* be given the benefit of its earliest provisional (Zhang B1) with respect to Count 1. That provisional application includes the experimental work recited in the manuscript that Dr. Zhang and his colleagues submitted to *Science* on October 5, 2012 (Ex. 2564, "October 5 Manuscript") that was a basis for awarding Broad priority in the 115 Interference. Thus, Sigma argues, through a Catch-22 style argument, that Count 1 excludes not just Broad's dual-molecule RNA proofs, but ***all*** of Broad's best proofs to both the eukaryotic invention with a

generic RNA and to Donor Template Integration.

In its Motion 1, Sigma argues Broad should be denied the benefit of Zhang B1 with respect to Sigma's half of Count 1 because, despite the fact Zhang B1 discloses an undisputed, actual working example of what Sigma told the PTO was its patentable invention—Donor Template Integration—the specific example disclosed in Zhang B1 does not include the immaterial limitation in Sigma's half of Count 1 requiring "only one NLS." At the same time, Sigma argues in its Motion 1 that all of Broad's other working examples in Zhang B1 do not meet the Broad half of Count 1 because they allegedly do not show that "expression of the at least one gene product is altered." While Sigma is wrong on this point (*see* Broad Opposition 1), Sigma's argument alone confirms the unfairness of proceeding with Count 1. As the Federal Circuit instructed in *University of Southern California v. DePuy Spine, Inc.*, 473 F. App'x 893, 895 (Fed. Cir. 2012), adopting a count that prevents a party from relying on its best proofs (including its priority application) while rejecting requests to modify the count is improper.

Sigma argues at 12:16-13:21 that "Proposed Count 3 does not conform to Broad's purported best proofs of invention." Opp. 1 at 12:16-13:21. The first response is that this is false, and second is that it misses the point of Broad's motion entirely.

First, Broad's best proofs, ***as to the commonly claimed invention*** between the parties, are unequivocally encompassed by Proposed Count 3. As Broad demonstrated in Motion 1 (Mot. 1 at 20:3-21:4; Appendix C; Ex. 2464 (Seeger Decl.) ¶¶ 48-111; MF 12-16)—and as is undisputed by Sigma—Zhang B1 discloses a working example of Donor Template Integration. Specifically, Embodiment E17+ in Zhang B1 discloses successful integration of a 2000-bp sequence into the EMX1 gene in a eukaryotic cell. Ex. 2464 (Seeger Decl.) ¶¶ 48-111. Sigma does not dispute that E17+ is a constructive reduction to practice of Proposed Count 3. Moreover, the same embodiment

is reproduced in the October 5 Manuscript reporting the development of "a new class of precision genome engineering tools" based on RNA-guided CRISPR-Cas9 nucleases. Ex. 2564 (October 5 Manuscript) at 6-7. The experiments reflected in Zhang B1 and the October 5 Manuscript are within Broad's best proofs as to the commonly claimed invention set forth in Proposed Count 3.

Sigma also contends elsewhere in Opposition 1 that "Broad does ***not*** contend that its Proposed Count 3 is needed to conform to Broad's best proofs of invention." Opp. 1 at 11:9-10 (emphasis in original). But, in fact, if Sigma's Motion 1 arguments are accepted, Proposed Count 3 is needed to conform to Broad's best Donor Template Integration proofs because, as Sigma argues in its Motion 1, Broad's Donor Template Integration experiments used two NLSs rather than "only one NLS" (an unnecessary limitation of Sigma's half of Count 1) and Sigma argues these experiments do not meet the Broad half of Count 1 either (based on an incorrect reading of Count 1 and Zhang B1 disclosure). *See* Sigma Mot. 1 and Broad Opp. 1.

Second, Sigma misunderstands Broad's Motion 1. Sigma relies on Broad's undisputed showing that Broad has earlier dual-molecule RNA proofs that are excluded by Count 1—one of the reasons why Count 1 must be replaced. Sigma thus misses the point of Broad's motion, which is not to broaden, but rather to properly narrow the count, and its showing that Donor Template Integration is not among its earliest proofs—that showing proves Proposed Count 3 should be substituted for Count 1. While one remedy for this issue is broadening the count (*Louis v. Okada*, 59 U.S.P.Q.2d 1073, 2001 WL 775529 (Bd. Pat. App. & Int. 2001)), because Sigma has limited its claims to Donor Template Integration, it is also an appropriate remedy to limit the count (and the involved claims) to Donor Template Integration. Both parties will have access to the same scope of proofs, with claims coextensive with those proofs designated to Proposed Count 3.

Thus, contrary to Sigma's arguments, Broad in no way "effectively concedes that its best

proofs (which do not include a donor template) fall outside the scope of Proposed Count 3 (specifically reciting 'a template polynucleotide')." Opp. 1 at 11:10-12.

Finally, at 19:14-20:4, Sigma argues that Broad's motion fails because Proposed Count 3 is not limited to sgRNA. Opp. 1 at 19:14-20:4. Sigma says Broad does not attempt to show its proofs regarding Donor Template Integration are directed to both dual RNA and sgRNA. *Id.* at 19:14-20:4. The response is that, first, Broad's Proposed Count 3 is generic as to RNA because the Sigma half of Count 1 is also generic as to RNA, and Broad's claims are as well. Second, as Sigma acknowledges, because Proposed Count 3 is generic as to the RNA, even if all of Broad's Donor Template Integration proofs were sgRNA, they still properly fall within that Count.

