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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 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)

SIGMA OPPOSITION TO CVC MOTION 3 (to Change the Count)

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OPPOSITION TO CVC MOTION 3
(to Change the Count)

I. INTRODUCTION

CVC seeks to change current Count 1 to CVC Proposed Count 2, but not (as would normally be expected) to better conform the count to CVC's proofs of invention. Indeed, CVC's half of the two-part "McKelvey" count would remain the same. Instead, CVC's sole purpose is to narrow ***Sigma's*** half of the count to limit ***Sigma's*** proofs of invention, which (not surprisingly) would significantly prejudice Sigma. CVC cites no authority to support a request to the Board to change the count solely to prejudice an adversary.

CVC's makeweight "inconsistency" and "public interest" rationales are self-serving and find no support in the law. Indeed, CVC has long been aware that Sigma's proofs of invention encompass both single-molecule guide RNA ("sgRNA") and dual-molecule guide RNA ("dgRNA"), as revealed by CVC's challenges to Sigma's sgRNA proofs made by CVC's exclusive licensee in EPO opposition proceedings. Moreover, Sigma's more comprehensive sgRNA ***and*** dgRNA proofs of invention are in distinct contrast to the sgRNA-only proofs of the other parties involved in other co-pending CRISPR-Cas9-related interferences. And the disclosure of Sigma P1, including key teachings that CVC overlooks, fully support Sigma's claimed "guide RNA" to generically encompassing both sgRNA and dgRNA. Thus, it is perfectly reasonable and entirely appropriate for the Board to define Sigma's half of the count in this interference to encompass Sigma's proofs of invention (*i.e.*, both sgRNA and dgRNA), as shown in Sigma P1. Accordingly, because CVC's motion fails to provide a legally cognizable basis to change the count, and changing the count as CVC requests would unfairly prejudice Sigma, CVC fails to carry its burden on CVC Motion 3.

II. PRECISE RELIEF REQUESTED

Sigma requests that the PTAB deny CVC Motion 3, in which CVC requests that the Board exercise its discretion to substitute CVC Proposed Count 2 for current Count 1.

III. LEGAL STANDARDS

In a motion to change the count, the identification of the parties' interfering applications is conducted using a two-way obviousness test, namely, whether each Sigma application contains at least one claim that is patentably indistinct from CVC Proposed Count 2. *See Ledenev v. Adest*, Int'f No. 106,112 (JTM), Decision on Motions, at 31, 35 (PTAB Mar. 25, 2020) (In moving to add patents to an interference, "[t]he standard to be applied is whether the claim is patentably distinct from the Count . . . . [T]he burden placed upon movant [is] to compare the claims to the count in the required two-way analysis."). In the frequent case where the count is broader than the claims to be considered, then this analysis effectively becomes a one-way obviousness test.[1] *See Ritzberger v. Durschange*, Int'f No. 106,012 (SGL), Decision on Motions,

[1] In CVC Motion 3, CVC does not address the initial identification of the parties' interfering applications using the two-way obviousness test. *See* CVC Mot. 3 at 9-12. However, Sigma does not dispute that claim 31 of Sigma's involved Application 15/456,204 is patentably indistinct from claim 164 of CVC's involved Application 15/947,680. *See* Sigma Mot. 1 at 24-25. Further, because CVC Proposed Count 1 is a "cleavage only/eukaryotic cell" count based on its inclusion of CVC Application 15/981,807, claim 156 (CVC's half of the two-part "McKelvey Count"), and because Sigma bears the burden on this motion to "show why [each of movant's claims] does or does not correspond to the proposed new count" (S.O. ¶ 208.2), Sigma does not dispute CVC's decision to designate ***all*** of its currently involved claims as corresponding to CVC Proposed Count 2. CVC Mot. 3 at 12.

at 20 (PTAB Sept. 29, 2016). The second analysis of identifying claim correspondence is a one-way obviousness test, namely, whether each of the claims of the interfering application is obvious in view of the count. S.O. ¶ 208.3.1.

