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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 3
(to Designate Claims as Not Corresponding to Count 1)

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OPPOSITION TO BROAD MOTION 3
(to Designate Claims as Not Corresponding to Count 1)

I. INTRODUCTION

On this Motion 3, Broad requests that all of its involved claims directed to a "generic" guide RNA (*i.e.*, claims encompassing both a sgRNA and a dgRNA) be designated as not corresponding to Count 1. But nowhere does Broad even cite the proper legal standard for de-designating an involved claim (*viz.*, a one-way obviousness test), let alone apply that standard. Further, Broad does not address how the prior art teachings—particularly those of Jinek (2012), which discusses an *in vitro*, extra-cellular CRISPR-Cas9 system using both a sgRNA and a dgRNA—would have impacted the obviousness inquiry for a POSITA in December 2012. And Broad fails to reconcile Broad Motion 2, which seeks to involve Broad's generic RNA claim (Claim 52), dgRNA claim (Claim 53), and sgRNA claim (Claim 54) in this interference. Accordingly, in these respects, Broad fails to carry its burden on Motion 3.

Notwithstanding the foregoing, Sigma has endeavored to review all 461 of Broad's involved claims in all 16 of Broad's involved patents and applications, and determine which claims should remain in this interference. For example, and as Broad points out, in the *CVC v. Sigma* interference (Int'f No. 106,132), Sigma has stated the following:

> To simplify the issues on this motion and to avoid disputes that would be ancillary to the limited focus of defining the proper interference count here, Sigma does not contest that CVC's claims directed to the following subject matter should *not* be designated as corresponding to the count: (a) > 1 targeting RNA (aka "multiplexing"); (b) a Cas9 protein that includes a Protein Transduction Domain (PTD); (c) one or more mutation(s) in the Cas9 RuvC/HNH domain(s); (d) a nickase for a creating a "nick" or a single stranded break in the target DNA; and (e) a chimeric Cas9 protein.

Ex. 1538 (Sigma Mot. 1 ('132 Int'f)) at 27 (emphasis in original). Thus, on this motion, Sigma does not alter its position with respect to Broad's involved claims having similar claim limitations.

Similarly, to simplify the issues on this motion and to avoid disputes that would be ancillary to the limited focus of this interference, on this motion Sigma does not contest that Broad's claims directed to the following subject matter should *not* be designated as corresponding to the count: (a) SaCas9; (b) a chimeric Cas9; (c) two or more NLSs; and (d) a Cas9 protein fused to one or more protein domains. Thus, for purposes of this motion, Sigma does not contest that each of the limitations referenced above would have been nonobvious in view of Count 1, and thus Sigma does not contest Broad's request to de-designate those particular claims.

II. PRECISE RELIEF REQUESTED

Sigma respectfully requests that the Board deny in part Broad Motion 3 to designate claims as not corresponding to Count 1. As prefaced above and as explained in more detail in this opposition, the following Broad claims should remain designated as corresponding to Count 1, and thus should remain involved in this interference:

In Response to Broad Motion 3:		Claims Correspond	
Involved Broad Case	Currently Correspond	alter gene expression	insert template via HDR
8,867,359	1-20	1-20	
8,771,945	1-29	1-29	
8,795,965	1-30	1-30	
8,906,616	1-30		30
8,945,839	1-28	1, 4-5, 7-11, 14-15, 17-21, 24-25, 27-28	
9,840,713	1-41	1, 3-4, 7-17, 20-24, 26-28, 31-35, 37-38, 40-41	14
14/704,551	2, 4-18	13	14-15, 16

See infra Part V. On this motion, Sigma does not dispute the part of Broad's motion requesting

that the Board de-designate the remaining involved claims from corresponding to Count 1.

III. LEGAL STANDARDS

"[A] claim corresponds to a count if the subject matter of the count, if treated as prior art, would have anticipated or rendered obvious the subject matter of [each] claim." S.O. ¶ 208.3.1; 37 C.F.R. § 41.207(b)(2). As part of this analysis, "additional references and other evidence may be relied upon to establish the obviousness of the differences between the count and the claims." *Desjardins v Wax*, Int'f No. 105,915, Decision on Motions (Paper 125) at 19 n.3 (PTAB Jan. 21, 2014) (granting motion to add claims to the count where the prior art disclosed "the difference between" the count and claims).