B. All of Sigma's Other Arguments Opposing Proposed Count 3 Also Fail

Sigma does not meaningfully dispute any of the above independently dispositive reasons to change the Count and, accordingly, Broad respectfully submits that the Board should re-declare the Interference with Proposed Count 3. Rather than confront the fundamental reasons the Count should be changed, Sigma presents a ragbag of irrelevant challenges to the Broad half of Proposed Count 3. Those arguments are legally and factually erroneous, as addressed below.

1. Claim 52 Was And Is Allowable To Broad

Sigma argues, at 2:13-11:5, that Claim 52 was allegedly not allowable when Broad filed Motion 1, despite the fact Claim 52 was indicated as allowable as entered on November 15, 2021, before Broad filed its Motion 1. Opp. 1 at 2:13-11:5. The crux of Sigma's argument is that the Examiner did not expressly include the word "allowed" in the office action entering the final amendments to Claim 52 on November 15, 2021. Ex. 2075 (Part 1) (October 5, 2021 Misc. Action) at 2, 19-20. The first response is that on March 7, 2022, the Examiner, prior to Sigma's Opposition 2, *sua sponte* entered an office action expressly noting Claim 52 was allowable, mooting Sigma's argument. Ex. 1521 (March 7, 2022 Misc. Action) ("All claims are allowable."); MFs 82-83.

The second response is that Claim 52 was allowable on November 15, 2021 when Broad's proposed amendments were entered by the Examiner into the already allowable Claim 52. This is shown by the fact that the initial Claim 52 was indicated as allowable on October 5, 2021, and then the Examiner entered the final amendments on November 15, 2021 (Ex. 2075 (Part 1) (October 5, 2021 Misc. Action) at 2, 19-20), demonstrating the allowability of the amendments. Further, nothing in the file history changed between these two events—i.e., Broad submitted no further arguments or amendments. Thus, the claim was ***allowable as entered*** on November 15, 2021, as confirmed by the Examiner's recent March 7, 2022 action specifically stating that "[a]ll claims are allowable." Ex. 1521 (March 7, 2022 Misc. Action) at 2.

2. Claim 52 Properly Defines The Interfering Subject Matter And Is Not Overbroad

Sigma argues, at 23:22-36:15, that Proposed Count 3 is "excessively broad and thus grossly inadequate to reasonably conform to either of the parties' inventions." Opp. 1 at 23:22-36:15. The response is that Sigma's argument depends on a far-fetched, implausible, and unreasonable reading of the claim contrary to its plain language, the teachings of Zhang B1, and the POSA's knowledge of the CRISPR-Cas9 system by December 2012. Rather than using the broadest ***reasonable*** interpretation, Sigma's argument is based on a markedly ***unreasonable*** *view* of Claim 52, one that ignores both the intrinsic and extrinsic evidence. Moreover, Sigma's Claim 31, were it read in the same incorrect manner Sigma proposes for Claim 52, would fall prey to the same problems Sigma alleges are present Claim 52. The Broad half of proposed Count 3 is of similar breadth to the Sigma half, if read reasonably. Sigma's unreasonable reading should be rejected. As to Sigma's specific criticisms, Broad briefly addresses each below:

"**Broad's Claim 52 is not limited to a standard CRISPR-Cas system known to a POSITA in December 2012.**" Opp. 1 at 25:5-6. Sigma argues that because Claim 52 does not

include the specific words "Type II CRISPR-Cas system" or "CRISPR-Cas," the POSA would somehow conclude it encompasses "non-standard CRISPR-Cas9 systems." Opp. 1 at 25:3-26:7. Sigma cites examples of alleged non-standard CRISPR systems in its expert's declaration.

The first response is that Claim 52 expressly recites the components of a CRISPR-Cas9 system, including a "Cas9 protein" that "cleaves both strands of the DNA molecule." A POSA would understand from Zhang B1 that Cas9 proteins are found in Type II CRISPR-Cas9 systems. *See, e.g.,* Ex. 2001 (Zhang B1) at [0004]. Indeed, Jinek 2012, of which the POSA would have been aware, reports that "Cas9 [is the] ***hallmark protein*** of type II systems." Ex. 1539 (Jinek 2012) at 816. At her deposition, Dr. Cannon agreed that Cas9 is a hallmark protein of the type II systems, and that she was not aware of any literature ever describing "Cas9" as present in anything other than a Type II CRISPR system. Ex. 1549 (Cannon Supp. Dep.) at 30:13-16, 33:2-9. Dr. Cannon also admitted that Claim 52's scope covers standard Type II Cas9 systems. *Id*. at 57:10-15.

The second response is that a POSA would reasonably read Claim 52 in light of Zhang B1 and the art as disclosing a CRISPR-Cas9 system in which, in Sigma's words, "crRNA is based-paired to tracrRNA to form a guide RNA that guides Cas9 to cleave both strands of a target DNA sequence at sites complementary to a portion of the crRNA sequence." Opp. 1 at 25:3-26:7. Indeed, Claim 52 expressly recites that the Cas9 cleaves a DNA target and, as Sigma's expert admitted, as of the relevant date, a POSA would have known that Cas9 *must* interact with both a tracrRNA and a crRNA to so cleave a DNA target. Ex. 1549 (Cannon Supp. Dep.) at 44:18-45:3; 48:13-49:1. Moreover, Zhang B1 discloses that crRNA is based-paired to tracrRNA to form a guide RNA that guides Cas9 to cleave both strands of a target DNA sequence at sites complementary to a portion of the crRNA sequence. *See, e.g.,* Ex. 2001 (Zhang B1) at [0004].