IV. CVC MOTION 3 WOULD BE MOOT UPON GRANTING OF SIGMA MOTION 1

In the event that the Board grants Sigma Motion 1 (to Substitute Proposed Count 2 for Count 1), CVC Motion 3 would be moot. More specifically, CVC's Proposed Count 2 includes CVC Claim 156, which (for purposes of this interference, as shown below) is substantively the same as Claim 156 of Sigma's Proposed Count 2. *See* CVC Mot. 3 at 1.

CVC Proposed Count 2 (CVC's Half)	**Sigma Proposed Count 2 (Part of CVC's Half)**
CVC Application 15/981,807, claim 156	**CVC Application 15/947,680, claim 156**
156. A eukaryotic cell comprising a target DNA molecule and an engineered and/or nonnaturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising a) a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein; and b) a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises: i) a targeter-RNA that is capable of hybridizing with a target sequence in the target DNA molecule, and ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides; and wherein the single molecule DNA-targeting RNA is capable of forming a	156. A method of cleaving or editing a target DNA molecule or modulating transcription of at least one gene encoded thereon, the method comprising: contacting a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising: a) a single molecule DNA-targeting RNA comprising i) a targeter-RNA that hybridizes with the target sequence, and ii) an activator-RNA that hybridizes with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, wherein the targeter-RNA and the activator-RNA are covalently linked to one another with intervening nucleotides; and b) a Cas9 protein, wherein the single molecule DNA-targeting RNA forms a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said target DNA molecule is

complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, 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.	cleaved or edited or transcription of at least one gene encoded by the target DNA molecule is modulated, and wherein said contacting occurs in a eukaryotic cell.

As explained in detail in Sigma Motion 1, Sigma independent Claim 31 (and hence Sigma dependent Claim 33), is directed to cleavage ***plus*** integration of a donor polynucleotide via HDR. Sigma Mot. 1 at 5-6; Declaration (Paper 1) at 6-7 (June 21, 2021). This additional and technically challenging step of integrating a donor polynucleotide via HDR would have been non-obvious to a POSITA in the early December 2012 time frame. Sigma Mot. 1 at 6-24. Accordingly, Sigma's Proposed Count 2 is directed to the patentably distinct invention of cleavage plus integration via HDR, which both parties expressly claim in their involved applications. Here, as shown above, CVC's claim 156 of CVC Proposed Count 2 is directed to cleavage only, as is CVC's claim 156 in CVC Application 15/947,680. Thus, CVC claim 156 of CVC Proposed Count 2 is patentably distinct from Sigma claim 31 for the same reasons discussed in Sigma Motion 1. *See* Sigma Mot. 1 at 1-24. Accordingly, by granting Sigma Motion 1, the Board may exercise its discretion to deny this motion as moot.

V. CVC'S PURPORTED CONCERNS REGARDING "INCONSISTENCY" AND "THE PUBLIC INTEREST" WOULD BE RESOLVED BY THE GRANT OF SIGMA MOTION 1

CVC repeatedly complains that unless the counts in all of the co-pending interferences are somehow universally conformed, "irreconcilable decisions" from the Board may ensue:

> The inconsistency between the count in this interference and the co-pending interferences creates the possibility of irreconcilable decisions among interferences that involve the same claims for each party. Such inconsistency would be prejudicial to any party in CVC's position, and the public. The Board owes the parties and the public finality, not uncertainty, over who owns this ground-breaking invention.

CVC Mot. 3 at 2.

CVC's repetitive worries here, à la Chicken Little's dire predictions, are highly remote and purely speculative at best. The Board has decades of experience in deciding each interference on the merits of the individual involved cases, regardless of the relatedness of the subject matter. And despite CVC's laments about possible "inconsistencies", "uncertainties", and "ambiguities", CVC nowhere explains how CVC Proposed Count 2, which includes the ***same*** CVC Application 15/981,807, claim 156, could affect CVC's ability to introduce its own proofs of invention. As discussed below, CVC's ulterior motives are not to enable CVC to better make out CVC's priority case, but instead to hamstring Sigma from making out Sigma's priority case. Such an objective is not a legitimate basis to seek to change the count.

