Filed on behalf of Junior Party
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER

Paper No. ___

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER

Applications 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374,
Junior Party,

v.

SIGMA-ALDRICH, CO., LLC
Application 15/456,204

Senior Party.

Patent Interference No. 106,132 (DK)
(Technology Center 1600)

CVC REPLY MOTION 3
(to change the Count)

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INTRODUCTION

The count in this interference should reflect the common invention defining multiple pending, related interferences - single-guide CRISPR-Cas9 systems useful in eukaryotic cells. *See* SO ¶ 208.2. CVC's half of Count 1 aligns with the counts in the interferences between CVC and Broad (Interference No. 106,115), Ex. 2560, 12-13; CVC and ToolGen (Interference No. 106,127), Ex. 2561 at 5-6; and Broad and ToolGen (Interference No. 106,126), Ex. 2562, 12-13; MF 1. CVC's halves of the counts and CVC's involved claims in those interferences are the same as in this one. Broad's and ToolGen's halves of the counts in those interferences are also commensurate in scope with CVC's half of the count here. However, that is not the case in this interference - Sigma's half of Count 1 is not aligned with CVC's half or any other parties' halves. Sigma argues that this misalignment is justified because it has generic-guide claims, ignoring that CVC also has such generic-guide claims involved in this interference. In the '115 interference, the PTAB specifically rejected the argument that alleging dual-guide proofs mandates a generic-guide count. *See Regents of the University of California v. The Broad Institute*, Int. No. 106,115 Paper 877 (Decision on Motions) at 39:22-40:8 (P.T.A.B. Sept. 10, 2020). There is no reason for the PTAB to treat Sigma—and Sigma alone—differently than CVC, Broad, and ToolGen. The PTAB should grant CVC Motion 3 and substitute a count aligned with the other interferences.

I. The Motion Will Not be Moot if the PTAB Grants Sigma's Substantive Motion 1

On page 3 line 5 through page 4 line 13, Sigma argues that CVC's substantive Motion 3 (to change the count) would be moot if the Board grants Sigma's Substantive Motion 1 (to change the count). The reply is that CVC's Motion 3 will not be moot because whether or not the scope of the interference is limited to cleavage *plus* donor integration (as Sigma requests in its Motion 1) is a separate issue that does not impact whether or not the Count should recite single-

guide RNA. Sigma's Proposed Count 2 propagates the mismatched guide RNA format: CVC's half of the count is directed to *single-guide* RNA, while Sigma's half of its proposed count is directed to *generic guide* RNA (encompassing both dual-molecule and single-molecule RNAs). CVC's Motion 3 proposes to change Sigma's half of the count so that it too recites a single-molecule RNA, making the CVC and Sigma halves of the count consistent.

Accordingly, the relief requested in CVC's Motion 3 would not be mooted by the grant of Sigma's Motion 1 as Sigma argues. It would, however, be mooted by any disposition of Sigma's Motion 1 that results in a judgment in favor of CVC, as explained in CVC Opposition 1. If the PTAB does not enter such judgment at this time, then it should grant CVC's Motion 3 to substitute the count *regardless* of how it decides Sigma's Motion 1.

II. The PTAB Should Exercise its Discretion to Change the Scope of the Count to Better Reflect the Counts in the Related Interferences.

The PTAB has discretion to substitute the count in an interference. *See Hitzeman v. Rutter*, 243 F.3d 1345, 1359 (Fed. Cir. 2001) (finding no abuse of discretion in narrowing the scope of a count). Sigma identifies no contrary authority. Sigma cites no authority refuting that general principles of consistency, fairness, and clarity justify exercising that discretion—especially where the Federal Circuit has so recently endorsed following these general principles in administering Patent Office proceedings. *See In re Vivint, Inc.*, 14 F.4th 1342, 1351 (Fed. Cir. 2021) (supporting the general proposition that the PTAB should not act arbitrarily and capriciously across multiple proceedings).

On page 6 line 11 through page 10 line 4, Sigma argues that the count here should differ from the counts in the related interferences because Sigma is the only party to allege proofs relating to both single-guide and dual-molecule RNA. Sigma is wrong. Broad also alleged such proofs (which CVC disputed), but the PTAB did not find Broad's allegations a sufficiently

compelling reason to broaden the '115 interference count beyond single-guide RNA. *See* Ex. 2400, 36:6-8. Broad even alleged that its dual-molecule proofs were earlier than its single-guide proofs, *id*., something Sigma does not even allege. CVC also has claims directed to both single-guide and dual-molecule RNAs in all pending interferences, yet its half of the count has always been limited to single-guide. Ex. 2560, 14-16; Ex. 2561, 7-10; *see also* Ex. 2655, 109:16-117:19 (admitting that CVC has involved dual-guide claims and not disputing that CVC has involved generic-guide claims). Sigma's entire rebuttal to CVC's argument for consistency and fairness across proceedings is thus based on the false premise that it is uniquely situated.