IV. BROAD FAILS TO CARRY ITS BURDEN OF CLAIM DE-DESIGNATION IN PART IV.E. OF MOTION 3

With respect to Part IV.E. of its Motion 3, Broad bears the burden of establishing that Broad's so-called "generic" guide RNA claims (*i.e.*, claims that encompass both sgRNA/ chimeric RNA and dgRNA) would have been nonobvious in view of Count 1. But Broad never even asserts that those claims would have been nonobvious over either Broad's half of Count 1 (Claim 18, a sgRNA/chimeric RNA claim), or Sigma's half of Count 1 (Sigma Claim 31, a generic guide RNA claim). Thus, Broad fails to carry its burden on this motion.

A. Broad Does Not Evaluate Whether So-Called "Generic" RNA Claims Would Have Been Obvious In View Of sgRNA Claims

With respect to the two-part "McKelvey" Count 1, Broad does not dispute that Broad Claim 18 is a sgRNA/chimeric RNA claim, and Sigma Claim 31 is a generic guide RNA claim:[1]

[1] Broad argues (incorrectly) that "in the 132 Interference, Sigma argued that claims to 'cleavage alone' are 'patentably distinct' from claims directed to Donor Template Integration." Broad Mot. 3 at 21. In Sigma Opposition 1, Sigma explains in detail why that Broad argument is

> The Sigma half of Count 1 requires Donor Template Integration but is generic with regard to the RNA configuration encompassing both sgRNA and dual-molecule RNA ("dualRNA") configurations; the Broad half of Count 1 requires sgRNA but does not require Donor Template Integration.

Broad Mot. 3 at 2; *id.* at 20 ("[T]the Broad half of Count 1 is directed to eukaryotic CRISPR-Cas9 systems that require sgRNA (also called 'chimeric RNA')."

Broad then argues that "the only claims that should remain designated as corresponding to Count 1 are those that are . . . limited to single molecule RNA ("sgRNA")." Broad Mot. 3 at 1; *id.* at 3 ("The only claims that should correspond to Count 1 are those that . . . are limited to use of sgRNA (and so correspond to the Broad half of Count 1)". But Broad nowhere evaluates or even mentions the pivotal legal inquiry, namely, whether Broad's so-called "generic" guide RNA claims would have been obvious in view of Count 1. The entirety of Broad's "non-correspondence" argument is set forth below:

> Broad's half of Count 1 requires that the CRISPR-Cas9 system use sgRNA. But Broad's generic claims that do not limit the RNA configuration to sgRNA are currently designated as corresponding to Count 1, even claims that do not use the term "guide RNA." ***These claims are indisputably not limited to sgRNA, and thus do not correspond to the Broad half of Count 1***.

Broad Mot. 3 at 3 (emphasis added).

Of course, the question on this motion is not whether the involved claims are "not limited

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incorrect. Sigma Opp'n 1 at 13-23. 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 1. *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.").

to sgRNA". Rather, the question is whether the involved claims would have been obvious in view of Count 1. *See* 37 C.F.R. § 41.207(b)(2); S.O. ¶¶ 208.3.1 & 208.3.2. On this motion, Broad does not even make such a contention, let alone bear its burden of establishing non-obviousness. Thus, for this reason alone, the Board may deny this part of Broad Motion 3.

B. Broad Fails To Consider What A POSITA Would Have Considered Obvious In The December 2012 Time Frame

Broad does not address how the prior art teachings—particularly those of Jinek (2012), which discusses an *in vitro*, extra-cellular CRISPR-Cas9 system using both a sgRNA and a dgRNA—would have impacted the obviousness inquiry for a POSITA in December 2012. Indeed, Broad's discussions regarding the prior art are facially inconsistent with any possible Broad contention that a "generic" guide RNA claim would have been non-obvious in view of a sgRNA claim:

> Jinek 2012 taught a POSA that "guide RNA" was a generic term covering systems with either sgRNA or dualRNA.

Broad Mot. 3 at 26 (citations omitted).

> Sigma's and ToolGen's applications, when considered in view of Jinek 2012 and other multiple references available at the time, provide substantial evidence that POSAs at the time of the invention understood "guide RNA" to include systems with either sgRNA or dualRNA.

Id. at 27.

Broad nowhere explains how these discussions of the prior art impact Broad's burden on this motion. Accordingly, Broad fails to carry its burden on this motion for this additional reason, and the Board may therefore deny this part of Broad Motion 3.