In any event, the Board's grant of Sigma Motion 1 would resolve any such concerns regarding potential inconsistencies in the Board's interference decisions. As Sigma explained in Sigma Motion 1, in three of the CRISPR-Cas9 interferences currently pending before the Board, the three involved parties (*viz.*, CVC, Broad, and ToolGen) are contesting priority of invention of CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA. *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. *See* Sigma Mot. 1 at 4, 34. In contrast, in the two most recently declared interferences, the disputes are (or at least should be) directed to the parties' claimed patentable ***improvements*** to genome editing beyond mere DNA destruction caused by CRISPR-Cas9 cleavage. *CVC v. Sigma*, Int'f No. 106,132 (CVC & Sigma: cleavage *plus donor integration via HDR*); *Broad v. Sigma*, Int'f No. 106,133 (Broad: cleavage *plus altering gene product expression*; & Sigma: cleavage *plus donor integration via HDR*). Notably, the Board did not declare an interference between ToolGen and Sigma—and correctly so—because ToolGen did not pursue patent claims beyond using CRISPR-Cas9 in a eukaryotic cell for simply cleaving a target DNA. And ToolGen's

claiming strategy in that regard was reasonable because ToolGen P1 does not disclose a donor polynucleotide, nor integration of any kind (including HDR), consistent with the Board's correct determination to not declare an interference between Sigma and ToolGen. Accordingly, CVC's complaints about potential harm to the public because of the possibility of inconsistent decisions are unfounded and in any event would be entirely resolved by the grant of Sigma Motion 1.

VI. CVC FAILS TO CARRY ITS BURDEN ON CVC MOTION 3

A. CVC Makes No Attempt To Show That CVC Would Suffer Any Prejudice From The Current Count 1

CVC's Motion 3 nowhere argues that the current Count 1 prejudices CVC in any cognizable way. For example, CVC does not argue that changing the count would somehow better conform to CVC's proofs of invention. Indeed, CVC proposes to retain ***identically*** the CVC half of the current two-part McKelvey count, namely, CVC claim 156 of CVC Application 15/981,807. Rather, CVC seeks solely to narrow ***Sigma's*** half of the count to thereby limit Sigma's proofs of invention, a strategic maneuver to try to prejudice Sigma's ability to proffer its proofs of invention. Sigma is unaware of any Board precedent that supports the proposition that a party may seek to change the count solely to prejudice its opponent, and CVC has cited none.

On this CVC Motion 3, CVC has not demonstrated any legitimate basis to change the count. For this reason alone, the Board may exercise its discretion to deny CVC Motion 3.

B. CVC Acknowledges That Sigma's Proofs Of Invention Include Both Single-Molecule Guide RNA And Dual-Molecule Guide RNA

CVC's Motion 3 attempts to limit Sigma's proofs of invention to only those directed to single-molecule guide RNA ("sgRNA"), and purposely exclude Sigma's proofs of invention directed to dual-molecule guide RNA ("dgRNA"). Such dgRNA proofs are encompassed within Sigma's independent claim 31, Sigma's half of current two-part Count 1. CVC presents no justifiable basis to unfairly prejudice Sigma in this manner.

Here, CVC acknowledges that Sigma's proofs of invention are directed to the use of ***both*** sgRNA and dgRNA in a CRISPR-Cas9 system, in which Sigma demonstrated cleavage plus integration via HDR in eukaryotic cells using both types of guide RNA:

> Sigma's first provisional specification discloses data from a single experiment: a gel that has lanes for ***both single-guide RNA and dual-guide RNA molecules***. Ex. 2549, ¶103; MF 10. Sigma also cannot claim any prejudice due to its earliest proofs falling outside the scope of a sgRNA Count, as Sigma's proofs ***appear*** to be identical either way. *Id.*

CVC Mot. 3 at 9 (emphases added).