The PTAB should treat similarly situated parties similarly across multiple related proceedings. *See Vivint*, 14 F.4th at 1351. Such consistency is only achieved here by granting CVC's motion, which presents a count where Sigma's half (Sigma claim 33) recites limitations that match the single-guide aspect of CVC's half of the count in this interference as well as CVC's, Broad's, and ToolGen's halves of the counts of similar related interferences. 37 C.F.R. § 41.1(b). Administering the interference with CVC's proposed count will provide the public a clearer record as to who was first to invent the common subject matter involved in these related interferences among the multiple parties involved.

Substituting CVC's proposed count will also limit the inherent prejudice to CVC that results from arbitrarily giving Sigma special treatment. Sigma requested this interference, which the PTAB declared long after having declared other interferences involving all of the same CVC applications and claims. CVC is litigating materially the same count for all of its involved claims across those other interferences. Yet the count in this interference (not limited to sgRNA) is the only one different from the other interferences (limited to sgRNA). Any arbitrary and undeserved treatment afforded to Sigma in this interference necessarily prejudices CVC. CVC has sufficiently shown why all of these interferences should be administered consistently. Sigma

offered no compelling reason or authority to administer this interference differently. The PTAB should therefore substitute Sigma's claim 31 with claim 33 of Sigma's '204 Application in the count.

III. Sigma Fails to Establish That its Best Proofs Fall Outside the Scope of the Count.

For all its accusations that CVC is attempting to hamstring Sigma by excluding Sigma's best proofs, *see, e.g.*, Paper 708, Sigma Opp. at 5:8-10, Sigma failed to make a proffer that its best proofs fall outside the scope of CVC's proposed count. To the contrary, Sigma agrees that the same gel evidencing its alleged invention includes lanes for both single-guide and dual-molecule RNAs. Indeed, Sigma's counterarguments justifying its "outlier" treatment rely on "both" its alleged single-guide and dual-guide proofs equally. *Id*. at 11:13-12:17. Because it need only show one embodiment within the scope of the count to prevail on priority, Sigma cannot be prejudiced by narrowing the count to single-guide RNA unless doing so would *exclude* its best proofs. *See Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (C.C.P.A. 1975). Sigma's repeated assertion that its proofs include *both* single-guide and dual-guide RNA fails to establish that its *best* proofs are confined to dual-guide RNA. Paper 708 at 11:13-12:17.

Sigma does not allege that its single-guide proofs relying on FACS experiments may be inadequate. Sigma's only purported difference between its single-guide and dual-molecule proofs is that it has later, confirmatory PCR evidence regarding the dual-molecule experiments that it does not have for the single-guide experiments. Paper 708, Sigma Opp at 7:11-24; MF 63. Sigma offers no evidence that PCR evidence is necessary. Indeed, Sigma's own expert dismisses Sigma's PCR data as merely "further confirmation" and does not rely on it. Ex.1080, ¶ 79 n.1. Sigma also does not allege that its alleged date of invention would be earlier or better-corroborated for its dual-guide proofs than its single-guide proofs. MF 64. Sigma thus has not

established that it will suffer any prejudice if the Board substitutes CVC's Proposed Court 2 for current Count 1.

IV. Substituting the Count Will Streamline the Issues in the Interference.

Sigma's involved application is ambiguous as to the scope of the "guide RNA" recited in Sigma's claim 31, a claim construction the PTAB may justifiably avoid by defining Sigma's half of the count as claim 33. Specifically, Sigma's Claim 31 recites "guide RNA" without specifying whether the guide RNA is a single molecule (with three regions) as described in the specification. Claim 33 depends from claim 31 and specifies that the guide RNA is a single molecule. Changing the scope of the count to recite Sigma's claim 33 instead of Sigma's claim 31 will clarify that the common, interfering subject matter is a sgRNA CRISPR-Cas9 system in a eukaryotic cell. It will also simplify the interference by focusing on who was the first to invent sgRNA CRISPR-Cas9 in a eukaryotic cell, and eliminate any dispute over whether Sigma's alleged dual-guide proofs actually satisfy Sigma's own definition of "guiding RNA" and fall within the scope of a count that recites "guide RNA."