Sigma also speculates that a POSA, rather than concluding that Claim 52 is directed to the

standard CRISPR-Cas9 system described in Zhang B1 and the art, would instead hypothesize that it encompasses systems where the first RNA could be an aptamer and the second RNA an aptazyme. But Sigma's expert admitted that ***no such system was known in the art in 2012***. Ex. 1549 (Cannon Supp. Dep.) at 37:18-38:5. Nor does Zhang B1 disclose an example of any such system. Instead, Sigma is misreading Claim 52 using disclosures of non-standard aptamer-aptazyme CRISPR systems published ***in 2015***; but, again, the 2012 POSA would not have been aware of any such system. Finally, if such a reading of the Broad half of Count 3 were plausible and reasonable, Sigma does not show how its own half of the counts excludes such system.

"**Claim 52… encompasses NHEJ-mediated end ligation**" (Opp. at 26:16). The response is that Claim 52 was modified during prosecution to specify, accurately, that cleavage of the DNA molecule "is repaired by integration of the template polynucleotide into the DNA molecule." The cellular mechanism actually resulting in integration of the template is irrelevant to the parties' dispute. As Sigma's expert admitted, regardless of the repair mechanism used, the end result in Claim 52 is that there be integration of a donor template polynucleotide into the target molecule. Ex. 1549 (Cannon Supp. Dep.) at 66:12-67:18 ("Q. But regardless of the mechanism that's being used, claim 52 still requires, as an end result, that there be integration of the template polynucleotide into the DNA molecule, right? [Attorney objection]. THE DEPONENT: Yes.").

"**The 'second RNA' is not recited as a tracrRNA**" (Opp. 1 at 28:2). The response is that a POSA would reasonably read Claim 52 in light of Zhang B1 and the art as disclosing a system in which the "second RNA" is tracrRNA. Sigma's expert acknowledged that an RNA functioning as a tracrRNA was known to a POSA to be necessary for cleavage as of December 2012. Ex. 1549 (Cannon Supp. Dep.) at 44:18-22 ("Q. Okay. And would you agree that by December 2012, it was known in the art that Cas9 must interact with the tracrRNA to cleave a DNA target? A. Yes.").

She also acknowledged that she could not point to anything in Zhang B1 other than a tracrRNA, that with the crRNA, formed part of the RNA duplex recited in Claim 52. *Id.* at 51:16-53:4. Moreover, Sigma's half of the counts does not recite that the first and second "regions" of the guide RNA are tracrRNA or crRNA, as Sigma's expert admitted, and thus Sigma's own half of the counts has the same scope. *Id.* at 100:3-102:7.

"**[T]he first RNA [1] performs *all* of the guide RNA's functions… while the second RNA [2] performs *none* of the guide RNA's functions**" (Opp. 1 at 30:10-15) (emphasis in original). The response is that this misreads Claim 52, which recites that the second RNA "forms an RNA duplex with the second ribonucleotide sequence [of the first RNA]." It also ignores the teaching of Zhang B1 in view of the prior art. *See, e.g.* Ex. 2001 (Zhang B1). Moreover, Sigma's own claim recites that the guide RNA comprises various RNA sequences, and in no way specifies which portion of the guide RNA "guides the CRISPR-Cas type II protein to the target site." Thus, Sigma's half of the counts would also include such systems under its unreasonable interpretation.

Claim 52 "**encompasses a system in which the first RNA does not necessarily hybridize with the target DNA**" (Opp. 1 at 31:13-14). The response is that, first, a POSA would read Claim 52 in light of Zhang B1 and the art as disclosing such a system, which is necessary to the recited cleavage step. *See, e.g.* Ex. 2001 (Zhang B1). Second, Sigma's half of the counts does not recite hybridization or binding either; thus, to the extent Sigma's unreasonable interpretation is correct, Broad's half of Proposed Count 3 merely is of the same scope as Sigma's on this point.

"**Claim 52 encompasses an RNA 'genus', namely, both sgRNA and dgRNA**" (Opp. 1 at 32:10-11). The response is that so, too, does the Sigma half of the counts. And, as Broad showed in its Motion 1, its claims are not limited to sgRNA; thus, the commonly claimed subject matter at issue between the parties need not be and should not be limited to sgRNA.

Claim 52 "**include[s] a split-Cas9 system in which two (or even more) nucleotide sequences encode the Cas9 protein**" (Opp. at 35:10-12). The response is that Sigma's argument is premised on the claim's recitation that one or more nucleotide sequences encode the Cas9. Sigma's own half of Count 1 recites "a nucleic acid encoding the CRISPR-Cas type II protein," which, in accord with common principles of claim interpretation for the article "a," includes the use of one or more nucleic acid sequences. Thus, to the extent Sigma's interpretation is correct, Broad's half of Proposed Count 3 merely is of the same scope as Sigma's on this point.

Claim 52 has "**no requirement regarding whether the Cas9 protein is natural (*i.e.*, wild-type) or non-natural (*i.e.*, engineered)**" (Opp. at 36:1-3). The response is that Sigma itself concedes Zhang B1 does not disclose a CRISPR-Cas9 system using a wild-type Cas9 protein in a eukaryotic cell. Opp. 1 at 36:4-6. Sigma is again reading Claim 52 unreasonably and entirely out of the context in which it would be understood by the POSA.

