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Filed on behalf of Senior Party
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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; 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)

SIGMA OPPOSITION TO BROAD MOTION 1
(to Substitute Proposed Count 3 for Count 1)

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OPPOSITION TO BROAD MOTION 1
(to Substitute Proposed Count 3 for Count 1)

I. INTRODUCTION

Broad fails to carry its burden on Motion 1 for multiple reasons. First, when Broad filed Motion 1, Claim 52 had not been determined to be allowable by the Examiner, despite Broad's assertions to the contrary. Further, Broad drafted Claim 52 to include both a donor template and a generic guide RNA, but Broad acknowledges that Claim 52 does not conform to any of Broad's proofs of invention. And with respect to current Count 1, Broad never even asserts, let alone demonstrates, that "cleavage plus altering gene expression" is patentably distinct from "cleavage plus integration by HDR".[1] As detailed herein, Broad's Claim 52 is exceedingly broad for at least eight reasons, and fails to conform to either parties' CRISPR-Cas9-related inventions. Further, Broad fails to address the consequences of Claim 52 being subject to AIA, despite being on notice of that very issue. And Broad fails to explain how Claim 52 is patentable over Sigma P1. For at least these reasons, the Board may exercise its discretion to deny Broad Motion 1.

II. PRECISE RELIEF REQUESTED

Sigma respectfully requests that the Board deny Broad Motion 1 to substitute Proposed Count 3 for current Count 1.

III. LEGAL STANDARDS

As the moving party, Broad must demonstrate, in its motion, "a genuine need to ***change the count***, and not simply cause a change for change's sake." *Louis v. Okada*, 2011 Pat. App. LEXIS 24048, at *10 (BPAI May 25, 2011) (emphasis in original); *see* Ex. 1528, *CVC v. Broad*,

[1] Of Broad's 461 involved patent claims, 340 claims are directed to "cleavage plus altering gene expression" (or an analogous recital), 42 claims are directed to insertion of a "template", and 8 dependent claims are directed to "cleavage plus integration by HDR". *See* Ex. 1518 at Appx. C.

Int'f No. 106,115, Decision on Motions (Paper 877) at 33 (Sept. 10, 2020) ("We will make such a change only if there is a compelling reason to do so."). As the Board has further explained:

> [A] preliminary motion to broaden out the count on the basis that a party's best or earliest proofs are outside of the current count (1) should make a proffer of the party's best proofs, (2) show that such best proofs indeed lie outside of the scope of the current count, and (3) further show that the proposed new count is not excessively broad with respect to what the party needs for its best proofs.

Louis, 2011 Pat. App. LEXIS 24048, at *11-12.

IV. UPON FILING OF MOTION 1, BROAD CLAIM 52 HAD NOT BEEN DETERMINED TO BE ALLOWABLE BY THE EXAMINER, AND PROSECUTION OF BROAD'S '403 APPLICATION HAD BEEN (AND REMAINS) SUSPENDED

Broad seeks to substitute Claim 52 of the '403 application for Broad's half of the current two-part "McKelvey" Count 1. On September 20, 2022, the Board authorized the filing of Motion 1 only to the extent that the Broad claim sought to be substituted had been determined to be allowable by the Examiner:

> Broad's proposed Count 3 also includes Sigma application 15/456,204 claim 31, as in Count 1, but replaces Broad patent 8,697,359, claim 15 with Broad application 16/177,403 claim 52, which has not yet been determined to be allowable. (*See* Broad List, Paper 21, 5:7–6:12.)
>
> Authorization for this motion is GRANTED to the extent that Broad may present arguments to substitute current Count 1 with proposed Count 3 wherein the Broad portion of the count reflects a patented or allowable claim. The motion shall be entitled "BROAD MOTION 1."

Order Authorizing Motions (Paper 27) at 4-5 (Sept. 20, 2021) (highlighting added).

Contrary to the Board's express authorization, however, Broad filed this motion while Claim 52 remained pending and had ***not*** been determined to be allowable by the Examiner. Moreover, the '403 application had been suspended in view of this interference, and remains suspended today. Inexplicably, 9 days before Time Period 3 in this interference (after, and while the '403 application remained suspended,) the Examiner indicated that Claim 52 is allowable.

But that after-the-fact (and procedurally improper) event does not justify Broad's filing of its Motion 1 seeking to substitute the Count with Claim 52 that had not been allowed. Accordingly, for this reason alone, the Board should exercise its discretion to deny this motion.

A. BROAD STRATEGICALLY CHOSE TO AMEND CLAIM 52 AFTER THE '403 APPLICATION HAD BEEN SUSPENDED, AND CLAIM 52 HAD NOT BEEN DETERMINED TO BE ALLOWABLE BY TIME PERIOD 1

In its Motion 1, Broad contends that in Proposed Count 3, "the Broad half of the count [is] replaced with ***allowable*** claim 52 of Broad Application 16/177,403 ('403 application')." Mot. 1 at 6 (emphasis added). But Broad's assertion of allowability in its Motion 1 is belied by a review of the prosecution of Claim 52, which reveals that when Broad filed Motion 1 on December 3, 2021, Claim 52 had ***not*** been determined to be allowable and the prosecution of the '403 application had been suspended:

Date	Filer	Document	Content
2021-08-04	Broad	Amendment - Claims	Broad presents new Claim 52 in an Amendment
2021-08-09 (filed: 2021-08-11)	Examiner	PTOL-413 (Examiner Interview Summary Record)	"The Reply filed August 4, 2021 will be reviewed in due course, and an Office Action issued at that time."
2021-09-03	Broad	Statement of Substance of Interview	"The official interview summary dated August 11, 2021, accurately reflects the substance of that discussion."
2021-09-20	**PTAB**	**Order Authorizing Motions**	"to the extent that . . . the Broad portion of the count reflects a patented or allowable claim."
2021-10-05	Examiner	Code CTMS (Miscellaneous Action with SSP)	"All claims are allowable. However, due to a potential interference, ex parte prosecution is SUSPENDED FOR A PERIOD OF 6 MONTHS from the date of this letter."
2021-10-07 (filed: 2021-10-18)	Examiner	PTOL-413 (Examiner Interview Summary Record)	"Discussed proposed amendments to claims for the purpose of potentially moving application into pending interference. Applicants were informed that a Supplemental Amendment could be filed, which would be entered and considered. The application will remain suspended with no extension to the suspension period. No agreement was reached at this time."

2021-10-15	Broad	Supplemental Amendment - Claims	**"AMENDMENTS TO THE CLAIMS** *This listing of claims will replace all prior versions and listings of claims in the application:* * * * 52. (Currently Amended) . . . ."
2021-10-15	Broad	Supplemental Amendment - Remarks	"Applicants hereby submit claim amendments consistent with the October 7, 2021 interview. Specifically, claim 52 is amended to more clearly and particularly describe the claimed invention, with support in previous claim 55."
2021-10-18	**Broad**	**Updated Notice of Related Proceedings**	"16/177,403 . . . Allowed October 5, 2021–Prosecution Suspended"
2021-11-15	Examiner	Code M327 (Miscellaneous Communication to Applicant – No Action Count)	"Applicant's Supplemental Response to the February 5, 2021 Office Action has been considered. The application remains suspended, with the period of suspension ending on April 5, 2022 (six months from the suspension letter of October 5, 2021)."
2021-12-03	**Broad**	**Motion 1 (to Change the Count)**	"the Broad half of the count being replaced with allowable claim 52 of Broad Application 16/177,403 . . . ."

Ex. 1520 at 1-24 (highlighting added).

As set forth in the chronology above, the Board authorized Broad Motion 1 "to the extent that . . . the Broad portion of the count reflects a patented or allowable claim." Order Authorizing Motions (Paper 27) at 5 (Sept. 20, 2021). Thereafter, in a "Miscellaneous Action with SSP" the Examiner indicated that an ***earlier version*** of Claim 52 was allowable. Ex. 1520 at 10 ("All claims are allowable.") (Oct. 5, 2021). At that same time, the Examiner also suspended prosecution of the '403 application until April 5, 2022. *Id.* Two days later, however, Broad interviewed the Examiner to discuss amending Claim 52 "for the purpose of potentially moving application into pending interference." *Id.* at 8 (Oct. 7, 2021). During the interview, the Examiner informed Broad that a "Supplemental Amendment could be filed, which would be entered and considered." *Id.* at 8. But the Examiner expressly cautioned Broad that "***The application will remain suspended*** with no extension to the suspension period. ***No agreement was reached at this time***." *Id.* (emphases added). Despite the Examiner's warning, and for

unknown strategic reasons, Broad nonetheless chose to substantively amend Claim 52 on October 15, 2021. *Id.* at 4. With the claim amendments pending, Broad then filed a Notice of Related Proceedings stating that the claims of the '403 application had been "allowed". (Paper 29) at 1. A month later, in a "Miscellaneous Communication to Applicant – No Action Count", the Examiner indicated that Broad's amendment to Claim 52 "has been considered. The application remains suspended." Ex. 1520 at 2. Importantly, as discussed further below, the Examiner's communication nowhere indicated that Claim 52 had been determined to be allowable, unlike the Examiner's previous "Miscellaneous Action with SSP", which expressly so stated. *Compare id.* at 2 with *id.* at 10. Accordingly, when Broad filed its Motion 1, the current version of Claim 52—the only claim at issue on this motion—had ***not*** been determined to be allowable, and prosecution of the '403 application had been (and remains) suspended.

B. The Examiner's November 15, 2021 "Miscellaneous Communication to Applicant – No Action Count" Nowhere Indicated Allowability Of Claim 52

Broad strategically elected to amend Claim 52 ***after*** the Examiner had suspended prosecution of the '403 application, and ***after*** the Examiner had informed Broad that prosecution of the '403 application had been suspended:

> [A] Supplemental Amendment could be filed, which would be entered and considered. The application will remain suspended with no extension to the suspension period. No agreement was reached at this time.

Ex. 1520 at 8 (highlighting added). Despite the Examiner's indication of allowable claims and suspension of prosecution on October 5, 2021, Broad nonetheless chose to substantively amend Claim 52 thereafter on October 15, 2021, as shown below:

> target sequence of the DNA molecule, whereby the Cas9 cleaves both strands of the DNA molecule and ~~the template polynucleotide repairs~~ the cleavage is repaired by integration of the template polynucleotide into the DNA molecule ~~by homology directed repair~~ in the eukaryotic cell.