C. Broad Fails To Reconcile Its Arguments Here With Its Arguments In Broad Motion 2

In Broad Motion 2, Broad seeks to add Claims 52-54 of the '403 application to this interference:

> Claim 52 is generic as to RNA and so encompasses both dualRNA and sgRNA embodiments of CRISPR-Cas9 systems. Dependent claims 53 and 54 each separately specify either a dualRNA or sgRNA embodiment of claim 52 respectively.
>
> * * *
>
> [Claim 52] encompasses both dualRNA and sgRNA embodiments. Dependent claims 53 and 54 each specify either dualRNA or sgRNA embodiments of independent claim 52 respectively.
>
> * * *
>
> Claims 52-54 of the 403 application should be designated as corresponding to Proposed Count 3.

Broad Mot. 2 at 1, 2-3, 4.

As set forth above, Broad argues in Motion 2 that Broad's claims to so-called "generic" guide RNA (Claim 52), dgRNA/dualRNA (Claim 53), and sgRNA (Claim 54) should all be designated as corresponding to Broad's Proposed Count 3. As with Broad Motion 3 here, Broad fails to allege in Broad Motion 2 that the dependent sgRNA and dgRNA claims would have been obvious in view of a "generic" guide RNA claim. And while Count 1 and Proposed Count 3 are significantly different in many respects (*see* Sigma Opp'n 1 at 23-36), Broad nonetheless bears the burden of reconciling its two facially inconsistent arguments on these two Broad motions.

V. SIGMA DOES NOT DISPUTE BROAD'S REQUESTED CLAIM DE-DESIGNATION IN PARTS IV.A. THROUGH IV.D. OF MOTION 3

With respect to Parts IV.A – IV.D. of Broad's Motion 3, Sigma does not dispute Broad's request to de-designate four categories of claims as not corresponding to the count, namely, claims directed to SaCas9,[2] chimeric Cas9, two or more NLSs, and protein domains.[3]

[2] Broad P1 does not discuss SaCas9. It appears that Broad's first discussion of SaCas9 is Broad P8, filed March 15, 2013. Ex. 1522 ¶ [0189]; *see* Ex. 1518 (Cannon Supp'l Decl.) ¶ 36.

[3] As set forth in Sigma Motion 1 in *CVC v. Sigma* (Int'f No. 106,132), and as relevant to Broad's involved claims in this interference, Sigma also does not contest that claims directed to

However, with respect to Broad's claims reciting "guide RNA", Sigma concurs with the Board's detailed decision in the *CVC v. Broad* interference (No. 106,115) that those Broad claims are properly construed to be limited to sgRNA/chimeric RNA claims, as set forth in part below:

> Broad and CVC point to the portion of the Broad specification that reads:
>
> In aspects of the invention ***the terms "chimeric RNA", "chimeric guide RNA", "guide RNA", "single guide RNA" and "synthetic guide RNA" are used interchangeably and refer to the polynucleotide sequence comprising the guide sequence, the tracr sequence and the tracr mate sequence***. The term "guide sequence" refers to the about 20 bp sequence within the guide RNA that specifies the target site and may be used interchangeably with the terms "guide" or "spacer". The term "tracr mate sequence" may also be used interchangeably with the term "direct repeat(s)". An exemplary CRISPR-Cas system is illustrated in FIG. 1.
>
> (*E.g.*, '359 patent, Ex. 3011, 12:6–16; *see* Broad Motion 3, Paper 268, 24:2–5; *see* CVC Opp.3, Paper 591, 18:10–17.) The parties dispute whether this paragraph defines the term "guide RNA."

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the following subject matter should *not* be designated as corresponding to the count: (i) > 1 targeting RNA (aka "multiplexing"); (ii) one or more mutation(s) in the Cas9 RuvC/HNH domain(s); and (iii) a nickase for a creating a "nick" or a single stranded break in the target DNA. *See CVC v. Sigma*, Int'f No. 106,132, Sigma Mot. 1 (Paper 482) at 27-28. Sigma therefore proposes that the following Broad claims be designated as *not* corresponding to Count 1, based on at least the subject matter identified as subject matter i-iii above:

Broad Involved Patents/Applications	**Non-Corresponding Claims** [subject matter]
8,889,356	1-30[iii], 5[ii], 17[ii], 26-28[ii]
8,932,814	1-30[iii], 5[ii], 18[ii], 27-29[ii]
8,945,839	2-3[ii], 6[ii], 12-13[ii], 16[ii] , 22-23[ii], 26[ii]
8,993,233	2[i], 4[i], 5-6[ii]
9,840,713	2[iii], 5-6[ii], 19[ii], 30[ii], 39[i]
14/704,551	5[iii]
15/330,876	16[iii]