Here, Sigma's proofs of invention are not identical for both types of guide RNAs. Ex. 1080 (Supp'l Cannon Decl.) ¶ 73. While Sigma's FACS data for sgRNA and dgRNA are similar—and all demonstrate successful HDR integration for both types of guide RNA—Sigma's ***additional and confirmatory*** PCR data is not the same. *Id*. In particular, the dgRNA lane (Lane A) includes an additional PCR confirmation; the sgRNAs (Lanes B, C, and D) do not include an additional PCR confirmation. *Id*. Thus, while Sigma's data for both guide RNAs demonstrates a successful reduction to practice of the invention of Count 1 (Sigma Claim 31), Sigma's dgRNA data is uniquely even more compelling. *Id*. Accordingly, CVC's strategic goal of its Motion 3 is an unfair (and thinly disguised) attempt to prejudice Sigma's ability to rely upon Sigma's dgRNA PCR confirmation data as a component of Sigma's proofs of invention. The remainder of CVC's arguments, directed to supposed "uniformity" among the various interferences, and the "public interest," are all smoke and mirrors designed to disguise CVC's true objective here, namely, to unfairly preclude Sigma from relying upon the entirety of the data from Sigma's successful experiments.

Moreover, CVC's argument on this motion is misleading, signaled in the block quote above by CVC's use of the word "appear" ("as Sigma's proofs ***appear*** to be identical either way"). CVC Mot. 3 at 9 (emphases added). While not disclosed to the Board in its motion,

CVC understands full well that Sigma's proofs of invention are not identical for both types of guide RNAs. In opposition proceedings before the European Patent Office ("EPO"), CVC's exclusive licensee Intellia Therapeutics (via Intellia's European Patent Attorney George Schlich) has challenged Sigma's European applications related to CRISPR-Cas9:

OPPOSITION

Opposition Against European Patent No. EP 3138911 B1

Title	"CRISPR-BASED GENOME MODIFICATION AND REGULATION"
Patent proprietor	Sigma-Aldrich Co. LLC
Granted on application	16183724.0
Grant date	5 December 2018
Opposition filed by	
Opponent	George W. Schlich
Address	9 St Catherine's Road Littlehampton West Sussex BN17 5HS UK

Ex. 1085 (EPO Opposition of EP 3138911 B1) at 1. Opponent George Schlich's relationship to CVC has been revealed in U.S. litigation proceedings:

> Petitioner George W. Schlich ("Petitioner" or "Schlich"), as an agent for Intellia Therapeutics, Inc. ("Intellia") . . . .
>
> Intellia is a genome-editing company co-founded by Dr. Jennifer Doudna of the University of California, Berkeley. On May 25, 2012, Dr. Doudna and her colleagues filed U.S. Provisional Patent Application No. 61/652,086, which led to a number of United States and foreign patent applications relating to the biotechnology. Intellia licensed these patents. Schlich is Intellia's European patent agent and claims that Doudna and her colleagues are the rightful inventors of CRISPR/Cas9.
>
> * * *
>
> Intellia's European patent agent, George Schlich, filed four oppositions with the EPO seeking revocations of the European Patents. Although Schlich filed the oppositions in his name, he did so as an agent of Intellia, and Intellia owns and controls the oppositions. "Filing in the attorney's name is common practice in oppositions in front of the European Patent Office."

Ex. 1086 (*In re Schlich*, Case No. 16-MC-319 (VSB) (S.D.N.Y. Sept. 18, 2017)) at 2-4 (citations

omitted).

> Intellia is a "genome editing company" whose primary focus is the development of "potentially curative therapeutics" using the CRISPR-Cas9 system. Schlich is a European patent attorney providing legal services to Intellia in the EPO opposition Cas9. Dr. Jennifer Doudna is a founding member of Intellia, and the company holds an exclusive license to Dr. Doudna's intellectual property in the CRISPR-Cas9 therapeutics field.

In re Schlich, 893 F.3d 40, 43-44 (1st Cir. 2018).

In particular, in those EPO proceedings, Intellia criticized Sigma's experimental data using sgRNA (Lanes B, C, & D), arguing (albeit incorrectly and unsuccessfully) that Sigma's lack of PCR confirmations in those lanes demonstrated lack of successful donor integration via HDR, despite Sigma's strong FACS data and the known difficulties in getting PCR to work:

> [299] Importantly, example 5 purports to "confirm" the data presented in Example 4 using a PCR-based assay to look for integrated GFP template in the four experimental treatments reported above. However, no PCR product is detected in any of lanes B-D of Fig. 3. Samples B, C, and D thus show no signal in Fig. 3 and appear to be negative results, which is inconsistent with the reported FACS data.
>
> [300] Specifically, the PCR data indicate that the three experimental treatments that appear to express the highest levels of GFP by FACS do not give rise to a PCR product of the expected size. Thus, the data indicate that the fluorescence observed in Example 4 likely arises for reasons other than expression of an integrated GFP sequence.
>
> * * *
>
> [304] The lack of confirmation by PCR of the FACS results for treatments B-D would also lead the skilled person to reasonably conclude that the seemingly positive results in at least Fig. 2 B-D are false positive results. Accordingly, it is not plausible to interpret the contradictory data presented in Fig. 2 and Fig. 3 of the patent as evidence of successful integration of a donor sequence into a chromosomal sequence of a eukaryotic cell.
>
> [305] The Patent thus fails to plausibly disclose the claimed methods for integrating a donor sequence into a chromosomal sequence of a eukaryotic cell.

Ex. 1084 (EPO Opposition of EP 3138911 B1) at 50-51 (highlighting added).

Accordingly, CVC's thinly disguised strategy here is to narrow the count to the parties' sgRNA experiments only, thereby hoping to exclude Sigma's dgRNA experimental data (which includes *both* strong FACs data *and further compelling PCR confirmation* data), and then repeat Intellia's same attacks on Sigma's sgRNA experimental data in this interference. That result

would have no effect on CVC's proofs of invention (because CVC used ***only*** sgRNA for its cleavage only experiments), but it would be prejudicial to Sigma's proofs of invention. This reason alone—CVC's purposeful attempt to exclude relevant portions of Sigma's proofs of invention—supports the Board's exercise of its discretion to deny CVC Motion 3.

C. CVC Fails To Inform That Board That All Of The Other Interferents' Proofs Of Invention For DNA Repair Are Limited To Single-Molecule Guide RNA

In its Motion 3, CVC argues repeatedly that there is no "apparent" reason to treat Sigma differently than CVC, Broad, and ToolGen, who are all involved in other CRISPR-Cas9-related interferences:

> In each of these pending interferences, 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). MF 2; MF 3. Sigma's half of the count is an outlier in this respect, ***with no apparent reason*** to treat Sigma differently than CVC, Broad, or ToolGen.

CVC Mot. 3 at 1-2 (emphasis added).

> ***There is no apparent reason*** that the Count in this Interference should have a different scope than the multiple other co-pending interferences involving the same invention and the same CVC claims. There is also no reason that Sigma should be treated differently than CVC, Broad, or ToolGen with respect to the structure of the guide RNA recited in the count.

Id. at 4-5 (emphasis added).

But CVC fails to inform the Board that in the context of using CRISPR-Cas9 in a eukaryotic cell, and particularly in demonstrating cleavage of DNA in a eukaryotic cell, each of the other three parties' relevant proofs of invention (at least as set forth in their provisional patent applications to which they have been initially accorded priority benefit) are limited to ***single-molecule guide RNA only***. Ex. 1080 (Supp'l Cannon Decl.) ¶ 77. In particular, CVC P3 demonstrated cleavage in eukaryotic cells using only a sgRNA. Ex. 1013 at 103 ("The dual-tracrRNA:crRNA, when engineered as a ***single RNA chimera***, also directs sequence-specific

Cas9 dsDNA cleavage.") (emphasis added); Ex. 1080 (Supp'l Cannon Decl.) ¶ 77. Likewise, in its pertinent disclosure of Figure 4, Broad P1 demonstrated cleavage in eukaryotic cells using only a sgRNA. Ex. 1087 at ¶ [00176] ("[A] ***chimeric crRNA-tracrRNA*** hybrid design was adapted, where a mature crRNA (comprising a guide sequence) is fused to a partial tracrRNA via a stem-loop to mimic the natural crRNA:tracrRNA duplex (Figure 2A).") (emphasis added); *id.* Fig. 4 ("chimeric RNA"); Ex. 1080 (Supp'l Cannon Decl.) ¶ 77. Similarly, ToolGen P1 demonstrated cleavage in eukaryotic cells using only a sgRNA. Ex. 1088 at 9 ("After 24h, 10-40 μg of *in vitro* transcribed ***chimeric RNA*** was nucleofected into 1x106 K562 cells.") (emphasis added); Ex. 1080 (Supp'l Cannon Decl.) ¶ 77. Accordingly, for those other parties involved in other CRISPR-Cas9-related interferences, any patent claims directed to generic guide RNA (*i.e.*, claims encompassing both sgRNA and dgRNA) would raise issues about adequate written description support under 35 U.S.C. § 112.