Id. at 4. These substantive amendments would require further evaluation by the Examiner, who

(not surprisingly) chose ***not*** to conduct any necessary further examination at that time while the prosecution of the '403 application remained suspended. In particular, as reflected in Broad's amendment above, amended Claim 52 makes at least four substantive changes: (1) introduces the new limitation of cleaving "both strands" of the DNA; (2) converts the active language limitation that "the template polynucleotide repairs" the cleavage, to the passive language limitation that the cleavage "is repaired by integration of the polynucleotide into the DNA molecule"; (3) introduces the term "integration" into the claim for the first time; and (4) removes the limitation that the cleavage repair is "by homology directed repair". *Id.* Thus, because of these substantive claim amendments, the Examiner did ***not*** indicate that the claims were allowable, as she had done with respect to a previous version of Claim 52 on October 5, 2021. *Id.* at 10 ("All claims are allowable."). Indeed, these substantive amendments would require further consideration by the Examiner in the future. *See infra* Part VI.A-H.

C. The Examiner's Coding Of The "Miscellaneous Communication To Applicant – No Action Count" Confirms That The Examiner Had Taken No Action Regarding Claim 52 On The Merits

In its Motion 1, Broad misleadingly contends that Claim 52 had been determined to be allowable. Broad Mot. 1 at 6. But Broad's motion fails to explain the details of the above prosecution chronology, which demonstrates that when Broad filed Motion 1, ***the Examiner had actually made no such allowability determination*** with respect to amended Claim 52.

In addition to the discussion above, the USPTO's document codes confirm that the Code M327 "Miscellaneous Communication To Applicant – ***No Action*** Count" (dated Nov. 15, 2021) (emphasis added) is ***not*** an Office Action containing a substantive determination of claim patentability. In contrast, the Code CTMS "Miscellaneous ***Action*** with Shortened Statutory Period" (dated Oct. 5, 2021) (emphasis added) ***is*** an Office Action containing a substantive determination of claim patentability:

16/177,403 CRISPR-CAS SYSTEMS FOR ALTERING EXPRESSION OF GENE PRODUCTS 114203-1088

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This application is officially maintained in electronic form. To View: Click the desired Document Description. To Download and Print: Check the desired document(s) and click Start Download.

Available Documents

Mail Room Date	Document Code	Document Description	Document Category	Page Count	PDF
		* * *			
11-15-2021	M327	Miscellaneous Communication to Applicant - No Action Count	PROSECUTION	2	
		* * *			
10-05-2021	CTMS	Miscellaneous Action with shortened statutory period (SSP)	PROSECUTION	2	

Public PAIR for Application "16/177,403" (highlighting added).

IFW Doc Code	IFW Document Description
	* * *
M327	Miscellaneous Communication to Applicant - No Action Count
	* * *
CTMS	Miscellaneous Action with SSP

https://www.uspto.gov/patents/apply/checking-application-status/e-office-action-program ("Top 40 e-Office Action Document Codes") (highlighting added).

Further, the Examiner's statement that the multiple amendments to Claim 52 "ha[ve] been considered" does not indicate that the claim has been "determined to be allowable." The Examiner reasonably chose not to make any substantive patentability determinations at that time while the prosecution of the '403 application remained suspended in view of this interference. Ex. 1520 at 2 ("The application remains suspended."). Indeed, in normal English usage, the term "considered" does not mean "determined" on the merits. *E.g.*, https://www.merriam-webster.com/dictionary/ (*compare* "consider" – "[1]: to think about carefully: such as [a]: to think of especially with regard to taking some action" *with* "determine" – "[1]: [a]: to fix conclusively or authoritatively"). Not surprisingly, the USPTO routinely uses the term "consider" in its ordinary and customary manner:

REQUEST FOR RECONSIDERATION/OTHER

12. ☑ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

Ex Parte Bhagat, Appeal No. 2019-005232, Decision on Appeal at 6 n.5 & Attachment at 2) (PTAB Feb. 2, 2020) (highlighting and underlining added) (Ex. 1546).

> The Answer explains that "the after-final amendment received 28 December 2016 was ***considered*** in the Advisory action mailed 22 March 2017 with the amendment ***not entered***."

Ex Parte Max Out Golf LLC, Appeal No. 2020-001679, Decision on Appeal at 4 (PTAB Apr. 30, 2020) (emphases added) (Ex. 1547).

> The March 27, 2006, 37 CFR 1.312 amendment has been ***considered*** but is ***disapproved*** for the following reason.
>
> * * *
>
> 1. ☒ The amendment filed on *27 March 2006* under 37 CFR 1.312 has been considered, and has been:
>
> a) ☐ entered.
>
> b) ☐ entered as directed to matters of form not affecting the scope of the invention.
>
> c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
> Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
>
> d) ☒ disapproved. See explanation below.

In re Waschura, Application No. 09/996,342, Decision at 3 & Attachment at 1 (Comm'r Patents Jan. 4, 2008) (emphases, highlighting, and underlining added) (Ex. 1548).

D. The Examiner's Recent And Inexplicable Action—During The '403 Application's Suspension—Confirms That Claim 52 Had Not Been Allowed By Time Period 1, And Does Not Validate *Ex Post Facto* Broad's Decision To Contravene The Board's Order Authorizing Motions

On the eve of Time Period 3 (and after the cross-examination of the parties' respective expert witnesses, including Broad's expert witness, Dr. Christoph Seeger), Sigma was surprised to discover that despite the '403 application being formally suspended, the Examiner nonetheless issued *ex parte* a Code CTMS "Miscellaneous Action with Shortened Statutory Period" (dated March 7, 2021). Ex. 1521. The Examiner's action appears contrary to the USPTO's normal procedures. *See* MPEP § 709 II ("***When the suspension period has expired***, the examiner should take up action on the application or evaluate all possibilities for giving an action on the merits.") (emphasis added); *see also* MPEP § 709 I (D) ("[A]ction on the application will be

suspended until the suspension period has expired . . . ."). The Examiner nowhere indicated that the suspension (which was set to expire on April 5, 2022) had been lifted prematurely, and in fact the Examiner indicated that the '403 application remains suspended. Ex. 1521.

After Time Period 1 (December 3, 2021), when Broad formally filed Motion 1 requesting that the '403 application become involved in the pending interference, the Examiner's subsequent *ex parte* involvement in that application to change the fundamental operative facts for a contested Motion pending before the Board, particularly during suspended prosecution, is inconsistent with at least the spirit of the USPTO's rules. *See* MPEP § 2307.03 ("[T]he examiner may not act in a patent or an application directly involved in an interference as set forth in 37 CFR 41.103"). And the Examiner was aware that Broad was seeking to involve Claim 52 "for the purpose of potentially moving application into pending interference." Ex. 1520 at 8. Thus, countenancing such *ex parte* maneuvering to alter key facts that are in an active *inter partes* dispute—during the middle of ongoing interference briefing and cross-examinations—would undermine the Board's sole jurisdiction over the disputed subject matter, and would encourage future parties to similarly leverage ongoing *ex parte* prosecution to gain a possible strategic advantage in a co-pending interference. Such maneuvering seriously prejudiced Sigma, who had developed its opposition strategy, conducted its cross-examination, and prepared this opposition (sans this Part IV.D, of course) before being surprised by the Examiner's action from out of the blue while the '403 application remained suspended.

Further, the Examiner's recent issuance of a Code CTMS "Miscellaneous Action with Shortened Statutory Period" (dated March 7, 2022) confirms that the previous Code M327 "Miscellaneous Communication To Applicant – No Action Count" (dated Nov. 15, 2021) was ***not*** an indication that the claims were allowable. Thus, Broad's arguments to the contrary in its Motion 1 (***and*** Motion 2 ***and*** Notice of Related Proceedings) are even more demonstrably

incorrect. And while Broad will undoubtedly argue that the Examiner's recent March 7, 2022 *ex parte* action favoring Broad moots this entire "allowability" issue and absolves Broad of its misstatements in its Motions, as discussed above, such is not the case. Indeed, there is now no question that Claim 52 had ***not*** been deemed allowable by the Examiner when Broad filed Motion 1. And the Examiner's later *ex parte* action on Broad's behalf—whether *sua sponte* or prompted by Broad[2]—does not validate *ex post facto* Broad's decision to contravene the Board's Order Authorizing Motions based on the facts existing at Time Period 1. *See, e.g., Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods., Ltd.*, 559 F.3d 1317, 1338 (Fed. Cir. 2009) ("The '039 Continuation ***examiner's later view***, however, does not change the fact that the Third Office Action contained valuable reasoning and rejections at the time when it was made.") (emphasis in original; footnote omitted). When Broad filed Motion 1 on December 3, 2021, the issue of the allowability of Claim 52 of the '403 application was "fairly placed in issue" at that time:

> During the interference, Appellants filed a motion pursuant to 37 C.F.R. § 1.634 to correct the inventorship of their application, i.e., to remove Sherman as a co-inventor. ***The very filing of this motion fairly placed the issue of the inventorship of Appellants' application in the interference***.
>
> * * *
>
> Appellants raised the issue of proper inventorship, and Appellants had all of the facts necessary to present the issue. Therefore, because Appellants' patentability question of inventorship was fairly raised, could have been and still can be fully presented during the interference, ***it must be resolved inter partes***.

Schulze v. Green, 136 F.3d 786, 790 (Fed. Cir. 1998) (emphases added). Thus, the Board should

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[2] As of the filing date of Opp'n 1, no interview summary appears in the '403 application on PAIR. However, perhaps tellingly, in the "Miscellaneous Action with Shortened Statutory Period", the Examiner (apparently intentionally) replaced the MPEP standard form paragraph from "*ex parte* prosecution is SUSPENDED . . ." to "*ex parte* ***communication*** is SUSPENDED . . ." MPEP § 709 (II) ¶ 7.53 (emphasis added); *compare* Ex. 1520 at 10 *with* Ex. 1521 at 2.

resolve Motion 1 based on Broad's burden of proof at the time Broad filed this motion, not based on any later-developed facts through the Examiner's inexplicable and *ex parte* involvement in the '403 application thereafter, during the application's formal suspension.

Accordingly, because Claim 52 has not been determined to be allowable when Broad filed Motion 1, the Board may exercise its discretion to deny Broad Motion 1 on this basis alone.

V. BROAD FAILS TO CARRY ITS BURDEN ON THIS MOTION TO PROVIDE ANY COGNIZABLE BASIS TO CHANGE CURRENT COUNT 1

On this motion, Broad fails to carry its burden to demonstrate any legally cognizable reason to change current Count 1. In particular, Broad does ***not*** contend that its Proposed Count 3 is needed to conform to Broad's best proofs of invention. Indeed, Broad effectively concedes that its best proofs (which do not include a donor template) fall outside the scope of Proposed Count 3 (which specifically recites "a template polynucleotide").