3. The 403 Application Is Not An AIA Application

At 36:18-38:15, Sigma argues that U.S. Application 16/177,403 ("403 application"), which contains Claim 52 (the Broad half of Proposed Count 3), supposedly does not have a continuous § 120 benefit chain to Zhang B1 "because of the addition of 'wherein the gene product is luciferase' in the disclosure and claims of the '322 application [P20]" and thus is an AIA application. Opp. 1 at 36:18-38:15.

The first response is that the AIA does not support Sigma's position. U.S. Application 61/842,322 ("P20") is a provisional application. Benefit to a provisional application is claimed through ***35 U.S.C. § 119(e)***. Sigma relies on AIA §§ 3(n)(1) and 3(n)(2) for its argument, but these sections only address the effect of benefit claims under three sections—35 U.S.C. §§ 120 (benefit for continuations), 121 (benefit for divisionals), and 365(c) (benefit for international/national applications)—not benefit claims to provisionals under § 119(e). Specifically, § 3(n)(1) indicates

that, if an "application for patent" (not a "provisional application") and any patent issuing thereon, contains or contained at any time, a claim to an invention that has an effective filing date after March 15, 2013, or has a specific reference ***under §§ 120, 121 or 365(c)*** to a patent or application that contained such a claim, then the AIA applies to that "application for patent." Provisional applications are not included in this part of the statute (i.e. claims in a provisional are irrelevant to the AIA provision), so there is no statutory basis for Sigma to argue that the 403 application becomes a transitional application subject to the AIA merely because it contains a claim to priority to a provisional application under § 119.

Sigma's argument thus fails on its face because whether or not its allegations about P20 and new matter are true (they are not), the 403 application—the relevant application here—contains a claim to benefit of P20 only through § 119(e), not §§ 120, 121 or 365(c) (the sections specified by the AIA). Sigma does not otherwise allege that the 403 application claims an invention with an effective date that is after March 15, 2013 or that the 403 application makes specific reference ***under §§ 120, 121, or 365(c)*** to any patent or application that contains (or contained) such a claim. Sigma's argument fails on this independent ground.

The second response is that this argument is a rehash of Sigma's rejected argument in its List of Proposed Motions that "Broad's involved patents and applications are all AIA patents and applications." Opp. 1 at 37:27-38:7. Specifically, Sigma repeats the same rejected argument from its Motions List that one application, P20, is subject to the AIA "because of the addition of 'wherein the gene product is a luciferase' in the disclosure and claims." Opp. 1 at 36:19-23. The 403 application does recite a separate § 119 benefit claim to P20 that is irrelevant to this AIA argument because P20 is not part of the unbroken chain of benefit to Zhang B1 for claims 52-54, which are fully supported by each application in that chain. Sigma wrongly argues, however, that

P20 contains "new matter" and that as a result ***every application*** that makes a claim of benefit to P20, whether or not the claims in those applications are supported by the pre-AIA Zhang B1 as well as whether or not P20 is required for benefit, is subject to the AIA rules.

In denying authorization for Sigma's Proposed Motion 1 on these grounds, the PTAB noted that "Sigma does not articulate an argument why the interference was improperly declared." Order on Motions, Paper 27 at 9. In its Opposition 1, Sigma did not articulate any argument to show that substituting Proposed Count 3 would create an improper interference. And Sigma does not point to any authority for why its baseless allegation that the 403 application should be treated as an AIA application based on P20 is otherwise relevant to whether the Count should be changed. There is none. Sigma's argument can be rejected on this second, independent ground as well.

The third response is that Sigma's argument that P20 includes new matter not present in Broad's pre-AIA filings is incorrect: the alleged "new matter" Sigma identifies is fully supported by the disclosures in Zhang B1. Sigma's sole basis for its argument is that Zhang B1 does not contain the ***specific*** wording "wherein the gene product is luciferase" that is in P20, arguing "[t]his disclosure is not set forth in any of Broad's pre-AIA applications…." Opp. 1 at 37; Ex. 1518 (Cannon Supp. Dec.) at ¶ 35. But a verbatim disclosure is not required in an earlier application to avoid the charge of "new matter." *Application of Anderson*, 471 F.2d 1237, 1244 (C.C.P.A. 1973) ("The question, as we view it, is not whether 'carrying' was a word *used* in the specification as filed but whether there is *support* in the specification for employment of the term in a claim….") (emphasis in original).

Instead, the proper test is whether the matter in question "changed the invention," when compared to the disclosure in Zhang B1. *See Commonwealth Scientific and Indus. Research Organisation v. Buffalo Technology (USA), Inc.*, 542 F.3d 1363, 1380 (Fed. Cir. 2008). Prohibited

"new matter" is consistently defined as something added to the patent that has the effect of "changing the invention." *Giant Powder Co. v. Cali. Powder Works*, 98 U.S. 126, 138 (1878); *Dart Industries, Inc. v. Banner*, 636 F.2d 684, 688 (D.C. Cir. 1980). The Federal Circuit has emphasized the similarity of the new matter and written description inquiries, holding that, like written description, the question for new matter is "whether the specification of the original application contained a written description of the invention sufficient to allow persons of ordinary skill in the art to recognize that the inventor invented the subject matter that is claimed in the asserted claims." *Commonwealth*, 542 F.3d at 1379.