In contrast, and as discussed above, Sigma is an outlier among the four parties—and properly so—because Sigma's proofs of invention (at least as set forth in Sigma's P1 provisional patent application, to which Sigma has undisputedly been accorded priority benefit) are directed to ***both*** single-molecule guide RNA ***and*** dual-molecule guide RNA. Ex. 1080 (Supp'l Cannon Decl.) ¶ 78. As discussed in Sigma Motion 1, Sigma P1 demonstrated the use of both types of "Guiding RNA" in using CRISPR-Cas9 to successfully cleave eukaryotic cells and thereafter demonstrate successful integration of a donor polynucleotide via HDR. Sigma Mot. 1 at 29-31; *see* Ex. 1003 at 26-27 (Table 7) ("Treatment A" - "pre-annealed crRNA-tracrRNA ***duplex*** (0.3 nmol)"; "Treatments B & C" - "0.3 nmol of ***chimeric*** RNA (0.3 nmol)"; and "Treatment D" - "U6-***chimeric*** RNA plasmid DNA (5 μg)") (emphases added); Ex. 1080 (Supp'l Cannon Decl.) ¶ 78. In addition, to confirm targeted donor integration, Sigma P1 further demonstrated a

confirmatory PCR test (*viz.*, "PCR Confirmation of Targeted Integration")[2] for the dgRNA experiment of Treatment A:

> [0068] Cells transfected with 10 μg of Cas9 mRNA transcribed with an Anti-Reverse Cap Analog, 0.3 nmol of pre-annealed ***crRNA-tracrRNA duplex***, and 10 μg of AAVS1-GFP plasmid DNA displayed a PCR product of the expected size (see lane A, FIG. 2).

Ex. 1003 at 27 (emphasis added); Ex. 1080 (Supp'l Cannon Decl.) ¶ 79. As such, Drs. Chen and Davis' experiments set forth in Sigma P1 provide more than adequate support for Sigma's claims directed to generic guide RNA (Ex. 1080 (Supp'l Cannon Decl.) ¶ 79), and that Section 112 support has not been disputed.

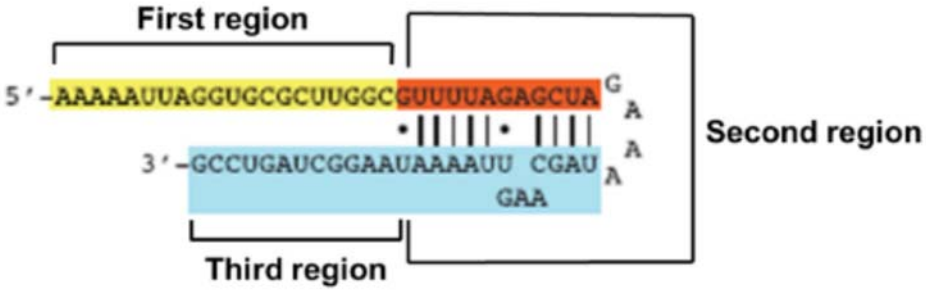
Accordingly, unlike the other parties in the other CRISPR-Cas9 interferences, Sigma alone demonstrated possession of ***both*** sgRNA and dgRNA in a CRISPR-Cas9 system to successfully cleave eukaryotic cells (and thereafter integrate a donor polynucleotide via HDR). *Id.* ¶¶ 76-79. It is therefore not only appropriate, but entirely reasonable, to define Sigma's half of the Count to encompass Sigma's proofs of invention, which include successful experiments using both sgRNA and dgRNA.