Further, Broad does ***not*** contend that current Count 1 encompasses two distinct patentable inventions. More particularly, while Broad contends (incorrectly) that ***Sigma*** has argued that claims directed to ***cleavage plus integration via HDR*** in a eukaryotic cell are patentably distinct from so-called "Non-Template Claims" (a new term coined by Broad for the first time in its Motion 1), Sigma has made no such argument. Sigma 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***. But Sigma has ***not*** argued that the invention of ***cleavage plus integration via HDR*** in a eukaryotic cell is patentably distinct from the invention of ***cleavage plus altering gene product expression***, as set forth in current Count 1.

In addition, nowhere in its Motion 1 does ***Broad itself***—as the movant—contend that current Count 1 is directed to two patentably distinct inventions, as Broad's burden on this motion requires. Rather, Broad remains purposely silent on that issue, relying solely on Broad's

own completely fabricated supposed "argument" by Sigma. Silence on this fundamental issue cannot satisfy Broad's burden on this motion. And nowhere does Broad even contend—let alone present evidence—that Sigma's claims to ***cleavage plus integration via HDR*** in a eukaryotic cell are patentably distinct from Broad's claims to ***cleavage plus altering gene product expression***.

Finally, Broad demonstrates no basis to adopt Proposed Count 3 because Broad nowhere demonstrates that Proposed Count 3 conforms with ***any*** of Broad's proofs of invention. In particular, Broad argues that Proposed Count 3 is directed to a generic guide RNA (*i.e.*, encompassing both sgRNA and dgRNA), but Broad acknowledges that its "template" proofs directed to Proposed Count 3 are limited to sgRNA ("chimeric") guide RNA alone. Thus, Broad fails to show that Proposed Count 3 has been crafted in conformance with ***any*** of Broad's proofs.

Broad provides no other purported basis to support its request to change the count. Accordingly, Broad fails to carry its burden on this motion.

A. Broad Readily Acknowledges That Its Alleged Best Proofs Of Invention Do *Not* Include A Donor Template, Even Though Proposed Count 3 Expressly *Requires* A Donor Template

Broad's Proposed Count 3 expressly requires a "template polynucleotide", otherwise referred to as a "donor template" or simply a "template". Broad Mot. 1 at 7 ("a template polynucleotide . . . whereby . . . the cleavage is repaired by integration of the template polynucleotide into the DNA molecule in the eukaryotic cell"). But Broad readily acknowledges that its best proofs of invention do ***not*** include a donor template:

> Broad's ***best proofs*** . . . involve CRISPR-Cas9 systems that ***do not include a donor polynucleotide template*** . . . .

Broad Mot. 1 at 4 (emphases added).

> Broad's ***earliest proofs*** involve Dr. Feng Zhang's use of dualRNA CRISPR-Cas9 systems in a eukaryotic cell to induce cleavage and NHEJ repair (***sans template***).

Id. at 10 (emphases added).

> Broad's ***best and earliest proofs***—like many of its designated claims—are dualRNA and ***not directed to Donor Template Integration***.

Id. at 18 (emphases added). Broad's expert agrees that "none of [Broads' best and earliest proofs] used a donor template[.]" Ex. 2467 at 168:6-11; *see* Ex. 2464 (Seeger Decl.) ¶¶ 151-166.

Accordingly, as Broad effectively concedes, Proposed Count 3 does not conform to Broad's purported best proofs of invention. And on this motion, where Broad bears the burden of showing a need to change the current count, Broad is intentionally equivocal in that regard:

> The Broad claim and the Sigma claim that make up Count 1 both contain limitations that ***may*** unnecessarily limit Broad's proofs on priority.

Id. (emphasis added); *see id.* at 4 ("[I]f this Interference goes forward with Count 1 as written, Broad's best proofs ***could*** be excluded . . . .") (emphasis added). The Board has found that such equivocation fails to carry the movant's burden to change the count:

> While Sauer's preliminary motion 2 does state that the fastening means is arguably not shown in the earliest proofs, the equivocal nature of the term "arguably" and the conclusory nature of the statement, without analysis, lead us to conclude that Sauer's preliminary motion failed to demonstrate a genuine need for the count to be changed or that its preliminary motion gave Kanzaki a fair opportunity to address the need for a change.

Louis, 2011 Pat. App. LEXIS 24048, at *11-12. Broad thus fails to bear its burden on this motion to demonstrate that Proposed Count 3 should be substituted for current Count 1 to conform to Broad's proofs of invention.

B. Broad's Coining Of The New Term "Non-Template Claims", In An Attempt To Fabricate A Non-Existent Argument By Sigma, Cannot Withstand Scrutiny

In Broad Motion 1, Broad coins a new term for the first time: "Non-Template Claims":

> Sigma thus has expressly argued time and time again that Donor Template Integration was a separately patentable invention and distinct from claims that do not recite Donor Template Integration, but instead recite ***no cleavage, cleavage only, altering gene expression, or other forms of cleavage and repair*** (***hereinafter referred to as "Non-Template" claims***).

Broad Mot. 1 at 2 (emphases added). As block-quoted above, Broad unilaterally defines so-

called "Non-Template Claims" as claims reciting (1) "no cleavage", (2) "cleavage only", (3) "altering gene expression", and (4) "other forms of cleavage and repair". *Id.* Based on this unilateral, Broad-crafted (and false) premise, Broad then proceeds to argue *ad nauseum* that ***Sigma*** has advocated for this new definition. Broad Mot. 1 at 1-5, 11-19. But Broad's analysis is correct ***only*** with respect to claims reciting (2) "cleavage only". Broad's argument, and its newly minted definition of "Non-Template Claims" is otherwise demonstrably false.

Sigma has nowhere disputed that Sigma's "***cleavage plus integration by HDR***" claims are patentably distinct from Broad's "***cleavage plus altered gene expression***" claims. In particular, with respect to Count 1, Broad's half of the two-part "McKelvey" count (Claim 15 of Patent 8,697,359) recites, in pertinent part, "wherein the DNA molecule encodes and the eukaryotic cell expresses at least one gene product and the Cas9 protein ***cleaves the DNA molecules***, whereby ***expression of the at least one gene product is altered*** . . . ." Declaration (Paper 1) at 12 (June 12, 2021). Reciprocally, Sigma's half of the two-part "McKelvey" count (Claim 31 of Application 15/456,204) recites, in pertinent part, "wherein . . . the CRISPR-Cas type II protein ***introduces a double-stranded break*** at the target site, and ***repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence*** into the chromosomal sequence." *Id.* at 12-13. For ease of discussion, Sigma has routinely abbreviated Broad's limitations as "cleavage plus altered gene product expression" (or simply "cleavage plus altered gene expression"), and Sigma's limitations as "cleavage plus integration by HDR" (or simply "cleavage plus integration"). Importantly, neither of these claim limitations are directed to ***cleavage only***. While the parties' respective claim limitations are not the same, they are both directed to cleavage ***plus*** a further demonstrable genomic engineering result, as recited in the parties' express claim language. Indeed, Sigma has not disputed that these limitations, in the context of the parties' claims, represent patentably

indistinct inventions. Indeed, a review of Broad's claims suggests the relatedness of these claimed concepts. *See, e.g.*, Ex. 1518, Appx. C at 39-42 (Cls. 2, 4 & 15-16), 48-49 (Cls. 2-3).

After crafting its own self-serving definition, Broad then devotes much of its brief to arguing (incorrectly) that Sigma's positions in the parallel *CVC v. Sigma* interference (No. 106,132) and elsewhere support Broad's false premise.[3] Broad Mot. 1 at 1-5, 11-19. But none of Broad's citations support Broad's arguments. In particular, in Sigma's interference filings in *CVC v. Sigma* interference (and in Sigma's 202 Statement filed to provoke that interference), Sigma has consistently—and only—distinguished Sigma's ***cleavage plus integration*** claims with CVC's ***cleavage only*** claims. *See id.* at 1, 12, 14, 17 (quotes from Sigma).

Moreover, Broad alters the quotes of Sigma's arguments in that parallel interference in a misleading attempt to redraft CVC's claim limitation into two separate components:

> such as "cleaving or editing" or "modulating transcription."

Broad Mot. 1 at 15. But as Sigma made clear in that parallel case, CVC's claim permits proofs of invention directed to ***cleavage alone***:

---

[3] In the *CVC v. Sigma* interference (No. 106,132), Sigma has explained its use of the shorthand phrase "cleavage plus integration":

> Sigma's claim of the count (Sigma Application 15/456,204, claim 31) is directed solely to cleavage plus integration (namely, "the CRISPR-Cas type II protein introduces a double-stranded break at the target site, and repair of the double-stranded break by a DNA homology directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.").

Ex. 1536 (Sigma List of Proposed Motions) at 3 (Aug. 10, 2021) (emphases omitted).

> CRISPR-Cas9 in a eukaryotic cell to cleave a target DNA *and subsequently to integrate a donor DNA sequence into the target DNA via homology-directed repair ("HDR")* (hereinafter often shorthanded as . . . "cleavage plus integration").

Ex. 1538 (Sigma Mot. 1) at 1 (Nov. 19, 2021) (emphasis in original).

> Here, CVC's claim of the current 2-part "McKelvey count" (CVC Application 15/981,807, claim 156) encompasses CVC's purported invention of *cleavage alone* (namely, "whereby said system is capable of *cleaving* **or** editing the target DNA molecule **or** modulating transcription of at least one gene encoded by the target DNA molecule") (emphases added).
>
> * * *
>
> Here, current Count 1 permits CVC to submit proofs of invention for cleavage alone, which do *not* constitute proofs of invention for the separately patentable cleavage plus integration invention.

Ex. 1538 (Sigma Mot. 1) at 2-3. Indeed, other than reciting the entirety of CVC's claim 156 (*id.* at 5-6), the above passage is Sigma's ***only*** mention of modulating transcription in that motion.

Further, Sigma has not disputed that Broad's claims to "cleavage plus altered gene product expression" and Sigma's claims to "cleavage plus integration by HDR" are properly included in Count 1. Sigma did not seek authorization to file any motion to change the count, as Sigma did in the *CVC v. Sigma* interference (No. 106,132). Moreover, in ***this*** interference, Sigma made its position in that regard clear in its List of Proposed Motions, filed on August 10, 2021, nearly four (4) months before Broad filed its Motion 1:

> [T]he scope of Count 1 [is], namely, a method of using CRISPR-Cas9 in a eukaryotic cell ***to successfully cleave a target DNA and thereafter to successfully either integrate a donor DNA sequence into that cleaved target DNA, or alter the expression of the gene product of that cleaved target DNA***.