Sigma's argument that the term "guide RNA" used in claim 31 includes both single-guide and dual-guide RNAs is based on a description of two-molecule "guiding RNA." Paper 708, Sigma Opp at 12-13 (citing Sigma's P1 at ¶¶ [0019], [0023]). Specifically, Sigma's involved application defines "the guiding RNA" as comprising a first single-stranded region, "a second internal region that forms a stem loop structure," and a third single-stranded region. Ex. 2026, ¶¶ [0021], [0019]; MF 9; *Cf.* Ex. 2031, Fig. 5A (annotated) (cited in Sigma's '204 application); Ex. 2549, ¶ 99; Ex. 2585, ¶¶ [0071]-[0072]. This structure as described is necessarily a single-guide RNA because the crRNA and tracrRNA are physically linked by loop to form a "stem loop structure." MF 9. When so linked, they must constitute a single molecule. MF 65.

At best, Sigma points to *some* intrinsic evidence that is confusing in view of the definition of guide RNA in the application. Sigma points to ¶ [0023] of its specification, which notes that each "guiding RNA" can alternatively comprise two molecules, each of which includes a portion of the stem from the previously described stem loop structure. Paper 708, Sigma Opp at 13:22-28. This paragraph, however, conflicts with the overall weight of the intrinsic evidence regarding the scope of the term "guide RNA," and therefore does not establish that a POSA would construe the term "guide RNA" more broadly.

Sigma argues, falsely, that "CVC and its expert (Dr. Scott Bailey) fail to consider the [language of] subsequent ¶ [0023], which unambiguously explains that the guide RNA—including a 'stem loop'—can be a dual-molecule guide RNA." *Id*. at 13:20-22. Therein lies Sigma's problem: There is no physically possible guide-RNA structure that is both (a) a dual-molecule guide RNA and (b) a guide RNA with "a second internal region that forms a stem loop structure", i.e., comprising a linker loop as defined by Sigma's specification. *See* Ex. 1082, 85:4-86:6 (explaining that the only way a guide RNA can comprise two molecules is if it does *not* have an intact stem loop in the second region); MF 66.

Sigma's application—as Sigma urges the PTAB to read it here—thus contradicts itself. Sigma's expert did not consider that contradiction. *See* Ex.2655, 119:16-127:13 (admitting that she offered no analysis of the structure of the single-guide or dual-guide RNA, and refusing to provide that analysis during her cross-examination); MF 67. CVC's expert Bailey did consider the contradictory language. According to Bailey, a POSA would resolve the inconsistency in Sigma's specification by reading the three-region single-molecule definition of "guiding RNA" to describe the claimed "guide RNA" and treating the inadequately explained dual-molecule as another way of describing the single-guide structure (which does "comprise two separate molecules" that are then joined with a linker loop), or an unclaimed alternative. *See* Ex 2549, ¶¶

98, 102 (explaining how a POSA would interpret Sigma's "ambiguous" and "inconsistent" descriptions of the guiding RNA).

The intrinsic evidence Sigma cites only supports construing the guide RNA recited in claim 31 as single-guide RNA. Substituting the count to expressly recite that which Sigma is properly limited to through claim construction anyway is yet another reason why Sigma is not prejudiced by this Motion. The economy of avoiding this dispute and focusing the issues for the priority phase on the common inventive subject matter further supports ensuring Sigma's half of the count is Sigma claim 33.

V. Granting CVC's Motion 3 Will Not Impact the Designation of Claims, Priority Benefit, and Patentability Over the Art.

Ordinarily, substitution of a count would include an assessment of (a) whether the count is patentable over prior art, (b) which of each party's claims correspond to the count, and (c) each party's accorded benefit. But, the substitution of CVC's proposed count has no impact on any of these analyses. Sigma does not dispute that the substitution of the count has no impact. Sigma also does not dispute that the analysis and relief requested in CVC Substantive Motion 4 to Add the Claims of Sigma Patent No. 10,731,181 ("the '181 patent) and No. 10,745,716 ("the '716 patent") to this Interference are equally applicable if Count 1 is substituted with CVC's proposed count. These additional considerations all weigh in favor of granting CVC's Motion 3.