Here, Sigma's contention is that the "new matter" supposedly added to P20 is the phrase "wherein the gene product is luciferase." But, the question is whether adding those words broadened or changed the invention. It did not because a POSA would understand that the inventors possessed a CRISPR-Cas9 system wherein the targeted gene product is luciferase based on the disclosures of Zhang B1. Luciferase was a well-known reporter gene target at the time, as Sigma's own expert admitted, Ex. 1549 (Cannon Supp. Dep.) at 21:20-23:13, and Zhang B1 ***expressly discloses*** introducing "reporter genes" including "luciferase" in a eukaryotic cell, as for example, a fusion protein to the CRISPR enzyme. Ex. 2001 (Zhang B1) at [0069]. Zhang B1 also discloses examples in which the luciferase gene is not fused to the Cas9 and thus would be expressed as a separate, targetable reporter gene. *Id*. (Cas9 may include "any additional protein sequence, and ***optionally*** a linker sequence between any two domains.") (emphasis added). As Dr. Cannon admitted at her deposition, a POSA in 2012 would have known how to design a luciferase reporter experiment testing whether an endonuclease could cleave a DNA target. *Id*. at 23:14-24:9. The combination of this basic knowledge with the express disclosure of "luciferase" reporter genes in Zhang B1 demonstrates possession of the alleged "new matter".

Thus, the invention was not ***broadened*** or ***changed*** in P20. Thus, there is no "new matter" issue—rather, as is commonplace, a specific aspect of the original disclosure was spotlighted, clarified, and claimed. *See, e.g. Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1302-04 (Fed. Cir. 2003); *Commonwealth*, 542 F.3d at 1381 (finding even broadening change to range did not introduce new matter where "even in the original specification the references to frequency range were not limited.").

4. Sigma Improperly Incorporates Designation Arguments By Reference

At 38:18-39:4, Sigma improperly incorporates arguments from its Opposition 3 regarding designation claims to the Count. Opp. 1 at 38:18-39:4. This 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." Sigma's incorporation by reference is a problem not just because it is an inappropriate way of increasing the page limits for its "kitchen sink" approach to opposing Broad's motions, raising frivolous points rather than substantively engaging the question and frequently block quoting arguments from so-called motions list for "substantive points." By incorporating by reference, Sigma avoids providing its position on whether claims that include the "altering gene expression" element should be designated to Proposed Count 3 that is limited to Donor Template Integration—an issue not addressed by Opposition 3. Sigma waived any opposition to Broad's designation of claims positions. *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)).

5. Claim 52 Is Patentable To Broad Over Sigma P1

At 39:8-25, Sigma argues that Broad did not show Proposed Count 3 is patentable over Sigma P1. Opp. 1 at 39:8-25. As an initial matter, Sigma does not cite to any authority that a

proposed count must be patentable over another party's benefit application.

Regardless, the first response is that Sigma P1 is a provisional and thus by itself is not prior art. Ex. 1524 (Sigma P1); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1380, n.5 (Fed. Cir. 2017) ("[P]rovisional applications are not themselves prior art under § 102(e)(1) because they are not applications published under § 122(b)"). The second response is that Claim 52 has been determined allowable over the actual art. The third response is that Sigma does not contest that embodiment E17+ is an embodiment of Proposed Count 3. Thus, even if § 102(e)(1) were applicable (it is not), the October 5, 2012 manuscript, disclosing the same work, antedates Sigma's P1, filed December 6, 2012 and therefore would remove as a potential reference any Sigma patent or published application for which Sigma claims the benefit of Sigma's P1.

IV. CONCLUSION

For the foregoing reasons, Broad respectfully requests the PTAB grant Broad Motion 1.

Dated: April 26, 2022

Respectfully submitted,

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APPENDIX A: LIST OF EXHIBITS CITED

Ex.	Description
Ex. 1518	Supp. Decl. of Paula M. Cannon, Ph.D., dated March 16, 2022
Ex. 1521	16-177,403 Miscellaneous Action, dated July 3, 2022
Ex. 1524	Sigma Application 61/734,256 ("Sigma P1")
Ex. 1539	Jinek (2012) (with Supp'l Mat'ls)
Ex. 1549	Deposition of Paula M. Cannon, Ph.D., dated April 13, 2022 (Cannon Supp. Dep.)
Ex. 2001	U.S. Application 61/736,527, Zhang et al., December 12, 2012.
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. 2464	Declaration of Christoph Seeger, executed December 3, 2021.
Ex. 2564	Cong et al., "CRISPR-Assisted Mammalian Genome Engineering," *Science*, Manuscript (October 5, 2012) ("Oct. 5 Manuscript")

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 U.S. 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 1 at 11-13.

Response: Denied

2. The Sigma half of Count 1 requires integration of a donor template but is generic with regard to RNA and encompasses both sgRNA and dualRNA configurations. *Id*.

Response: Denied

3. The Broad half of Count 1 does not recite a donor template polynucleotide, and only recites cleavage of the DNA molecule "whereby expression of the at least one gene product is altered." Paper 12 at 12. The Broad half of Count 1 recites the sgRNA species. *Id*.

Response: Denied

4. Proposed Count 3, like Count 1, is an "or" type count with the Sigma 204 application, claim 31, retained as one half of the count, but with the Broad half of the count being replaced with allowable claim 52 of Broad Application 16/177,403 ("403 application") (Ex. 2075).

Response: Denied

5. Proposed Count 3 reads as follows:

Proposed Count 3

Broad application 16/177,403, claim 52

or

Sigma Application 15/456,204, claim 31.