Sigma List of Proposed Motions (Paper 22) at 5 (Aug. 10, 2021) (emphases added).

> Both parts of Count 1 require ***cleavage of a target DNA molecule and thereafter either integration of a donor sequence into the target DNA molecule, or alteration of the expression of the target DNA molecule's gene product*** . . . .

Id. (emphases added).

> All of the claims in the [Broad] '876 application are directed solely to, *inter alia*, a composition of CRISPR-Cas9 in a eukaryotic cell ***to simply cleave a target DNA molecule***. ***None of the claims in the '876 application recite further that the composition subsequently integrates a donor DNA sequence into the target DNA molecule, nor do they recite further that the composition alters the expression of the gene product of the cleaved target DNA molecule***.

Id. at 6 (emphases added).

And shortly thereafter in the *CVC v. Sigma* interference, Sigma publicly explained its position in this regard to the Board:

> I think the fundamental question -- the fundamental point that CVC is making is incorrect. If you look at the Broad count, there's no inconsistency with this request and any of the other interferences that are involved. Those interferences all involve -- the three active interferences involve a basic issue of cleavage in eukaryotic cells. The first interference was prokaryotic versus eukaryotic. The second set of interferences is who came up with eukaryotic first -- cleavage in eukaryotic cells. ***This set of interferences is actually another, another step beyond cleavage. Both the claims of the parties in this case involve integration, or in Broad, you notice the claims don't stop at cleavage. They have a further step, and that's called alteration of gene expression. So they aren't simple cleavage cases. All the Broad cases are cleavage plus.***
>
> And again, the question is, well, if Broad didn't claim integration specifically in its broadest claims, but they did claim something in addition to cleavage. They claim alteration of gene expression, which is something that we have to evaluate whether or not that's obvious in view of integration. ***We've concluded it would be a difficult motion to argue, that integration is patentability distinct from alteration of gene compression [sic – expression] and vice versa. It's a two-way task [sic – test].***
>
> ***So we haven't made that argument for the Broad cases because we don't think that we would be successful, or at least it would be a difficult motion to argue patentable distinctiveness between cleavage plus integration versus cleavage plus, plus alteration of gene expression.*** And that's in our Broad motions. We explained that -- or at least we explained that Broad's count is cleavage plus.

Ex. 1537 (Tr. Hearing on Authorizing Motions ('132 Int'f)) at 23:18 – 25:11 (emphases added).

Accordingly, the record belies Broad's argument that Sigma has argued that its "***cleavage plus integration by HDR***" claims are patentably distinct from Broad's "***cleavage plus altered gene expression***" claims. Indeed, as the above citations reveal, the opposite is true.

C. Broad Nowhere Even Advocates For Its Own Newly Devised Theory That "Cleavage Plus Integration" Claims Are Patentably Distinct From So-Called "Non-Template Claims"

Even assuming *arguendo* that Sigma had raised a distinction between "cleavage plus

integration" claims and so-called "Non-Template Claims" (which as discussed above is not true), Broad itself—as the movant—does not make any such contention in its motion. Indeed, throughout Motion 1, Broad consistently—and solely—relies on ***Sigma's*** supposed arguments, while purposely taking ***no position*** itself on that (completely self-fabricated) issue. *E.g.*, Broad Mot. at 1 (Sigma "argued", "stressed", "continues to make the same argument", "sought", "further argued"), 2 (Sigma "also argued", "acknowledges", "expressly argued"), 3 ("Sigma acknowledged"; Sigma's "arguments", "position"), 4 (Sigma "consistently represented"), 13 ("based on Sigma's arguments", "Sigma has taken the position"), 15 ("According to Sigma"), 16 ("Sigma argued", "following Sigma's reasoning", "Sigma . . . in prosecution argued"), 17 (Sigma "has consistently argued", "contends", "argued"), 18 ("what Sigma regards").

But on this motion, Broad fails to carry its burden ***by taking no position whatsoever*** on the purported patentable distinctiveness of the two alternative parts of current Count 1, instead relying solely on a wholly fabricated argument supposedly made by Sigma. Broad's failure is particularly egregious here because Sigma has ***not*** actually made that supposed argument, and Sigma even explained its position regarding that issue to Broad. *See supra* Part V.B. Thus, for this additional reason, the Board may exercise its discretion to deny Broad Motion 1.

D. Nowhere Does Broad Even Contend That Sigma's "Cleavage Plus Integration By HDR" Claims Are Patentably Distinct From Broad's "Cleavage Plus Altering Gene Expression" Claims

On its Motion 1, Broad entirely ignores that its Claim 18 is ***not*** a "cleavage only" claim. In particular, Claim 18 initially recites that "the Cas9 protein cleaves the DNA molecules", which—standing alone—would be a "cleavage only" claim. But the claim does not end there. Importantly, Claim 18 then adds the further recital "whereby expression of the at least one gene product is altered", which further limits the claim and whose express language cannot be ignored. Indeed, this express recital narrows Claim 18 from using CRISRP-Cas9 in a eukaryotic

cell for simple DNA destruction (cleavage only) to using CRISRP-Cas9 in a eukaryotic cell to thereafter achieve a demonstrable genomic engineering result (altering gene product expression). Thus, as discussed above and as Sigma pointed out in its Proposed List of Motions, Broad Claim 18 is a ***cleavage plus altering gene product expression*** claim. *See supra* Part V.B.

On this motion, Broad bears the burden to not only ***assert*** that Broad's claims (***cleavage plus altering gene product expression***) are patentably distinct from Sigma's claims (***cleavage plus integration via HDR***), but also to ***present evidence*** supporting such an assertion. But Broad does ***neither***. Here, Broad does not even address this pivotal comparison. And Sigma has made no such argument, having not challenged the Board's initial determination in the Declaration that the parties' claims interfere. Broad's deafening silence on this issue falls far short of Broad meeting its burden on this motion of demonstrating why the count should be changed.

E. Broad Does Not Demonstrate That Any Of Its Alleged Proofs Of Invention With Respect To Proposed Count 3 Include Both sgRNA And dgRNA

Broad argues that Proposed Count 3 is directed to a generic guide RNA (*i.e.*, a sgRNA or a dgRNA). Broad Mot. 1 at 7 ("Broad's 403 application ***claim 52 does not limit the RNA configurations*** . . . .") (emphasis added); *see id.* at 17 ("generic RNA"). But Broad further argues that it has unspecified "later" proofs of invention that include a donor polynucleotide, which Broad then readily concedes are limited to a sgRNA:

> [A]fter establishing the components for achieving CRISPR-modified gene editing in mammalian cells, the inventors used ***chimeric RNA*** . . . to perform Donor Template Integration . . . .

Id. at 20 (emphasis added); *see also id.* ("Accordingly, the inventors "co-transfect[ed] HEK 293FT cells with the ***chimeric RNA*** . . . .") (emphasis added).

Indeed, with respect to Proposed Count 3, nowhere does Broad make any attempt to show that ***any*** of its proofs with respect to that proposed count encompass (a) a donor template, and

(b) both sgRNA and dgRNA. *See* Ex. 2467 at 171:21 – 172:3 (Dr. Seeger has not seen "any experiments by Dr. Zhang that had a donor template and used a dual-guide RNA."). Accordingly, on this motion, Broad fails to carry its burden that Proposed Count 3 has been crafted to conform to any of Broad's proofs of inventions.

F. Sigma's Arguments In The *CVC v. Sigma* Interference (No. 106,132) Are Entirely Consistent With Sigma's Arguments Here

Broad makes much of Sigma's arguments in the parallel *CVC v. Sigma* interference (No. 106,132), contending that Sigma's arguments somehow demonstrate that current Count 1 in this interference includes two patentably distinct inventions. But such is not the case. As Sigma has explained in the *CVC v. Sigma* interference, in three of the other CRISPR-Cas9-related interferences, the other parties have strategically chosen to limit their respective priority contests to ***cleavage only*** in a eukaryotic cell:

> Notably, three interferences directed to the subject matter of Count 1 (*viz.*, cleavage only in a eukaryotic cell) are currently pending before the Board: *CVC v. Broad*, Int'f No. 106,115; *Broad v. ToolGen*, Int'f No. 106,126; and *CVC v. ToolGen*, Int'f No. 106,127. ***As the papers filed in those cases reveal, the three parties involved in those interferences*** (*viz.*, CVC, Broad, and ToolGen) ***are contesting priority of invention of CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA***.

Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 4 (emphases added). As discussed below, Sigma's above analysis is accurate and in no way inconsistent with Sigma's position in this interference.

In particular, Sigma appreciates that in the *CVC v. Broad* interference, Broad's part of the two-part McKelvey Count 1 is Broad Claim 18 of Patent 8,697,359, the same claim at issue here. Ex. 1526 (Declaration ('115 Int'f)) at 12-13 (June 24, 2019). But in that case (unlike Sigma here), CVC did not challenge Broad's accorded benefit to Broad P1. *See* Ex. 1527 (CVC List of Intended Motions ('115 Int'f)) at 1-23 (Jul. 30, 2019).

Moreover, in its priority briefings, Broad relied solely on its evidence of cleavage (with

NHEJ-generated indels)[4] in a eukaryotic cell, with only a conclusory assertion—without any supporting data—that "this break ***can be*** repaired to alter the sequence of the gene and thereby results in a change in the expression of the product encoded by the gene, here EMX1." Ex. 1530 (Broad Mot. 5 ('115 Int'f)) at 35 (emphasis added). Broad's expert provided a similarly conclusory opinion on this issue with respect to the mouse TH gene:

> [T]he chimeric RNA had formed a CRISPR complex in the eukaryotic (mouse) cells which targeted, ***cleaved, and edited*** the mTH gene in some of the mouse cells (as shown by the presence of indels in the sequencing results).

Ex. 1533 (Ex. 3430 (Ellington Decl.) ('115 Int'f)) ¶ 47 (emphasis added).

> [T]he two deletions observed in the mTH gene were the result of ***targeting and cleavage*** at the intended location in the genomic DNA by the hSpCas9 that was guided by the chimeric RNA designed by Dr. Zhang, ***followed by subsequent double-strand break repair***, and that the POSA in 2012 would have understood this to be the case. Further, a POSA would also have understood that introduction of ***these 2 or 16 bp deletions in the target resulted in a frameshift or other modification that would alter expression of the product encoded by the gene***.

Id. ¶ 48 (emphases added).