VI. Conclusion

The PTAB should grant CVC's Motion 3 or ensure that whatever count it may substitute is limited to a sgRNA CRISPR-Cas 9 system, consistent with multiple, related, pending interferences.

Respectfully submitted,

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APPENDIX A: EXHIBIT LIST

Exhibit No.	Description
1080	Cannon Supp'l Decl.
1082	Bailey Tr. 01/24/22
2006	U.S. Appl. No. 14/685,504, filed April 13, 2015
2007	U.S. Appl. No. 15/138,604, filed April 16, 2016
2009	Prov. Appl. No. 61/652,086, filed May 25, 2012
2010	Prov. Appl. No. 61/716,256, filed October 19, 2012
2011	Prov. Appl. No. 61/757,640, filed January 28, 2013
2015	U.S. Appl. No. 13/842,859, filed March 15, 2013
2017	U.S. Patent No. 10,731,181
2019	U.S. Patent No. 10,745,716
2023	Krebber, H. and Silver, P.A., "Directing Proteins to Nucleus by Fusion to Nuclear Localization Signal Tags," *Methods in Enzymology* 327: 283-296 (2000)
2026	Prov. Appl. No. 61/734,256, filed December 6, 2012
2031	Jinek, M., *et al*., "A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity," *Science* 337(6096):816-821, with Supplementary Information (2012)
2221	Lange, A., *et al*., "Classical Nuclear Localization Signals: Definition, Function, and Interaction with Importin α," *J. Biol. Chem.* 282(8): 5101–5105 (2007)
2348	Doudna, J.A., and Lorsch, J.R., "Ribozyme catalysis: not different, just worse," *Nature Structure & Molecular Biology* 12(5):395-402 (2005)
2400	Decision on Motions 37 C.F.R. § 41.125(a), *The Regents of the University of California v. The Broad Institute, Inc.,* Patent Interference No. 106,115, Paper 877, (September 10, 2020)
2543	Declaration of Yannick Doyon, Ph.D.
2548	Declaration of Samuel Sternberg, Ph.D.
2549	Declaration of Scott Bailey, Ph.D.
2550	van der Aa, M.A.E.M., *et al*., "The Nuclear Pore Complex: The Gateway to Successful Nonviral Gene Delivery," *Pharmaceutical Research* 23(3): 447- 459 (2006)
2560	Declaration 37 C.F.R. § 41.203(b), Count and claims of the parties, *The Regents of the University of California v. The Broad Institute, Inc*., Patent Interference No. 106,115, Paper 1, (June 24, 2019)
2561	Declaration 37 C.F.R. § 41.203(b), Count and claims of the parties, *The Regents of the University of California v. ToolGen, Inc.,* Patent Interference No. 106,127, Paper 1, (December 14, 2020)
2562	Declaration 37 C.F.R. § 41.203(b), Count and claims of the parties, *The Broad Institute, Inc. v. ToolGen, Inc*., Patent Interference No. 106,126, Paper 1, (December 14, 2020)
2585	U.S. Appl. No. 15/456,204 with current claims appended
2655	Deposition Transcript of Paula Cannon, Ph.D., (March 28, 2022)

APPENDIX B: STATEMENT OF MATERIAL FACTS

CVC'S STATEMENT OF MATERIAL FACTS AND SIGMA'S RESPONSES

1. CVC's half of Count 1 aligns with the scope of the counts in multiple ongoing interferences, including interferences between: CVC and Broad (Interference No. 106,115), Ex. 2560 at 12-13; CVC and ToolGen (Interference No. 106,127), Ex. 2561 at 5-6; and Broad and ToolGen (Interference No. 106,126), Ex. 2562 at 12-13.

Response: Denied

2. In each of these Interferences 106,115, 106,127 and 106,126, both halves of the count recite single-guide ("sgRNA") CRISPR-Cas9 systems, whether or not the parties have claims that are generic as to the format of the guide RNA (i.e., "generic-guide" claims). Ex. 2560, 12-13; Ex. 2561 at 5-6; Ex. 2562, 12-13; *see* Ex. 2400, 31-33.

Response: Admitted

3. CVC has involved claims directed to both generic guide RNA and single-guide RNA embodiments. *See, e.g.*, CVC Application Nos. 15/947,700; 15/947,718; 15/981,808; 15/981,809 (reciting CRISPR-Cas9 systems in eukaryotic cells that are not limited to single-molecule RNA).