Response: Admitted

6. All of Sigma's involved claims are limited to Donor Template Integration. Paper 12 at 2; *see also* Ex. 2124 (132 Sigma Mot. 1) at 4:14-23.

Response: Denied

7. Broad's 418 patent, claim 1, recites a chimeric Cas9 only. Ex. 2060.

Response: Denied

8. Broad's 356 patent, claim 24, recites "whereby the Cas9 protein is a nickase that cleaves only one strand of the DNA molecule, whereby expression of the at least one gene product is altered." Ex. 2016.

Response: Admitted

9. Broad's 551 application, claim 4, recites "wherein the Cas9 protein is a nuclease directing cleavage of both strands of the target sequence in the eukaryotic cell." Ex. 2051.

Response: Admitted

10. Broad's 445 patent, claim 12, recites "wherein the sequence-specific genome editing comprises creation of a double strand break (DSB) which is repaired by a nonhomologous end joining (NHEJ) cell repair mechanism generating indels thereby modifying the polynucleotide sequence." Ex. 2029.

Response: Admitted

11. Broad's earliest proofs involve use of dualRNA CRISPR-Cas9 systems in a eukaryotic cell to induce cleavage and NHEJ repair (sans template). *See* Ex. 2464 (Seeger Decl.)

¶¶ 20, 152-66.

Response: Lack sufficient information to admit or deny

12. Zhang B1, including in Figure 4C, describes testing "Cas9-mediated HDR… with a homology repair template to introduce a pair of restriction sites near the protospacer" by introducing the system, including a donor template for integration, into eukaryotic HEK 293FT cells. Ex. 2201 at 822; *see also* Ex. 2464 (Seeger Decl.) ¶ 20-22.

Response: Denied

13. Zhang B1 describes that "SpCas9 … catalyzed integration of the HR template into EMX1 locus…. [which] we further verified [via] Sanger sequencing." Ex. 2464 (Seeger Decl.) ¶ 20; *see also* Ex. 2001 (Zhang B1) ¶ [00183], Figs. 4C-D.

Response: Denied

14. Figure 4D shows a "restriction fragment length polymorphism gel analysis" of a successful Donor Template Integration experiment, with an HR template used for all three lanes. *Id*.

Response: Denied

15. As reported in Zhang B1 regarding Figure 4D, "PCR amplification of the target region followed by restriction digest with *Hind*III revealed cleavage products corresponding to expected fragment sizes…." *Id*.; *see also* Ex. 2201 at Supplementary Materials and Methods at 2; *id*. at Supplementary Sequence hEMX1-HRTemplate-*Hind*III-*Nhe*I; Ex. 2001 (Zhang B1) ¶ [00183], Figs. 4C-E.

Response: Admitted

16. During prosecution of its involved 204 application and in prosecution of other

related applications, Sigma argued that integration of a donor template via a CRISPR-Cas9 system in a eukaryotic cell is patentably distinct from cleavage and repair of DNA by other means. *See, e.g.*, Ex. 2073 (April 17, 2017 Supp. Response) at 3.

Response: Denied

17. During prosecution of Sigma's parent 911 application, which issued as U.S. Patent 10,731,181, Sigma expressly argued that the prior art—there, ToolGen's Kim P1 application—"fails to disclose, suggest, or contemplate using a Cas9/RNA complex to **integrate** an exogenous sequence at a target site…." Ex. 2073 (April 17, 2017 Supp. Response) at 3 (emphasis in original).

Response: Admitted

18. During prosecution of the 911 application, Sigma argued that Kim demonstrates only generating double-stranded breaks in DNA which it argued are repaired only by "small insertions and deletions (indels) around the target sequence via error-prone non-homologous end-joining (NHEJ)." *Id*. Sigma stated "[t]his is **not the same thing as integration….**" *Id*. (emphasis in original).

Response: Admitted

19. Sigma's claims requiring integration of a donor sequence were indicated as allowable over Jinek P1 and P2 during an Interview. Ex. 2074 (October 13, 2020 Applicant Remarks).

Response: Admitted

20. During that Interview, the Examiner suggested that Sigma add claims that do not require integration of a donor sequence. In response to the Examiner's suggestion, Sigma stated:

> the Applicant has not included CRISPR cleavage-only claims in this Amendment and Response. Upon further consideration of the Examiner's recommendation, including after recent consultation with inventor Fuqiang Chen and expert Paula Cannon, Ph.D., the ***Applicant has concluded that CRISPR cleavage + donor sequence integration claims***, as more specifically recited in the new claims presented herein, ***are patentably distinct from CRISPR cleavage-only claims.***

Id. at 8-9.

Response: Admitted

21. In a petition to the Director, Sigma stated that its claims and those of ToolGen's applications (over which they stood rejected) "do not claim the same invention… and therefore, there is no interfering subject matter between any of these applications." Ex. 2074 (April 9, 2018 Petition) at 7-9.

Response: Admitted

22. In a petition to the Director, Sigma included a comparison of the claims from the applications highlighting that its claims required Donor Template Integration while ToolGen's applications only recited introducing a double-stranded break. *Id*.

Response: Denied

23. In a petition to the Director, Sigma stated that "**the applicants [ToolGen] and Kim are claiming patentably distinct subject matter that are different inventions**" and stated that ToolGen's cleavage-only claims "do not anticipate or render obvious the applicants' pending claims and vice versa." *Id*. at 9 (emphasis in original).