But nowhere does Broad even allege that the Dr. Zhang's data demonstrates that the ***expression*** of the gene product was ***actually*** altered, as an actual reduction to practice requires. Broad P1 does not provide any information with respect to the indels observed in CRISPR cleavage of the mouse TH gene. Ex. 1518 (Cannon Supp'l Decl.) ¶ 17. A close examination of the evidence (Ex. 3784 ('115 Int'f)) relied upon by Broad's expert Dr. Ellington shows that the 2-bp deletion was downstream of the ORF, thus suggesting that even if the 2-bp deletion were produced, it would not be expected to alter expression of the mTH gene. Ex. 1518 ¶ 20. The 16-

[4] Sigma has explained in detail why "DNA repair by NHEJ is typically induced by a DSB," which is in stark contrast to donor integration via HDR. *E.g.,* Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 11-12 (emphasis omitted); *see generally id.* at 6-24 (discussion of HDR).

bp deletion would mutate the stop codon, which would have been predicted to produce a frameshift mutation resulting an elongated ORF. *Id.* However, as Sigma has explained in detail with respect to the comparable data in Broad P1, Dr. Zhang did not evaluate whether the expression of the mTH gene had actually been altered. *See* Sigma Mot. 1 at 4-11. Thus, the gene's expression—both before cleavage and after cleavage—was never shown (or even discussed), and whether any gene expression was affected by the CRISRP-Cas9 cleavage remains simply unknown. *Id.* In any event, CVC did not challenge Broad's hand-waving on this issue, thus leaving Broad's conclusory assertion undisputed. *See* Ex. 1531 (Decision on Priority ('115 Int'f)) at 63 ("CVC does not put forth an argument, or direct us to evidence to support an argument, . . ."); *id.* at 64 ("In the absence of such arguments . . ."); *id.* ("Broad presents persuasive evidence . . . which CVC does not dispute . . . ."). In stark contrast, in this interference Sigma ***has*** disputed Broad's conclusory assertions. *See* Sigma Mot. 1 at 4-11.

Not surprisingly, in that *CVC v. Broad* interference (No. 106,115), CVC also relied solely on its evidence of cleavage in a eukaryotic cell:

> East-Seletsky confirmed with Doudna and Jinek that the "singleton band" in her gel was the correct size, demonstrating CRISPR-Cas9-mediated DNA ***cleavage*** in human cells.

Ex. 1529 (CVC Mot. 2 ('115 Int'f)) at 32 (emphasis added); *see id.* at 29 (same). Thus, in the *CVC v. Broad* interference (No. 106,115), the parties are contesting priority of invention of CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA.

Similarly, in the *ToolGen v. Broad* interference (No. 106,126), the parties have also (at least thus far in the proceeding) focused their dispute on CRISPR-Cas9 for cleavage in a eukaryotic cell. In that interference, ToolGen requested, and the Board authorized, a motion to challenge Broad's accorded benefit to Broad P1:

> ToolGen requests authorization for a motion to argue that Broad should be

> denied the benefit of the filing date of provisional application 61/736,527. (See ToolGen List, Paper 18, 3:1-4.) Authorization for this motion is GRANTED. The motion shall be entitled "TOOLGEN MOTION 2."

Ex. 1535 (Order Authorizing Motions ('126 Int'f)) at 7; *see* Ex. 1534 at 3 ("ToolGen Motion 3").

But like CVC, ToolGen chose not to file any such motion, thus strategically electing not to challenge Broad's accorded benefit to Broad P1, including the "cleavage plus altering gene product expression" of Count 1 in that contest. Thus, at least to date in the *Broad v. ToolGen* interference (No. 106,126), the parties are also contesting priority of invention of CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA. And the same is true in the *CVC v. ToolGen* interference (No. 106,127).

Accordingly, in the *CVC v. Broad* (No. 106,115), *Broad v. ToolGen* (No. 106,126), and *CVC v. ToolGen* (No. 106,127) interferences currently pending before the Board, the three involved parties (CVC, Broad, and ToolGen) are contesting priority of invention of CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA. But the parties' strategic decisions in those other cases regarding which claim limitations to argue, and which claim limitations to overlook, have no bearing on Sigma's decision in this case to evaluate every limitation of Broad Claim 18, including the express recital of "whereby expression of the at least one gene product is altered." Sigma's simple recognition of CVC's and ToolGen's decisions to give Broad a free pass on that issue by no means constrains Sigma to do the same, and Sigma has not done so here.

VI. BROAD'S EXCEEDINGLY BROAD CLAIM 52 FAILS TO REASONABLY CONFORM TO EITHER PARTY'S CRISPR-CAS9-RELATED INVENTION

Broad's Proposed Count 3 seeks to substitute Claim 52 of the '403 application for Claim 18 of Patent 8,697,359 of current Count 1. Broad Mot. 1 at 7. But Broad's unallowed Claim 52 is excessively broad and thus grossly inadequate to reasonably conform to either of the parties' inventions, not the least of which is that Claim 52 is not even limited to a CRISPR-Cas9 system.

In Motion 1, Broad argues that "Proposed Count 3 only narrows the Broad half of Count 1 by requiring integration of a donor template, as in the Sigma half of the Count." Mot. 1 at 20. But to the contrary, a comparison of the Broad claims is set forth below shows that the claims bear little resemblance to each other, including many substantive differences, with added highlighting to assist the discussion that follows:

Count 1	Proposed Count 3
Broad Patent 8,697,359 Claims 15 & 18	**Broad Application 16/177,403 Claim 52**
15. An engineered, programmable, non-naturally occurring Type II CRISPR-Cas system comprising a Cas9 protein and at least one guide RNA that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell, wherein the DNA molecule encodes and the eukaryotic cell expresses at least one gene product and the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together. 18. The CRISPR-Cas system of claim 15, wherein the guide RNAs comprise a guide sequence fused to a tracr sequence.	52. (Currently Amended) A method comprising: introducing into, or expressing in, a eukaryotic cell having a DNA molecule, (I) a Cas9 protein or one or more nucleotide sequences encoding the Cas9 protein; (II) an RNA or one or more nucleotide sequences encoding the RNA, the RNA comprising: (a) a first RNA [1] comprising a first ribonucleotide sequence [1A] and a second ribonucleotide sequence [1B], and (b) a second RNA [2]; and (III) a template polynucleotide; wherein the second RNA [2] forms an RNA duplex with the second ribonucleotide sequence [1B], and wherein, in the eukaryotic cell, the first ribonucleotide sequence [1A] directs the Cas9 protein to a target sequence of the DNA molecule, whereby the Cas9 cleaves both strands of the DNA molecule and the cleavage is repaired by integration of the template polynucleotide into the DNA molecule in the eukaryotic cell.

Declaration (Paper 1) at 12 (June 21, 2021); Broad Mot. 1 at 7 (highlighting added). As discussed below, Broad Claim 52 is exceedingly broad, and an exceptionally deficient claim to be included as part of the Count in this interference. Yet, neither Broad nor its expert Dr. Seeger addresses any of these deficiencies in the claim language or provides a compelling reason to justify the request to change count to this overly broad claim. *See, e.g.*, Ex. 2467 at 93:10 ("I wasn't asked to opine on scope [of Claim 52]. . . ."), 103:3-4 ("I have no opinion on the detailed language of the claim."), 110:19 – 11:5 ("I have not been asked to question or investigate

language of the claim. . . . I have not worried about the language of the claim . . . .").

A. Broad Claim 52 Is Not Limited To A Standard CRISPR-Cas9 System

Broad Claim 18 of Current Count 1 expressly recites a "Type II CRISPR-Cas system". The claims of the other parties to CRISPR-Cas9-related interferences recite a similar limitation:

Sigma-Aldrich Application 15/456,204 Claim 31	CVC Application 15/947,680 Claim 164[5]
[A] Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR-Cas) type II protein	[A] Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system . . . .

However, Broad's Claim 52 is not limited to a standard CRISPR-Cas system known to a POSITA in December 2012, in which crRNA is based-paired to tracrRNA to form a guide RNA that guides Cas9 to cleave both strand of a target DNA sequence at sites complementary to a portion of the crRNA sequence, because Broad did not include the "CRISPR-Cas" limitation in this recent claim. Ex. 1518 (Cannon Supp'l Decl.) ¶ 21. Claim 52 thus encompasses a DNA targeting, cleavage, and integration system beyond a standard CRISPR-Cas9 system, which far exceeds the general subject matter of this interference (as well as *CVC v. Sigma*, No. 106,132). For example, Claim 52 would cover a first RNA that could both bind to Cas9 (*e.g.*, had the properties of an aptamer) combined with an antisense RNA sequence that could target a complementary DNA sequence, with the result being that the Cas9 protein then cleaves both strands of the DNA molecule. *Id.* ¶ 22. Claim 52 would also cover a system in which the claimed "second RNA" is an aptazyme. *Id.* ¶ 23; *see* Ex. 1540 (US 2020/0181619 A1) at 71 ("1. An engineered ribonucleic acid (RNA) comprising a single guide RNA (sgRNA) associated with an aptazyme, wherein the aptazyme hybridizes to a portion of the sgRNA . . . . 17. . . . wherein

[5] CVC Claim 164 of Sigma Proposed Count 2 includes the same recitals. Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 5.

the sgRNA directs the Cas9 . . . to a target sequence upon cleavage of the aptazyme from the sgRNA."). And Broad has not shown that Broad P1 (or any other of Broad's proofs of invention discussed in Broad Motion 1) discloses any such non-standard CRISPR-Cas9 systems.

Accordingly, Claim 52 is excessively broad and fails to reasonably conform to either of the parties' CRISPR-Cas9-related inventions. For this reason, Broad has failed to meet its burden on this motion of presenting a claim with a scope commensurate with either party's invention, thereby justifying the Board's exercise of its discretion to deny Broad Motion 1.

B. Broad Claim 52 Encompasses NHEJ End Ligation, Which Is Fundamentally Different From Homology Directed Repair

Claim 52 of Proposed Count 3 does not recite homology directed repair ("HDR"), Broad having intentionally removed that limitation as part of its October 15, 2021 claim amendment:

> target sequence of the DNA molecule, whereby the Cas9 cleaves both strands of the DNA molecule and ~~the template polynucleotide repairs~~ the cleavage is repaired by integration of the template polynucleotide into the DNA molecule ~~by homology directed repair~~ in the eukaryotic cell.

Ex. 1520 at 4. And Broad has involved claims directed to integration of a donor via HDR, which depend from broader donor "insertion" claims. *E.g.,* Ex. 1518, Appx. C at 82 (Cls. 15 & 16).

For the sake of comparison, both Sigma's and CVC's claims expressly recite HDR:

Sigma-Aldrich Application 15/456,204 Claim 31	CVC Application 15/947,680 Claim 164[6]
. . . repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.	. . . creation of a double strand break in the target DNA molecule which is repaired by a homology-directed repair mechanism which incorporates a sequence of a donor polynucleotide into the target DNA molecule . . . .