Response: Denied

4. Count 1 in this Interference is defined as CVC Application 15/981,807, claim 156 or Sigma Application 15/456,204 claim 31 (colloquially referred to as a "McKelvey count"). *See* Paper 1, Declaration of Interference, 5.

Response: Admitted

5. CVC claim 156 recites "a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA" and then goes on to define the three essential components of a single-molecule guide RNA. *See* Paper 1, Declaration of Interference, 5.

Response: Denied

6. Sigma's claim 31 recites "a guide RNA or DNA encoding the guide RNA, wherein the guide RNA comprises a first region that is complementary to a target site in the chromosomal sequence . . . and a second region that interacts with the CRISPR-Cas type-II protein, and wherein the guide RNA comprises a crRNA and a tracrRNA." *See* Paper 1, Declaration of Interference, 6.

Response: Denied

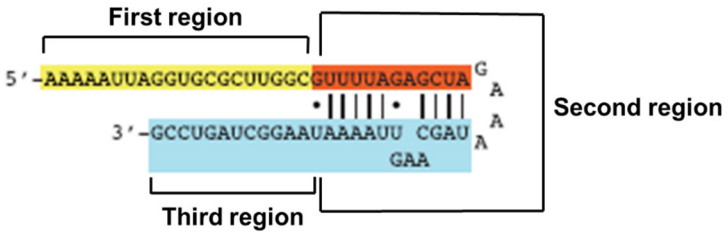
7. The PTAB construed the term "guide RNA" in the '115 Interference to refer to sgRNA. Ex. 2400, 31-33.

Response: Denied

8. Claim 33 of Sigma's '204 Application adds the limitation "wherein the guide RNA is a single molecule." Ex. 2585, 104.

Response: Admitted

9. Sigma's P1 application defines "guide RNA" as comprising a first region, "a second internal region that forms a stem loop structure," and a third region. Ex. 2026, ¶¶ [0021], [0019]. These regions can be illustrated according to the figure below:



Jinek, *Science* 2012 Fig. 5A (annotated) (cited in Sigma's '204 application). Ex. 2549, ¶ 99. The "loop" of claim 31 refers to the linker loop in the stem-loop region shown in purple in the diagram above, which joins the crRNA and the tracrRNA. Ex. 2549, ¶¶ 98-99, 101.

Response: Denied

10. Sigma's '204 application discloses data from a single experiment: a gel that has lanes for both single-guide RNA and dual-guide RNA molecules. Ex. 2585, 11-75; Ex. 2549, ¶103.

Response: Denied

11. CVC's co-pending motion for priority benefit (CVC's Substantive Motion 1) supports priority benefit based on CVC's half of the count (claim 156 of CVC's '807 Application).

Response: Denied

12. Application No. 61/652,086 ("P1"), filed on May 25, 2012, lists Martin Jinek, Jennifer Doudna, Emmanuelle Charpentier, and Krzysztof Chylinski as co-inventors. Ex. 2009, 195.

Response: Admitted

13. Application No. 61/716,256 ("P2"), filed on October 19, 2012, lists Jinek, Doudna, Charpentier, Chylinski, and James Harrison Doudna Cate as co-inventors. Ex. 2010, 277.

Response: Admitted

14. CVC's P1 describes CRISPR-Cas systems comprising a) a Cas9 protein and b) a single molecule DNA-targeting RNA. Ex. 2009, ¶¶ [00248]-[00251], Figs. 1-3; Ex. 2543, ¶¶ 90-242.

Response: Admitted

15. CVC's P1 describes a sgRNA comprising i) a targeter RNA capable of hybridizing with a target sequence in the target DNA and ii) an activator-RNA capable of hybridizing with the targeter RNA to form a double-stranded duplex, wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides. Ex. 2009, ¶¶ [0079], [00119], [00248], Figs. 1, 3, 9; Ex. 2543, ¶¶ 90-95, 106-108, 175-179, 223.

Response: Admitted

16. CVC's P1 describes a sgRNA capable of forming a complex with Cas9 and thereby targeting the Cas9 protein to the target DNA molecule. Ex. 2009, ¶¶ [0046], [0048], [0076], [0089], [00155]-[00156], [00248]-[00251], Figs. 1, 3; Ex. 2543, ¶¶ 90-95, 110-112, 180, 223.

Response: Admitted

17. CVC's P1 describes CRISPR-Cas9 systems capable of cleaving or editing target DNA or modulating transcription of at least one gene encoded by the target DNA. Ex. 2009, ¶¶ [00155]-[00159], [00248]-[00251], Figs. 3, 4; Ex. 2543, ¶¶ 90-95, 113-114, 180, 223.