Response: Admitted

24. Sigma filed a Suggestion of an Interference proposing a count that required integration of a donor template. In that Suggestion, Sigma alleged that only CVC's claims that expressly recite Donor Template Integration would correspond to it proposed count—and not

claims directed to more generally "cleaving or editing" or "modulating transcription" of a gene product. Ex. 2074 (October 13, 2020 Suggestion of an Interference).

Response: Denied

25. In that Suggestion, all of CVC's claims that Sigma suggested as corresponding to the Donor Template Integration count expressly recited incorporation of a donor template. *Id*.

Response: Denied

26. In that Suggestion, Sigma reserved the right to supplement its request only "to the extent that any such [CVC] application or patent contains one or more claims directed to methods of integrating a donor polynucleotide sequence into the chromosomal sequence of a eukaryotic cell…." *Id*. at 8.

Response: Denied

27. Sigma moved in the 132 Interference to substitute its Proposed Count 2 limited to Donor Template Integration for Count 1. Ex. 2124 (132 Sigma Mot. 1).

Response: Denied

28. In the 132 Interference, Count 1 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

29. Sigma stated in Motion 1 in the 132 Interference that "this final [donor template] integration step represents a ***milestone accomplishment*** in CRISPR-Cas9 genome engineering—not simply cleaving a DNA strand, but thereafter actually modifying the chromosomal sequence by integrating into that cleaved strand a donor polynucleotide by HDR." *Id*. at 3:1-3. **Response: Admitted**

30. 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

31. 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

32. 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

33. 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

34. In Motion 1 in the 132 Interference, Sigma stated "[t]he single Count 1 in this interference should not encompass two patentably distinct inventions." *Id*. at 1:12-13.

Response: Admitted

35. The PTAB determined that Broad is entitled to the benefit of Zhang B1 with respect to Count 1. Paper 1 at 16.

Response: Denied

36. During prosecution of Sigma's related parent 911 application, Sigma provided a comparison of its alleged working examples and Example 1 in Zhang B1, stating that Zhang B1 disclosed donor integration. Ex. 2073 (November 11, 2016 Remarks) at 15.

Response: Denied

37. The Broad half of Proposed Count 3 requires integration of a donor template, as in the Sigma half of both Count 1 and Proposed Count 3.

Response: Denied

38. During prosecution of Sigma's parent 911 application, Sigma provided a comparison of its alleged working examples and Example 1 in Zhang B1. *Id*.

Response: Admitted

39. Zhang B1 was continuously disclosed or incorporated by reference in its entirety through each chain of the patents and applications with claims that Broad contends correspond to Proposed Count 3.

Response: Denied

40. The 445 patent was issued on October 28, 2014 from application 14/259,420 (filed April 23, 2014), which is a continuation of application 14/105,035 filed on December 12, 2013 (from Zhang B1, filed on December 12, 2012).

Response: Denied

41. The 616 patent was issued on December 9, 2014 from application 14/290,575 (May 29, 2014), which is a continuation of application 14/104,990 filed on December 12, 2013 (from Zhang B1).

Response: Denied

42. The 713 patent issued on December 12, 2017 from application 14/523,799 (filed October 24, 2014), which is a continuation of application PCT/US2013/074611 filed on December 12, 2013 (from Zhang B1).

Response: Denied

43. The 551 application was filed on May 5, 2015 as a continuation of application PCT/US2013/74819 filed on December 12, 2013 (from Zhang B1).

Response: Denied

44. The 16/177,403 application sought to be added to the Interference was filed October 31, 2018 as a continuation of 15/217/489 filed on July 22, 2016, and as a continuation of 14/054,414 application filed October 14, 2013 (from Zhang B1).

Response: Denied

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

Response: Lack sufficient information to admit or deny

46. The 616 patent (Ex. 2014) and the 551 and 403 applications (Ex. 2051 and 2075), as well as their respective intervening applications, all also contain an explicit disclosure of the relevant portions of Zhang B1's E17+.

Response: Denied

47. The 445 and 713 patents incorporated Zhang B1, including embodiment E17+, by reference. *See* Ex. 2029 and 2043.

Response: Denied

48. Each patent and patent application with claim(s) that Broad contends correspond to Proposed Count 3, as well as the intervening applications between Zhang B1 and those patents and patent applications: (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: Denied

49. Zhang B1 (Ex. 2001) describes and enables the subject matter of Proposed Count 3 and has been continuously disclosed or incorporated by reference through each chain of the patents and patent applications relevant to Proposed Count 3.

Response: Denied

50. Broad is entitled to the benefit of the December 12, 2012, filing date of Zhang B1.

Response: Denied

51. None of the art prior to December 12, 2012, alone or in combination, anticipates or renders obvious the subject matter of Proposed Count 3.

Response: Denied

52. Sigma has repeatedly argued during prosecution of its patents that none of the art prior to December 12, 2012, alone or in combination, anticipates or renders obvious Donor Template Integration with a CRISPR-Cas9 system in a eukaryotic cell. *See, e.g.*, Ex. 2073 (April 17, 2017 Supp. Response) at 3.

Response: Denied

53. In Motion 1 in the 132 Interference, Sigma stated that its "Proposed Count 2 is patentable over the prior art." Ex. 2124 (132 Sigma Mot. 1) at 34:12-21.