Without reciting HDR, Claim 52 thus encompasses NHEJ-mediated end ligation, which

[6] CVC Claim 164 of Sigma Proposed Count 2 similarly recites "repaired by a homology-directed repair mechanism". Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 6.

is a far less complex and unpredictable DNA repair mechanism. Ex. 1518 (Cannon Supp'l Decl.) ¶ 30. For example, in addition to describing HDR processes that result in integration of a donor polynucleotide, Sigma P1 (which is prior art to all of Broad's involved cases under Section 102(e)) also discusses ***non-HDR*** processes that lead to DNA repair, including NHEJ ligation repair processes for integration of a donor template (*i.e.*, a "donor polynucleotide") and modification of a chromosomal sequence:

> [0042] In embodiments in which a donor polynucleotide comprising the targeted cleave site is introduced into the cell, the RNA-guided endonuclease can cleave both the targeted chromosomal sequence and the donor polynucleotide. The linearized donor polynucleotide can be integrated into the chromosomal sequence at the site of the double-stranded break by ligation between the donor polynucleotide and the cleaved chromosomal sequence via a NHEJ process.

Ex. 1524 (Sigma P1) ¶ [0042] (emphases added); Ex. 1518 (Cannon Supp'l Decl.) ¶ 30.

> [0043] Lastly, in embodiments in which a linear donor polynucleotide comprising a short donor sequence is introduced into the cell, the short donor sequence can be integrated into the chromosomal sequence at the site of the double-stranded break via a NHEJ process. The integration can proceed via the ligation of blunt ends between the short donor sequence and the double stranded break in the chromosomal sequence. Alternatively, the integration can proceed via the ligation of sticky ends (i.e., having 5′ or 3′ overhangs) between the short donor sequence and the cleaved chromosomal sequence.

Id. (Sigma P1) ¶ [0043] (emphases added); Ex. 1518 (Cannon Supp'l Decl.) ¶ 30.

In this interference, Broad does not contend that any of its proofs of invention are directed to NHEJ-mediated ligation of a donor template, although Broad is not required to reveal its proofs of invention at this stage of the proceeding. In any event, Broad nowhere explains its strategic decision to broaden Claim 52 by removing the "homology directed repair" to encompass non-HDR donor integration. Thus, on this motion, Broad fails to bear its burden of demonstrating that Claim 52's (excessive) breadth conforms to either party's proofs of invention.

C. Broad Claim 52 Encompasses A System With No tracrRNA/Activator RNA That Interacts With The Cas9 Protein

With regard to the function of the "second RNA", Broad Claim 52 only recites that "the

second RNA [2] forms an RNA duplex with the second ribonucleotide sequence [1B]" of the first RNA [1]. The "second RNA" is not recited as a tracrRNA, and the claim is entirely silent with regard to including any RNA component that interacts with the Cas9 protein, as discussed in Jinek (2012). Ex. 1539 at 818 ("This indicates that tracrRNA is required for target DNA recognition . . . ."); *see* Ex. 1545 (Richter (2012)) at 2299 (same). Not surprisingly, Sigma's and CVC's claims recite a tracrRNA/activator RNA component that interacts with the Cas9 protein:

Sigma-Aldrich Application 15/456,204 Claim 31	**CVC Application 15/947,680 Claim 164**[7]
[A] second region that interacts with the CRISPR-Cas type II protein, and wherein the guide RNA comprises a crRNA and a tracrRNA	[A]n activator-RNA . . . to form a double-stranded RNA duplex of a protein-binding segment . . . wherein the single molecule DNA-targeting RNA forms a complex with the Cas9 protein . . . .

Broad nowhere explains why it drafted Claim 52 to not include any recital that the RNA component interacts with the Cas9 protein. And as Broad's, Sigma's, and CVC's claims all demonstrate, an RNA *interacting/binding/forming a complex* with the Cas9 is a separate limitation from simply targeting/guiding/directing the Cas9 to the DNA. *See* Broad Claim 18 ("[a] guide RNA that targets . . . a DNA molecule"); Sigma Claim 31 ("the guide RNA guides the CRISPR-Cas type II protein to the target site"); CVC Claim 164 ("targeting the Cas9 protein to the target DNA molecule"); *see also* Ex. 1539 (Jinek (2012)) at 828 ("Following the first and second processing events, ***mature tracrRNA remains*** paired to the mature crRNAs and ***bound to the Cas9 protein***. In this ternary complex, the dual tracrRNA:crRNA structure acts as guide RNA that ***directs the endonuclease Cas9 to the cognate target DNA***.") (emphases added); Ex. 1545 (Richter (2012)) at 2301 ("In complex with the tracrRNA:crRNA structure, Cas9 binds the target dsDNA and creates a double strand break . . . ."); Ex. 1518, ¶ 25.

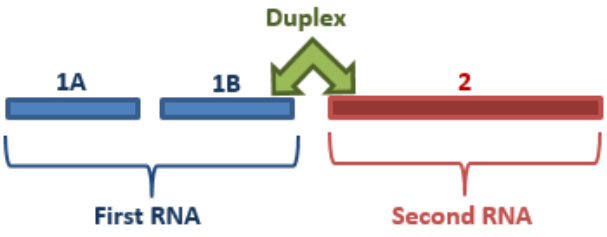
[7] CVC Claim 164 of Sigma Proposed Count 2 includes the same recitals. Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 5.

One possible explanation is that Broad's alleged best proofs of invention, which purportedly pre-date the publication of Jinek (2012), do not include a tracrRNA component. But that omission in Broad's proofs does not justify a count here that would encompass a system that does not require a tracrRNA, or at least an RNA component that interacts with the Cas9 protein. There is general scientific consensus that a CRISPR-Cas9 system requires a tracrRNA component to interact with the Cas9 protein. Ex. 1518 (Cannon Supp'l Decl.) ¶ 24; *see* Ex. 1539 (Jinek (2012)) at 816 ("We found that mature crRNA alone was incapable of directing Cas9-catalyzed plasmid DNA cleavage (Fig. 1A and fig. S3A). However, addition of tracrRNA, which can base pair with the repeat sequence of crRNA and is essential to crRNA maturation in this system, triggered Cas9 to cleave plasmid DNA (Fig. 1A and fig. S3A).").

Accordingly, Claim 52 is excessively broad and fails to reasonably conform to either of the parties' inventions in this interference. For this reason, Broad has failed to meet its burden on this motion of presenting a claim with a scope commensurate with either party's invention, thereby justifying the Board's exercise of its discretion to deny Broad Motion 1.

D. Broad Claim 52 Encompasses A crRNA/Targeter RNA That Performs *All* Of The Guiding Function Of The Guide RNA

With respect to the function of the guide RNA, Broad Claim 52 only requires that "the first ribonucleotide sequence [1A] [of the first RNA] directs the Cas9 protein to a target sequence of the DNA molecule". As explained above, the claim does not recite any tracrRNA to interact with the Cas9 protein. While Claim 52 does further recite that "the second RNA [2] forms an RNA duplex with the second ribonucleotide sequence [1B]", that recital does not require that the second RNA performs any of the guide RNA's guiding functions.



In particular, there is no requirement that the first RNA [1] be a single molecule, *i.e.*, that the first ribonucleotide sequence [1A] be linked to the second ribonucleotide sequence [1B]. That is, Claim 52 encompasses a guide RNA as conceptually illustrated above. Any Broad assertion that the first RNA is limited to a single-molecule RNA is belied by the language of Claim 52 itself, coupled with Broad's arguments on this motion. In particular, Broad contends that Claim 52's recital of "an RNA . . . ***comprising***: (a) a first RNA . . . and (b) a second RNA" encompasses both a single-molecule RNA and a dual-molecule RNA. Broad Mot. 1 at 7. Accordingly, Claim 52's analogous recital of "a first RNA ***comprising*** a first ribonucleotide sequence and a second ribonucleotide sequence" likewise encompasses both a single-molecule first RNA and a dual-molecule first RNA. As a result, Claim 52 encompasses a system in which the first ribonucleotide sequence [1A] of the first RNA [1] performs ***all*** of the guide RNA's functions (*viz.*, "the first ribonucleotide sequence [1A] directs the Cas9 protein to a target sequence of the DNA molecule"), while the second RNA [2] performs ***none*** of the guide RNA's functions, but instead simply forms a duplex with the second ribonucleotide sequence [1B], in which that duplex has no recited function. Such a system is not within the scope of this interference, nor within the scope of either party's provisional cases.

Broad nowhere explains why it drafted Claim 52 to encompass a system in which the first RNA performs all the guiding functions of the guide RNA. As discussed above, one possible explanation is that Broad's alleged best proofs of invention, which Broad argues pre-date the publication of Jinek (2012), include only a crRNA component that performs all of the functions of the guide RNA. But as mentioned previously, that omission in Broad's proofs does not justify a count here that would encompass a system in which a crRNA component alone performs all of the functions of the guide RNA. There is general scientific consensus that a CRISPR-Cas9 system requires not only a crRNA but also a tracrRNA component. Ex. 1518 (Cannon Supp'l

Decl.) ¶ 24.; Ex. 1539 (Jinek (2012)) at 816. Accordingly, Claim 52 is excessively broad and fails to conform to either of the parties' inventions in this interference. For this reason, Broad has failed to meet its burden on this motion of presenting a claim with a scope commensurate with either party's invention, thereby justifying the Board's exercise of its discretion to deny Broad Motion 1.

E. Broad Claim 52 Does Not Require That The Guide RNA Hybridize To/Bind With The Target Sequence

Claim 18 of current Count 1 recites that the guide RNA both "targets ***and hybridizes to*** a target sequence of a DNA molecule". In contrast, and for some unknown reason, Broad has removed the important hybridizing/binding function in Claim 52 of proposed Count 3.

For the sake of comparison, both Sigma's and CVC's claims recite that the guide RNA hybridizes with/bind to the target sequence:

Sigma-Aldrich Application 15/456,204 Claim 31	**CVC Application 15/947,680 Claim 164**[8]
[T]he guide RNA comprises a first region that is complementary to a target site in the chromosomal sequence . . . and wherein the guide RNA comprises a crRNA	[A] targeter-RNA that hybridizes with the target sequence . . . .