Response: Denied

18. CVC's P1 describes target cells including a fish, a human, and a fruit fly cell, and that a target cell may be "embryonic." Ex. 2009, ¶¶ [00165], [00216], [00218], [00050]-[00052], [00174].

Response: Denied

19. CVC's P1 describes making and using a single-molecule DNA-targeting RNA and a Cas9 RNA. Ex. 2009, ¶¶ [00173], [00248]; Ex. 2543, ¶¶ 90-95, 100, 170-173, 222.

Response: Denied

20. CVC's P1 describes that Cas9 can be delivered into a eukaryotic cell "as a polypeptide," as a nucleic acid encoding Cas9, or in a pre-formed RNP complex. Ex. 2009, ¶¶ [00120], [00126]-[00128], [00167]-[00172], [00177]-[00178]; Ex. 2543, ¶¶ 92, 96-99, 115, 132-135, 140.

Response: Denied

21. CVC's P1 describes that the sgRNA can be delivered into a eukaryotic cell "directly as RNA" or as a nucleic acid "comprising a nucleotide sequence encoding a subject DNA-targeting RNA." Ex. 2009, ¶¶ [00120], [00167], [00170]-[00173], [00177]; Ex. 2543, ¶¶ 92, 96-99, 137-140.

Response: Denied

22. CVC's P1's working example describes incubating a recombinant Cas9 protein with the sgRNA to make an RNP complex. Ex. 2009, ¶¶ [00248]-[00251]; Ex. 2543, ¶¶ 92, 96-99, 137-140.

Response: Admitted

23. CVC's P1's working example describes a sgRNA complexed with a Cas9 protein cleaving a target DNA. Ex. 2009, ¶¶ [00248]-[00251], Fig. 3A; Ex. 2543, ¶¶ 92, 96-99, 137-140.

Response: Admitted

24. CVC's P1 describes microinjection as a method of delivering Type II CRISPR-Cas9 into a cell. Ex. 2009, ¶¶ [0039], [00154], [00173]-[00175]; Ex. 2543, ¶¶ 141-146, 225.

Response: Denied

25. By May 25, 2012, microinjecting protein, RNA, or RNPs into eukaryotic cells were well-known, routine laboratory techniques. Ex. 2009, ¶ [00173]; Ex. 2543, ¶¶ 66-72.

Response: Denied

26. CVC's P1 describes transfection as a method for delivering Type II CRISPR-Cas9 systems into a cell. Ex. 2009, ¶¶ [00129], [0039], [00154], [00173-175], [00177]; Ex. 2543, ¶¶ 199-200.

Response: Denied

27. By May 25, 2012, transfecting proteins, RNA, and RNPs into eukaryotic cells human cell lines were well-known, routine laboratory techniques. Ex. 2009, ¶ [00173]; Ex. 2543, ¶¶ 73-82.

Response: Denied

28. By May 25, 2012, the art disclosed that a PAM must be adjacent to the target sequence for Type II CRISPR-Cas9 systems to cleave target DNA. Ex. 2543, ¶¶ 54-64, 249-259.

Response: Denied

29. CVC's P1 discloses a PAM sequence adjacent to the target in Target DNA A ("GGG"), Target DNA B ("GGG"), and Target DNA C ("TGG"). Ex. 2009, Fig. 3C; Ex. 2543, ¶¶ 249-259.

Response: Denied

30. CVC's P1 describes "replac[ing] a codon with a codon encoding the same amino acid." Ex. 2009, ¶ [0033]; Ex. 2543, ¶¶ 190, 285-289.

Response: Denied

31. CVC's P1 describes peptide that can be added to Cas9, including a polypeptide that facilitates traversing an organelle membrane. Ex. 2009, ¶ [00115]; Ex. 2543, ¶¶ 120-121, 277-284.

Response: Denied

32. All of the disclosures in CVC's P1 are in P2. Ex. 2009; Ex. 2010; Ex. 2543, ¶¶ 243-245.

Response: Admitted

33. CVC's P2 describes PAMs and cites Sapranauskas (Ex. 2132), Deveau (Ex. 2125), Mojica (Ex. 2127), Makarova (Ex. 2130), and Wiedenheft (Ex. 2134), which discuss PAMs in CRISPR-Cas systems. Ex. 2010, ¶¶ [00103], [00350]-[00352], [00359]; Ex. 2543, ¶¶ 243-245.