* * *

> We are persuaded by CVC's argument. Although the phrase "used interchangeably" could be interpreted as Broad argues, the phrase "refer to" indicates that each of the RNAs recited in this paragraph comprise three components: a guide sequence, a tracr sequence, and a tracr mate sequence. Thus, this paragraph of the Broad specification indicates that "chimeric RNA," "chimeric guide RNA," single guide RNA," as well as "guide RNA" include these three components.
>
> * * *
>
> Our review of the parties' arguments leads us to the conclusion that Broad's use of the term "guide RNA" in its involved claims is not a generic term, but is limited to a single-molecule RNA configuration of the guide sequence and tracrmate, which together make the crRNA, and the tracrRNA sequences. Although some dependent claims, such as claim 18 of the '359 patent, might indicate by claim differentiation that the term "guide RNA" is generic, that presumption is overcome by Broad's specification. The specification of Broad's involved patents, specifically the sentence providing that "guide RNA" and other terms "refer to the polynucleotide sequence comprising the guide sequence, the tracr sequence and the tracr mate sequence" ('359 patent, Ex. 3011, 12:6–10), limits the interpretation of the term. Broad fails to direct us to other uses of the term "guide RNA" in the specification that indicate a dual-molecule RNA configuration and we are not persuaded that the term was so clearly understood in the art to be a generic term that only a clear disavowal in the specification would define it to mean a single-molecule RNA configuration. Thus, we are persuaded that the broadest reasonable interpretation of Broad claim term "guide RNA" encompasses only a single-molecule RNA configuration.

Ex. 1528 (Decision on Motions ('115 Int'f)) at 27-28, 29-30, 32-33 (emphases added); *see* Ex. 1518 (Cannon Supp'l Decl.) ¶¶ 39-41. Thus, contrary to Broad's arguments on this motion, Broad's claims that recite "guide RNA" are properly construed as sgRNA claims. *Id.*

And a comparison of the Broad patents and applications involved in the *CVC v. Broad* interference (No. 106,115) and those involved in this interference reveals that they are essentially the same:

/ / /

/ / /

/ / /

Broad Involved Patents/Applications	
Int'f No. 106,115	**Int'f No. 106,133**
8,697,359	8,697,359
8,771,945	8,771,945
8,795,965	8,795,965
8,865,406	8,865,406
8,871,445	8,871,445
8,889,356	8,889,356
--	8,889,418*
8,895,308	8,895,308
8,906,616	8,906,616
8,932,814	8,932,814
8,945,839	8,945,839
8,993,233	8,993,233
8,999,641	8,999,641
9,840,713	9,840,713
14/704,551	14/704,551
--	15/330,876*

*Continuation of 14/104,977 (same specification as 8,895,308 and 8,865,406).

Thus, the Board's conclusions in in the *CVC v. Broad* interference (Int'f No. 106,115) regarding Broad's "guide RNA" claim recitals apply equally here. Sigma concurs that Broad's claim limitation "guide RNA" should be construed as limited to sgRNA. *Id.* Thus, Sigma requests that Broad's request to designate its "guide RNA" claims as not orresponding to Count 1 be denied.

However, with respect to the following claim limitations, on this motion Sigma does not contest Broad's request to designate those claims as not corresponding to Count 1: (a) SaCas9; (b) chimeric Cas9; (c) two or more NLSs; and (d) Cas9 protein fused to one or more protein domains.

The results of the foregoing discussions are summarized in the Claim Correspondence Table set forth below:

CLAIM CORRESPONDENCE TABLE

In Response to Broad Motion 3:		Sigma Does Not Contest Claims Do Not Correspond				FN 3	Claims Correspond		
Involved Broad Case	Currently Cor-respond	*Sa*Cas9	Chimeric Cas9	2 or More NLSs	Protein Domains	Nickase (i) & (ii)	"guide RNA"	alter gene expression[1]	insert template[2] via HDR[3]
8,867,359	1-20						1-20	1-20	
8,771,945	1-29						1-29	1-29	
8,795,965	1-30						1-30	1-30	
8,865,406	1-30	1-30					← see adjacent columns		
8,871,445	1-30			1-30			← see adjacent columns		
8,889,356	1-30					1-30	← see adjacent columns		
8,889,418	1-28		1-28				← see adjacent columns		
8,895,308	1-30	1-30					← see adjacent columns		
8,906,616	1-30						1-30		30
8,932,814	1-30			1-30		1-30	← see adjacent columns		
8,945,839	1-28					2-3, 6, 12-13, 16, 22-23, 26	← see adjacent columns 1-28	1, 4-5, 7-11, 14-15, 17-21, 24-25, 27-28	
8,993,233	1-43			7	1-43	2, 4, 5-6	← see adjacent columns		
8,999,641	1-28				1-28		← see adjacent columns		
9,840,713	1-41				18-19, 25, 29-30, 36	2 5-6, 19, 30, 39	← see adjacent columns 1-14, (8, 9, 16, 27)[4] (15, 17-26, 28-41)[5]	(1, 3-4, 7-17, 20-24, 26-28, 31-35, 37-38, 40-41)[6]	14
14/704,551	2, 4-18			9-11		5	← see adjacent columns (2, 4-18)[7]	13	14-15 16
15/330,876[8]	1, 16-21, 30-40	1, 16-21, 30-40		34	21	16	← see adjacent columns[9]		

NOTES TO CLAIM CORRESPONDENCE TABLE:

[1] Of Broad's 461 involved patent claims, 340 of those claims are directed to "cleavage plus altering gene expression" (or an analogous recital). *See* Ex. 1518 (Cannon Supp'l Decl.), Appx. C.

[2] Of Broad's 461 involved patent claims, 42 of those claims are directed to insertion of a "template." *Id.*

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

[4] The claims recite "a chimeric RNA" or "a guide sequence fused to the tracr sequence". *Id.* ¶ 43.

[5] The claims do not recite "RNA" (***not*** a recital of generic RNA). *Id.* ¶ 44.

[6] The claims recite "displays a phenotype or carries DNA to display a phenotype of the genetic modification", analogous to altering gene expression. *Id.* ¶ 45.

[7] The claims recite "a CRISPR-Cas system chimeric RNA (chiRNA)". *Id.* ¶ 46.

[8] Because Sigma does not dispute Broad's request that the '876 patent be removed from this interference (albeit for different reasons), the authorized Sigma Motion 2 to remove the '876 application from the interference is rendered moot by Broad Motion 3. *See* Sigma Notice Re: Sigma Motion 2 (to Remove Application 15/330,876 from the Interference) (Paper 52).

[9] Claim 35 also does not correspond to Count 1 because it recites "the vector comprises a U6 promoter operably linked to a nucleotide sequence encoding the chiRNA", which would not have been obvious in view of the count. Ex. 1518 (Cannon Supp'l Decl.) ¶ 47.

As set forth in the Claim Correspondence Table above, the Broad claims in the two right-hand columns labeled "Claims Correspond" should remain designated as corresponding to Count 1, and thus should remain involved in this interference. On this motion, Sigma does not contest that the Broad claims in the middle columns labeled "Claims Do Not Correspond" and "FN3" should be de-designated from corresponding to Count 1. Thus, for the reasons set forth above, the Board may deny in part Broad Motion 3 to designate claims as not corresponding to Count 1.

VI. CONCLUSION

For the foregoing reasons, Broad has failed to carry its burden on this motion, and accordingly Sigma respectfully requests that the Board deny in part Broad Motion 3.

Respectfully submitted,

Dated: March 16, 2022

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APPENDIX 1

LIST OF EXHIBITS CITED

Exhibit No.	Description
1518	Cannon Supp'l Decl.
1522	61-802,174 (Broad P8)
1528	106,115 [877] – Decision on Motions
1538	106,132 [482] – Sigma Mot. 1 (to Substitute Count)

APPENDIX 2

D6RESPONSE TO BROAD'S STATEMENT OF MATERIAL FACTS

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

Response: Denied

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

Response: Denied

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

Response: Admitted

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

Response: Admitted

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

Response: Lack sufficient information to admit or deny

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

Response: Denied

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

Response: Denied

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

Response: Lack sufficient information to admit or deny

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

Response: Lack sufficient information to admit or deny

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

Response: Lack sufficient information to admit or deny

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

Response: Admitted

12. During prosecution of the 204 application, Sigma argued that many aspects of the eukaryotic CRISPR-Cas9 system, including those associated with the Cas9 protein, were unpredictable. *See, e.g.*, Ex. 2074 (April 29, 2019 Applicant Remarks) at 19, 27-28; Ex. 2466 (October 17, 2017 Urnov Decl.) ¶¶ 15-17.