Claim 52 is excessively broad because it encompasses a system in which the first RNA does not necessarily hybridize with the target DNA. While Claim 52 recites that "the first ribonucleotide sequence [1A] directs the Cas9 protein to a target sequence of the DNA molecule, whereby the Cas9 cleaves both strands of the DNA molecule," that claim limitation does not specify that any component of the guide RNA hybridizes to/binds with the target DNA. Thus, Claim 52 encompasses a system in which neither the first RNA nor the second RNA performs the function of hybridizing to/binding with the target sequence. Such a system is inconsistent

[8] CVC Claim 164 of Sigma Proposed Count 2 includes the same recitals. Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 5.

with the general scientific consensus that a CRISPR-Cas9 system includes a first crisprRNA (targeter RNA) that hybridizes to/binds with the target sequence, while the second tracrRNA (activator RNA) interacts with the Cas9 protein.

Accordingly, Claim 52 is again excessively broad and fails to conform to either of the parties' inventions in this interference. For this additional reason, Broad has failed to meet its burden on this motion of presenting a claim with a scope commensurate with either party's invention, thereby justifying the Board's exercise of its discretion to deny Broad Motion 1.

F. Broad Claim 52 Encompasses A Guide RNA Genus, But Broad's Disclosed Proofs Of Invention Are Limited To A sgRNA Species

Broad argues that Claim 52 encompasses an RNA "genus", namely, both sgRNA and dgRNA. Broad Mot. 1 at 7, 15, 18 ("generic RNA"). Indeed, Broad makes clear that its Claim 52 recital of "an RNA" was expressly drafted to be different from its Claim 18 language that recites a "guide RNA", the latter of which the Board has construed to mean only a sgRNA in view, *inter alia*, of the disclosure of Broad P1. *Id.* at 7. Indeed, Broad repeatedly argues that its purported best proofs are experiments using dgRNA, and thus Broad has purposely crafted Claim 52 in an attempt to encompass those purported best proofs. *See supra* Part V.E.

Regardless of Broad's objectives in other interferences, Broad readily acknowledges here that its disclosed relevant proofs of invention with respect to a donor polynucleotide—as expressly recited in Claim 52—use only a sgRNA ("chimeric RNA"). Broad Mot. 1 at 20. Thus, there is absolutely no need in ***this interference*** for Broad to broaden the count to encompass a generic RNA. Moreover, because Broad P1 ***only*** uses a sgRNA in the context of a donor polynucleotide, Broad has not explained how Claim 52's recital of a generic RNA in the context of "a template polynucleotide" can be found in the disclosure of Broad P1.

Accordingly, Claim 52 is excessively broad in this interference with respect to Broad's

purported donor nucleotide proofs. For this reason, Broad has failed to meet its burden on this motion of presenting a claim with a scope commensurate with either party's invention, thereby justifying the Board's exercise of its discretion to deny Broad Motion 1.

G. Broad Claim 52 Encompasses A Split-Cas9 System, Which Is Beyond The Scope Of This Interference And Broad's Disclosed Proofs Of Invention

With respect to current Count 1, Broad Claim 18 recites "a Cas9 protein" and Sigma Claim 31 recites "a . . . (CRISPR-Cas) type II protein . . . or ***a*** nucleic acid encoding the CRISPR-Cas type II protein . . . , wherein the CRISPR-Cas type II protein is a Cas9 protein". Declaration (Paper 1) at 12 (June 21, 2021) (emphasis added). For sake of comparison, in the *CVC v. Sigma* interference (No. 106,132), CVC Claim 164 recites "a Cas9 protein".[9]

In contrast, with respect to Proposed Count 3, Broad has drafted Claim 52 to recite "a Cas9 protein or one or more nucleotide sequences encoding the Cas9 protein". Broad Mot. 1 at 7 (highlighting added). This claim limitation, which includes a ***split-Cas9 system*** in which a plurality of nucleotide sequences encode the Cas9 protein, does not conform to Broad's disclosed proofs of invention, and is not even found in Broad P1.

Broad P1 discusses "***an*** enzyme-coding sequence encoding said CRISPR enzyme". Ex. 1503 ¶¶ [0004], [0007], [0008], [0045], [0089], [00101]; *id.* at Claims 1, 26, 45; see also *id.* ¶¶ [0005], [0060], [0061], Claim 17 ("***an*** enzyme-coding sequence encoding a CRISPR enzyme") (emphasis added); *id.* ¶¶ [0061], [00101] ("***a*** sequence encoding a CRISPR enzyme") (emphasis added); *id.* ¶¶ [0060], [0062] ("***a*** vector encodes a CRISPR enzyme") (emphasis added); *id.* ¶¶ [0058] ("***a*** transcript encoding a CRISPR enzyme") (emphasis added). But Broad P1 does not discuss ***more than one*** nucleotide sequences (*e.g.*, more than one DNA or RNA

[9] CVC Claim 164 of Sigma Proposed Count 2 similarly recites "a Cas9 protein". Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 5.

sequence) encoding the Cas9 protein.

More importantly, with respect to Broad's potential proofs of invention, Broad P1 discloses using a single pCRISPR plasmid to encode the SpCas9 enzyme:

> **[00162]** Elements of the *S. pyogenes* CRISPR locus 1 sufficient for CRISPR activity were reconstituted in *E. coli* using pCRISPR plasmid (schematically illustrated in Figure 9A). pCRISPR contained tracrRNA, SpCas9, and a leader sequence driving the crRNA array.
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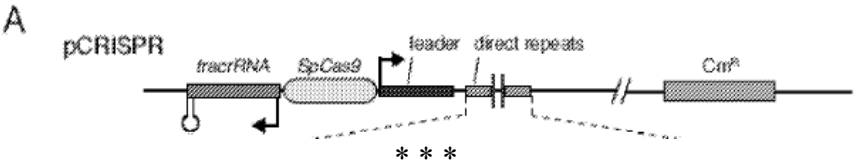
> 
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>
> * * *
>
> **Figure 9**

Id. at Fig. 9A.

Beyond the scope of this interference, and in the 2015 time frame, Broad published papers and filed patent applications on split-Cas9 systems (the latter of which claim priority benefit to Application 61/915,267 (filed on Dec. 12, 2013)). *See, e.g.*, Exs. 1541 (Zetsche (2015)) at 139-141; Ex. 1542 (Nishimasu (2016)) at 11 & Fig. 7; Ex. 1543 (WO 2015/089427 A1); Ex. 1544 (US 10,377,998). In those later disclosures, Broad discusses and illustrates "a dual vector system (each vector delivering one half of the split Cas9)." Ex. 543 ¶ [00139]:

Ex. 1541 (Zetsche (2015)) at 140, Figs. 1b & 1f; *see also* Ex. 1543 ¶ [00330] & Fig. 5A ("Sequenced verified clones were used for transfection into HEK293FT cells: HEK cells were transfected with 100ng of ***each*** SpCas9-FKBP and SpCas9-FRB and 100ng of sgRNA guide targeting EMX1.") (emphasis added). And in that 2015 time frame, Broad presented claims to this split-Cas9 system, such as the following:

> 1. A non-naturally occurring or engineered inducible CRISPR-Cas system, comprising:

> ***a first CRISPR enzyme fusion construct*** . . . and
> ***a second CRISPR enzyme fusion construct*** . . . .
> * * *
> 19. ***A vector for delivery of the first CRISPR enzyme fusion construct*** . . . according to any preceding claim.
>
> 20. ***A vector for delivery of the second CRISPR enzyme fusion construct*** . . . according to any of claims 1-18.

Ex. 1543 at 155, 157 (emphases added); *see id.* at ¶ [0010] (same).

In its Motion 1, however, Broad nowhere explains why Claim 52 has been drafted to include such a split-Cas9 system in which two (or even more) nucleotide sequences encode the Cas9 protein. Accordingly, Claim 52 is exceedingly broad for this reason as well, failing to conform to either party's disclosed proofs of invention. This reason further demonstrates that Broad has failed to meet its burden on Broad Motion 1 to change the count to Claim 52.

H. Broad Claim 52 Encompasses A Wild-Type Cas9 Protein That Would Not Be Capable Of Entering A Eukaryotic Cell

In current Count 1, Broad Claim 18 recites an "engineered, programmable, non-naturally occurring" CRISPR-Cas9 system. Declaration (Paper 1) at 12 (June 21, 2021). In this context, Sigma Claim 31 recites:

> [A] . . . (CRISPR-Cas) type II protein ***linked to only one nuclear localization signal (NLS)*** or a nucleic acid encoding the CRISPR-Cas type II protein ***linked to only one NLS***, wherein the CRISPR-Cas type II protein is a Cas9 protein, and the nucleic acid encoding the CRISPR-Cas type II protein is ***codon optimized for expression in the eukaryotic cell*** . . . .

Id. (emphases added).

For sake of comparison, in the *CVC v. Sigma* interference (No. 106,132), CVC Claim 164 recites "an engineered and/or non-naturally-occurring" CRISPR-Cas9 system.[10]

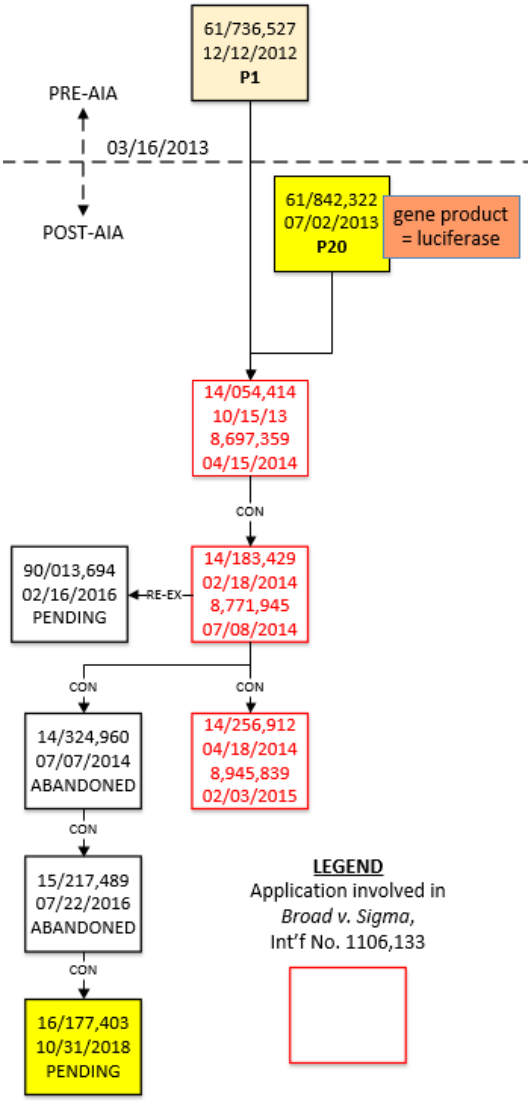
[10] CVC Claim 164 of Sigma Proposed Count 2 includes the same recitals. Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 5.