Response: Denied

34. CVC's '859 application was filed within 12 months of the filing dates of P1 and P2, and makes specific reference to CVC's P1 and P2 applications. Ex. 2015, 5.

Response: Admitted

35. CVC's '504 application was filed during the '859 application's pendency and makes specific reference to CVC's '859, P1, and P2 applications. Ex. 2006, 4-5.

Response: Admitted

36. CVC's '604 application was filed during the '504 application's pendency and makes specific reference to CVC's '504, '859, and P1 and P2 applications. Ex. 2007, 356-360.

Response: Admitted

37. Target DNA A, disclosed in Figure 3C of CVC's P1 and P2, is a non-natural target and P1 and P2 disclose Target DNA A as including a PAM. Ex. 2009, Fig. 3C; Ex. 2543, ¶¶ 255-259.

Response: Denied

38. CVC's P1 describes and enables modification of a chromosomal sequence in a eukaryotic cell by integrating a donor sequence, which occurs when the cell's own homology-directed repair process repairs DNA cut by a nuclease, whether a sgRNA-CRISPR-Cas9, a ZFN, or a TALEN. Ex. 2009, ¶¶ [0058], [0059], [00157], [00189]-[00193], Fig. 4, claims 77, 88, 99; Ex. 2543, ¶¶ 126-128, 303.

Response: Denied

39. The differences between claim 1 of the '181 or '716 patent and Sigma's half of Count 1, are that the claims specify which Cas9 protein to use (from *S. pyogenes*), where to locate the DNA-targeting region within the guide RNA (at the 5' end), and which NLS to use (C-terminal SEQ ID NO: 1 or SEQ ID NO: 2). Ex. 2017, 71:34-72:39; Ex. 2019, 71:14-51; Ex. 2549, ¶¶9, 30.

Response: Denied

40. Jinek 2012 discloses *in vitro* experiments that used *S. pyogenes* Cas9 to cleave target DNA, including GFP, a sequence from a eukaryote. Ex. 2031, Figs. 1-5; Ex. 2549, ¶¶47, 57.

Response: Denied

41. Jinek 2012 discloses *in vitro* experiments using guide RNAs comprising a DNA-targeting region at the 5' end that base pairs with a target site in the chromosomal sequence. Ex. 2031, Figs. 1E, 3C, 5B; Ex. 2549, ¶¶34-37.

Response: Denied

42. The natural location for the DNA-targeting region of a guide RNA in a CRISPR system is at the 5' end. Ex. 2031, 818; Ex. 2549, ¶34.

Response: Denied

43. Krebber 2000 discloses methods of using the NLS listed as SEQ ID NO: 1. Ex. 2023, 285; Ex. 2549, ¶¶39.

Response: Denied

44. Krebber 2000 discloses attaching an NLS at either the N-terminus or C-terminus of the tagged protein. Ex. 2023, 289-290; Ex. 2549, ¶39.

Response: Denied

45. Lange 2007 discloses methods of using the NLS listed as SEQ ID NO: 2. Ex. 2221, 3; Ex. 2549, ¶39.

Sigma did not respond to CVC's MF 45, and therefore this MF should be deemed admitted.

46. Before December 2012, the SV40 NLS was the most commonly used NLS peptide for tagging proteins. Ex. 2550, 451-452; Ex. 2023, 285; Ex. 2549, ¶39.

Response: Denied

47. Before December 2012, the SV40 NLS was "the model" for NLSs. Ex. 2348, 478; Ex. 2549, ¶39.

Response: Denied

48. All the disclosures of CVC's P1 application appear in CVC's P2 application, and in CVC's U.S. Provisional Application No. 61/757,640, as well as in CVC's U.S. Appl. No. 13/842,859. Ex. 2009; Ex. 2010; Ex. 2011; Ex. 2015; Ex. 2543, ¶¶ 219, 243-245, 316.

Response: Denied

49. Expressing a dual molecule guide RNA would require multiple promoters. Ex. 2549, ¶100.

Response: Denied

50. Sigma has not requested de-designating any claims from this proceeding. *See* Order Authorizing Motions and Setting Times 37 C.F.R. §§ 104(c) and 121.

Response: Denied

CVC'S RESPONSES TO SIGMA'S STATEMENT OF MATERIAL FACTS

51. CVC's Proposed Count 2 includes CVC Claim 156, which (for purposes of this interference) is substantively the same as Claim 156 of Sigma's Proposed Count 2.