Response: Admitted

13. Broad determined that using an CRISPR-SaCas9 system in a eukaryotic cell provides a surprising combination of benefits not taught or suggested by the prior art, namely high efficiency and small size. *See* Ex. 2464 (Seeger Decl.) ¶¶ 193-94.

Response: Denied

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

Response: Denied

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

Response: Denied

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

Response: Lack sufficient information to admit or deny

17. Ex. 2060, 418 patent at 4:21-25 recites "[t]hese chimeric Cas9 proteins may have a higher specificity or a higher efficiency than the original specificity or efficiency of either of the individual Cas9 enzymes from which the chimeric protein was generated."

Response: Admitted

18. The 418 patent (Ex. 2060 at 83:45-52) recites benefits of a chimeric Cas9. *See also* Ex. 2464 (Seeger Decl.) ¶¶ 201-07.

Response: Admitted

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

Response: Admitted

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

Response: Lack sufficient information to admit or deny

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

Response: Admitted

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

Response: Admitted

23. During prosecution of the 204 application, Sigma argued that "when a protein is expressed as a fusion, such as with an NLS or epitope or chimeric tag, there are unexpected results, further confirming that there was no reasonable expectation of success as to a eukaryotic CRISPR-Cas9 system wherein the Cas9 includes one or more NLSs." Ex. 2074 (April 29, 2019 Applicant Remarks) at 27 (citing Ex. 2465 (April 29, 2019 Cannon Decl.) ¶¶ 76-77).

Response: Admitted

24. Broad determined that, unexpectedly, the use of two or more NLSs resulted in CRISPR-Cas9 systems with significantly improved localization to the nucleus, as compared to systems lacking two or more NLSs. *See generally* Ex. 2464 (Seeger Decl.) ¶¶ 202-21; Ex. 2001, Zhang B1, Figure 1B; Ex. 2201, Cong 2013, Figure 1A; Ex. 2793.

Response: Lack sufficient information to admit or deny

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

Response: Admitted

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

Response: Admitted

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

Response: Lack sufficient information to admit or deny

28. The 233 patent notes that there is a benefit to fusing functional domains to Cas9, as doing so can "to turn the Cas9/gRNA CRISPR system into a generalized DNA binding system [which] can execute functions beyond DNA cleavage." Ex. 2024 at 73:22-37; Ex. 2464, ¶ 239.

Response: Admitted

29. Broad's 713 patent (Ex. 2043), includes claims, including claims 15-26 and 28-41, that are not limited to single-molecule RNA and do not contain the term "guide RNA." *See* Ex. 2464 (Seeger Decl.) ¶¶ 114-18.

Response: Denied

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

Response: Admitted

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

Response: Denied

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

Response: Denied

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

Response: Denied

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

Response: Denied

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

Response: Admitted

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

Response: Admitted

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

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

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

Response: Denied

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

Response: Denied

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

Response: Denied

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

Response: Denied

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

Response: Admitted

42. Sigma moved to change the count in the 132 Interference. Ex. 2124.

Response: Admitted

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

Response: Denied

44. 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

45. 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

46. 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

47. 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

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

Response: Denied

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

Response: Denied

50. Sigma argued that only claims from CVC's applications that expressly recite donor template integration would correspond to its proposed Count. *Id*.

Response: Denied

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

Response: Lack sufficient information to admit or deny

SIGMA'S STATEMENT OF MATERIAL FACTS

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

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

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

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

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

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

58. The Board's conclusions in in the *CVC v. Broad* interference (Int'f No. 106,115)

regarding Broad's "guide RNA" claim recitals apply equally here. Ex. 1518 ¶¶ 39-41.

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

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

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

62. The claims identified in the orange highlighting in Sigma's Claim Correspondence Table (Sigma Opp'n 3 at 10) all recite chimeric Cas9. *Id.*

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

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

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

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

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

RNA". *Id*.

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

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

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

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

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

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

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

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

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

77. Claim 35 of Broad Application 15/330,876 recites "the vector comprises a U6 promoter operably linked to a nucleotide sequence encoding the chiRNA", which would not have

been obvious in view of Count 1. *Id.* ¶ 47.

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 3
(to Designate Claims as Not Corresponding to 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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