In contrast, with respect to Proposed Count 3, Broad has broadly drafted Claim 52 with no requirement regarding whether the Cas9 protein is natural (*i.e.*, wild-type) or non-natural (*i.e.*, engineered). *See* Broad Mot. 1 at 7. ***And Broad P1 nowhere discloses a CRISPR-Cas9 system using a wild-type Cas9 protein.*** Indeed, because Cas9 evolved in a bacterial environment, it is unlikely that a wild-type Cas9 protein would be capable of entering the nucleus of a eukaryotic cell. Ex. 1518 (Cannon Supp'l Decl.) ¶ 34; Ex. 2467 (Seeger Depo. Tr.) at 66:4-9 (Dr. Seeger agrees that a POSITA would not expect that "just transferring a whole section of a bacterial genome into a eukaryotic cell would be successful in terms of [] functional expression of a particular locus."). In its Motion 1, Broad nowhere explains why it drafted Claim 52 to encompass a wild-type Cas9 protein. Accordingly, Claim 52 is exceedingly broad, failing to conform to either party's possible proofs of invention. This reason further demonstrates that Broad has failed to meet its burden on Broad Motion 1 to change the count to Claim 52.

In conclusion, as explained in the foregoing discussions, Broad's Claim 52 has been poorly crafted—in multiple ways—to reasonably conform to either of the party's inventions. These reasons alone are sufficient for the Board to, in its discretion, deny Broad Motion 1.

VII. BROAD'S '403 APPLICATION IS SUBJECT TO THE AIA, AND THUS LACKS A CONTINUOUS BENEFIT CHAIN TO BROAD P1

On this motion, Broad argues (incorrectly) that the '403 application has a continuous benefit chain to Broad P1 in compliance with Section 120. Broad Mot. 1 at 21. But as illustrated in the partial Broad patent family tree shown below, the intervening post-AIA '359 and '945 patents—through which the '403 application claims priority benefit—are AIA patents at least because of the addition of "wherein the gene product is luciferase" in the disclosure and claims of the '322 application. *See* Ex. 1523 (Broad P20) ¶ [0082] ("In a preferred embodiment of the invention the gene product is luciferase."); *id.* at Claims 8, 18, 28 ("wherein the gene product is



luciferase"). This disclosure is not set forth in any of Broad's pre-AIA applications to which the '403 application claims priority benefit, including Broad P1. *See* Ex. 1518 (Cannon Supp'l Decl.) ¶ 35. Accordingly, because the '322 application is an AIA application, and the '403 application contains a benefit claim to the '322 application, the '403 application is also an AIA application and is not entitled to the benefit of Broad P1.

Long before Broad filed Motion 1, Sigma provided notice to Broad regarding this priority defect in Broad's priority benefit claims, including Broad's benefit claims through the '359 and '945 patents. In particular, in Sigma's List of Proposed Motions, Sigma explained as follows:

> ***Each of Broad's involved patents and applications is subject to the first inventor-to-file ("FITF") law, regulations, rules, and procedures, as enacted and promulgated as a consequence of the AIA***. *E.g.*, 35 U.S.C. §§ 100(i), 102; M.P.E.P. §§ 2152, 2159. In particular, each of Broad's involved patents and applications contains claims to subject matter that (a) contains (or at one time contained) a claim to a claimed invention having an effective filing date after March 16, 2013; and/or (b) claims (or at one time claimed) the benefit of an earlier filing date based upon an earlier application that contained such a claim. *See, e.g.*, M.P.E.P. § 2159.02. As a consequence, AIA 35 U.S.C. §§ 102 and 103 apply to all of Broad's involved patents and applications (*i.e.*, Broad's involved patents and applications are all AIA patents and applications).
>
> Several examples of post-AIA claim limitations in each of Broad's involved AIA patents and applications are set forth in the ***Appendix to this List of Proposed Motions***. The example claim limitations include the following:
>
> - ***"altering expression of a gene product . . . wherein the gene product is luciferase"***;

* * *

> Because each of these claims has an effective filing date after March 16, 2013, they are all subject to the AIA. ***And because each of Broad's involved patents and applications*** either contains these claims, or ***claims the benefit of an earlier application that contained these claims, they are all also subject to the AIA***.

Sigma List of Proposed Motions (Paper 22) at 2-3 (Aug. 10, 2021) (emphases added).

The above-referenced Appendix provided Broad with even more details about this specific defect in the priority benefit claim made by the '359 and '945 patents:

BROAD AIA CASES

Involved Broad Case	Claimed AIA Benefit App'n	Post-AIA Filing Date	Example AIA Claim(s)	Example Post-AIA Claim Limitation
8,697,359	61/842,322	07/02/2013	8, 18, 28	altered gene product = luciferase
8,771,945	61/842,322	07/02/2013	8, 18, 28	altered gene product = luciferase

Id. at Appx.

Because the '403 application is an AIA application, it lacks an unbroken benefit chain to Broad P1. And because Broad was aware of this defect in the priority chain and did not address that issue in Broad Motion 1, the '403 application's lack of priority benefit to Broad P1 provides another reason why Broad failed to meet its burden on Motion 1.

VIII. SIGMA ADDRESSES BROAD'S ARGUMENTS REGARDING PURPORTED CLAIM CORRESPONDENCE IN SIGMA OPPOSITION 3

On this motion, Broad argues why certain of its involved claims purportedly correspond to Proposed Count 3, and certain of its involved claims purportedly do not. Mot. 1 at 25-30. The parties are in the process of extensively briefing this same issue in the context of Broad Motion 3. *See id.* at 25 ("Certain of Broad's claims recite Donor Template Integration but do not correspond to Proposed Count 3 (nor Count 1 . . .) because these claims are neither anticipated by nor obvious in view of Proposed Count 3."). Indeed, in Sigma's opposition to Broad Motion 3, Sigma explains in detail which of Broad's involved claims correspond to Count 1, and which claims do not correspond Count 1. Sigma Opp'n 3 (filed concurrently herewith). Those issues are the same with respect to Count 1 or Proposed Count 3. Accordingly, rather than duplicate

those explanations and analyses here, and to avoid unnecessarily consuming the Board's and Sigma's resources, Sigma relies here upon its analyses in the context of Broad Motion 3. *Id.*; *see* Order Authorizing Motions (Paper 27) at 11 (Sept. 20, 2021) ("The parties are encouraged to find ways to consolidate arguments when briefing the authorized motions.").

IX. BROAD FAILS TO CARRY ITS BURDEN ON THIS MOTION TO EVEN ASSERT THAT PROPOSED COUNT 3 IS PATENTABLE TO BROAD OVER SIGMA P1

On this motion, Broad fails to carry its burden to allege that Proposed Count 3 is patentable to Broad over the most pertinent prior art reference, namely, Sigma P1. Without any mention of Sigma P1, Broad simply argues as follows:

> As noted above, Broad is entitled to the benefit of the ***December 12, 2012***, filing date of Zhang B1. ***None of the art prior to that date, alone or in proper combination, anticipates or renders obvious the subject matter of Proposed Count 3***.

Broad Mot. 1 at 24 (emphases added; citation omitted).

> There is ***no reference prior to the December 12, 2012 date to which Broad is entitled that has a disclosure of a successful use of CRISPR-Cas9 in eukaryotic cells, let alone use including integration of a donor template***, and so the subject matter of Proposed Count is patentable to Broad over the prior art.

Id. at 24-25 (emphases added).

But Broad fails to address Sigma P1, which was filed on December 6, 2012, and is thus prior art to Broad P1 under Section 102(e). And Broad has not challenged Sigma's benefit to Sigma P1 (*see* Broad Mot. 1 at 22 ("Broad will not contest Sigma's entitlement to . . . [Sigma P1]),"" which discloses and claims a CRISPR-Cas9 system for cleavage plus integration by HDR in a eukaryotic cell. Thus, for this reason too, Broad fails to carry its burden on Motion 1.

X. CONCLUSION

For the foregoing reasons, Broad has failed to carry its burden on this motion, and accordingly Sigma respectfully requests that the Board deny Broad Motion 1.

Respectfully submitted,

Dated: March 16, 2022

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APPENDIX 1

LIST OF EXHIBITS CITED

Exhibit No.	Description
1503	Broad P1
1518	Cannon Supp'l Decl.
1520	16-177,403 (excerpts)
1521	16-177,403 Miscellaneous Action 2022-03-07
1523	61-842,322 (Broad P20) (post-AIA)
1524	Sigma P1 (Sigma)
1526	106,115 [1] – Declaration
1527	106,115 [19] – CVC List of Intended Motions
1528	106,115 [877] – Decision on Motions
1529	106,115 [1579] – CVC Mot. 2
1530	106,115 [2118] – Broad Mot. 5
1531	106,115 [2863] – Decision on Priority
1532	Zhang-Cong Emails (2012) (106,115 Ex. 3784)
1533	Ellington Decl. (106,115 Ex. 3430)
1534	106,126 [18] – ToolGen Motions List
1535	106,126 [20] – Order Authorizing Motions
1537	106,132 [28] – Tr. Hearing on Authorizing Motions
1538	106,132 [482] – Sigma Mot. 1 (to Substitute Count)
1539	Jinek (2012) (with Supp'l Mat'ls)
1540	US 2020-0181619 A1
1541	Zetsche (2015)
1542	Nishimasu (2016)
1543	WO 2015-089427 A1
1544	US 10,377,998
1545	Richter (2012)
1546	Ex Parte Bhagat (13-877,847)
1547	Ex Parte Max Out Golf LLC (90-013,618)
1548	In re Waschura (09-996,342)
2075	A Complete Copy of the 16/177,403 Application File
2464	Seeger Decl.
2467	Seeger Depo. Tr. 2022-03-01

APPENDIX 2

RESPONSE TO BROAD'S STATEMENT OF MATERIAL FACTS

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 non-homologous 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'S STATEMENT OF MATERIAL FACTS

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).

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.

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.

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

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

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

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

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

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

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

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

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

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.

CERTIFICATE OF FILING AND SERVICE

I hereby certify that:

I. The following paper is being filed March 16, 2022, with the Patent Trial and Appeal Board via:

✓ Interference Web Portal at https://acts.uspto.gov/filing/. Under SO ¶ 105.3, a paper filed through the Interference Web Portal is considered served. The web portal e-filing system is to send email notification of the filing to counsel for Junior Party THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE.

SIGMA OPPOSITION TO BROAD MOTION 1
(to Substitute Proposed Count 3 for Count 1)

II. A courtesy copy of the above paper is being sent to counsel for Junior Party THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and PRESIDENT AND FELLOWS OF HARVARD COLLEGE at the address(es) below on March 16, 2022, via e-mail:

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