Response: Denied.

52. In CVC's Motion 3, CVC does not contend that changing the count would better conform to CVC's proofs of invention.

Response: Admitted.

53. Sigma's proofs of invention, as set forth in Sigma P1, are directed to the use of both sgRNA and dgRNA in a CRISPR-Cas9 system. Ex. 1080 ¶¶ 76-79.

Response: Admitted that Sigma's P1, discloses both sgRNA and dgRNA in a CRISPR-Cas9 system, otherwise denied.

54. Sigma's proofs of invention, as set forth in Sigma P1, are not identical for both types of guide RNAs (sgRNA and dgRNA). *Id.*

Response: CVC does not have adequate information regarding Sigma's proofs of invention to admit or deny.

55. In opposition proceedings before the European Patent Office ("EPO"), CVC's exclusive licensee Intellia Therapeutics (via Intellia's European Patent Attorney George Schlich) challenged Sigma's European applications related to CRISPR-Cas9. Exs. 1085-86.

Response: Admitted that attorney George Schlich participated in EPO proceedings involving Sigma's European patent applications, otherwise denied.

56. In EPO proceedings, Intellia criticized Sigma's experimental data using sgRNA (Lanes B, C, & D), arguing that Sigma's lack of PCR confirmations in those lanes demonstrated lack of successful donor integration via HDR. *Id.*

Response: Admitted that attorney George Schlich participated in EPO proceedings involving Sigma's European patent applications, otherwise denied.

57. In its pertinent disclosure, CVC P3 demonstrated cleavage in eukaryotic cells using only a sgRNA. Ex. 1080 ¶ 77.

Response: Admitted that CVC P3 demonstrated cleavage in eukaryotic cells using a sgRNA.

58. In its pertinent disclosure, Broad P1 demonstrated cleavage in eukaryotic cells using only a sgRNA. *Id.*

Response: Denied.

59. In its pertinent disclosure, ToolGen P1 demonstrated cleavage in eukaryotic cells using only a sgRNA. *Id.*

Response: Admitted that ToolGen's P1 discloses only sgRNA.

60. The term "loop" is recited nowhere in Sigma's patent claims, including Sigma claim 31. *Id.* ¶ 81. A2-12.

Response: Admitted that the word "loop" does not appear in Sigma's patent claims, but denied that Sigma's claim 31, as properly construed, covers a guide RNA lacking a loop of a "stem loop structure."

61. CVC's inserted "Fig. 5A [sic] (annotated)" figure is adapted from Jinek (2012)'s illustration of a "chimera A" sgRNA discussed by Jinek (Ex. 2031, Fig. 5B), and is not a figure from Sigma P1. *Id.*

Response: Admitted.

62. Sigma P1 ¶ [0023] explains that the guide RNA—including a "stem loop"—can be a *dual-molecule* guide RNA. *Id.*

Denied.

CVC'S ADDITIONAL STATEMENT OF MATERIAL FACTS IN REPLY

63. Sigma's only purported difference between its single-guide and dual-molecule proofs is that it has PCR evidence confirming the dual-molecule experiments that it does not have for the single-guide experiments. Paper 708, Sigma Opp. at 7:11-24.

64. Sigma also does not allege that its alleged date of invention would be earlier for its dual-guide proofs than its single-guide proofs. Paper 708, Sigma Opp at 7:11-24.

65. Ex. 2585, ¶¶ [0071]-[0072] describes a single molecule of RNA in which the crRNA and tracrRNA are physically linked by a loop to form a "stem loop structure."

66. There is no physically possible guide RNA structure that is both (a) a dual-molecule guide RNA and (b) a guide RNA with a stem-loop in the second region as defined by Sigma's specification. *See* Ex. 1082, 85:4-86:6 (explaining that the only way a guide RNA can comprise two molecules is if it does *not* have an intact stem loop in the second region).

67. Sigma's expert offered no analysis of the structure of the single-guide or dual-guide RNA purportedly disclosed in Sigma's involved application. Ex. 2655, 119:16-127:13.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **JUNIOR PARTY'S REPLY MOTION 3,** is being filed via the Interference Web Portal by 8:00 PM Eastern Time on April 7, 2022, pursuant to the Order Authorizing Motions and Setting Times ("Order"; Paper 30), and thereby served on the attorney of record for the Senior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to the Order, the foregoing was also served via email by 11:00 PM Eastern Time on counsel for the Senior Party at:

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