Response: Admitted

54. 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)"; "a single nickase for a creating a 'nick' or a single stranded break in the target DNA"; and "chimeric Cas9 protein." Ex. 2124 (132 Sigma Mot. 1) at 27:11-28:2; Ex. 2463 (132 Cannon Decl.) ¶ 35.

Response: Admitted

55. Broad's 308 patent, claims 15 and 26 are limited to *Staphylococcus aureus* Cas9.

Response: Admitted

56. Proposed Count 3 does not recite any ortholog of Cas9 protein, including SaCas9.

Response: Admitted

57. There was no motivation for a POSA to use Cas9s other than the widely studied SpCas9 given the uncertainty in the art at the time. Ex. 2464 (Seeger Decl.) ¶¶ 175-96.

Response: Lack sufficient information to admit or deny

58. There was no reason to select SaCas9 from the large set of available Cas9 orthologs known in the art, including the large set of "small" orthologs, as other orthologs were smaller or believed to have higher efficiency.

Response: Lack sufficient information to admit or deny

59. Broad's 418 patent, claims 24 and 26-28 are limited to use of a chimeric Cas9.

Response: Admitted

60. The claims of Broad's 418 patent (Ex. 2060) require the Cas9 not be taken from a single organism but rather be a chimeric Cas9 that includes two fragments from Cas9 from different species.

Response: Denied

61. Nothing in Proposed Count 3 or in the prior art teaches, suggests, or provides motivation to design a chimeric Cas9 comprised of two fragments from different organisms.

Response: Lack sufficient information to admit or deny

62. Claim 13 of the 445 patent is directed to the use of two or more NLSs.

Response: Admitted

63. Proposed Count 3 does not recite the use of an NLS (Broad half) or expressly recites "only one NLS" (Sigma half).

Response: Admitted

64. During prosecution of the 204 application, Sigma submitted expert testimony 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

65. Both halves of Proposed Count 3 require introduction of a double-stranded break in the target DNA molecule.

Response: Admitted

66. Broad's 356 patent, claims 2 and 14, and 814 patent, claims 2 and 14, are limited to use of a nickase causing only a single-stranded break.

Response: Admitted

67. A nickase requires modification of the Cas9 molecule to inactivate one of the two nuclease domains.

Response: Admitted

68. During prosecution of the 204 application, Sigma submitted expert testimony that cleavage of a single-strand was distinct from and did not anticipate claims to double-stranded cleavage. *See* Ex. 2074 (April 29, 2019 Applicant Remarks) at 20-21.

Response: Denied

SIGMA STATEMENT OF MATERIAL FACTS AND BROAD RESPONSE

69. The Board authorized the filing of Broad Motion 1 only to the extent that the Broad claim sought to replace Broad's half of current Count 1 had been determined to be allowable by the Examiner in the prosecution of the '403 application. Order Authorizing Motions at 4-5 (Paper 27) (Sept. 20, 2021).

Response: Denied; the PTAB authorized Broad Motion 1 to the extent "the Broad portion of the count reflects a patented or allowable claim" (Paper 27 at 4).

70. Upon filing of Broad Motion 1 on December 3, 2021, the Examiner had not stated that any of Claims 52-54 of the '403 application had been determined to be allowable. Ex. 1520.

Response: Denied.

71. On October 5, 2021, before the filing of Broad Motion 1 on December 3, 2021, the Examiner suspended prosecution of the '403 application for six months. Ex. 1520; Ex. 2075.

Response: Admitted.

72. Broad's alleged "best" proofs do not include a donor template. Ex. 1518 ¶ 33.

Response: Denied as lacking necessary context including as to identity of Count.

73. Broad's alleged "template" proofs are limited to single guide RNA. *Id.*

Response: Denied.

74. Claim 52 is not limited to a standard CRISPR-Cas system. *Id.* ¶¶ 21-23.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

75. Claim 52 encompasses NHEJ-mediated end ligation. *Id.* ¶ 30.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as claim 52 does not specify the repair mechanism.

76. Claim 52 encompasses a system with no tracrRNA/activator RNA that interacts with the Cas9 protein. *Id*. ¶¶ 24-26.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

77. Claim 52 encompasses a crisprRNA/targeter RNA that performs all of the guiding function of the guide RNA. *Id*. ¶¶ 27-28.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

78. Claim 52 does not require that the guide RNA hybridize to, or bind with, the target sequence. *Id*. ¶ 29.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

79. Claim 52 encompasses a split-Cas9 system. *Id*. ¶¶ 31-32.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

80. Claim 52 encompasses a wild-type Cas9 protein. *Id*. ¶ 34.

Response: Denied as a legal conclusion not supported by the cited material, and further denied as vague and ambiguous.

81. The statement "wherein the gene product is luciferase" is not set forth in any of Broad's pre-AIA applications to which the '403 application claims priority benefit. *Id*. ¶ 35.

Response: Admitted that the exact words "wherein the gene product is luciferase" are not set forth in the chain of applications through which the 403 application claims benefit to Zhang B1; otherwise denied.

BROAD ADDITIONAL MATERIAL FACTS

82. On March 7, 2022 the Examiner entered an office action expressly confirming claims 52-54 of the 403 application are allowable. Ex. 1521 (March 7, 2022 Misc. Action) at 2 ("All claims are allowable.").

83. Sigma filed its Opposition 2 on March 16, 2022. *See* Opp. 2.

CERTIFICATE OF FILING AND SERVICE

I hereby certify that on April 26, 2022, a true and complete copy of the foregoing **BROAD OPPOSITION 1** 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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