D. Sigma P1 Fully Supports Interpreting Sigma Claim 31 To Include Both Single-Molecule Guide RNA And Dual-Molecule Guide RNA, Contrary To CVC's Highly Selective Quotations

CVC selectively quotes Sigma P1 to argue that "the PTAB may conclude that 'the guide RNA' of claim 31 is a single structure that includes all the recited parts. Ex. 2459 ¶ 102." CVC Mot. 3 at 7. In particular, CVC cites Sigma P1 ¶¶ [0019] and [0021] to argue:

> Sigma's P1 application defines "guide RNA" as comprising a first region, "a

[2] Sigma P1's FACS data is the primary data demonstrating successful cleavage plus integration via HDR, and Sigma P1's PCR data is a further confirmation of that successful demonstration. Ex. 1080 (Supp'l Cannon Decl.) ¶ 79 n.1.

> second internal region that forms a stem loop structure," and a third region. Ex. 2026, ¶¶ [0021], [0019]; MF 9. These regions are illustrated below.
>
> 
>
>
> *See* Ex. 2031, Fig. 5A (annotated) (cited in Sigma's '204 application); Ex. 2549 ¶ 99; MF 9.
>
> The "loop" of claim 31 refers to the linker loop in the stem-loop region shown in purple [sic] in the diagram above, which joins the crRNA and the tracrRNA. Ex. 2549, ¶¶ 98-99, 101; MF 9. The presence of the stem-loop in the second internal region necessarily denotes a single-guide RNA in which the loop joins the crRNA and the tracrRNA. Ex. 2549, ¶¶ 98-99, 101; MF 9.

CVC Mot. 3 at 6-7 (green highlighting added; other highlighting and annotations in original).

At the outset, CVC's argument about "[t]he 'loop' of claim 31" is nonsensical because that term is recited nowhere in Sigma's patent claims, including claim 31. Ex. 1080 (Supp'l Cannon Decl.) ¶¶ 80-81. Further, CVC's inserted "Fig. 5A [sic] (annotated)" figure is actually adapted from Jinek (2012)'s illustration of a "chimera A" sgRNA discussed by ***Jinek*** (Ex. 2031, Fig. 5B), ***not*** a figure from ***Sigma P1***. Ex. 1080 (Supp'l Cannon Decl.) ¶ 81. Moreover, while CVC cites Sigma P1 ¶¶ [0019] & [0021], CVC and its expert (Dr. Scott Bailey) fail to consider the subsequent ¶ [0023], which unambiguously explains that the guide RNA—including a "stem loop"—can be a ***dual-molecule*** guide RNA:

> [0023] In another embodiment, the guiding RNA can comprise two separate molecules. The first RNA molecule can comprise the first region of the guiding RNA and one half of the "stem" of the second region of the guiding RNA. The second RNA molecule can comprise the other half of the "stem" of the second region of the guiding RNA and the third region of the guiding RNA.

Ex. 1003 ¶ [0023] (highlighting added); Ex. 1080 (Supp'l Cannon Decl.) ¶ 81.

Indeed, during his cross-examination, Dr. Bailey acknowledged that this express disclosure in Sigma P1 is directed to a two-molecule guide RNA:

> Q . . . The question was, so paragraph 23 of Sigma P1 describes a guiding RNA that comprises two separate molecules; correct?
>
> A. Yes. Paragraph 23 describes an RNA comprising ***two separate molecules***.

Ex. 1082 at 77:22 – 78:5 (highlighting and emphasis added; objections omitted).

> Q. Okay. So if you start with a single-molecule RNA and it has a stem loop structure and if you cut the stem loop around the loop area, you will get half the stem loop to the first part and half the stem loop to the second part; correct?
>
> A. If you start off with a guiding RNA that comprises the three regions, a first region at a 5' end that is complementary to the target site in the chromosomal sequence and then a second region that forms the stem loop structure and a third region that remains essentially single-stranded and you cut it within the stem loop, ***you'll end up with two RNA molecules***.

Id. at 85:14 – 86:6 (highlighting and emphasis added; objections omitted).

And as discussed above, the experiments set forth in Sigma P1 demonstrated the use of ***both*** sgRNA and dgRNA in a CRISPR-Cas9 system to successfully cleave eukaryotic cells, and thereafter integrate a donor polynucleotide. *See supra* Part VI.B. Thus, not surprisingly, during his cross-examination, Dr. Bailey acknowledged that the experiments disclosed in Sigma P1 used both sgRNA ("chimeric) and dgRNA ("duplex"):

> Q. All right. And the treatments A through D all have Cas9, a guide RNA, and the donor construct; correct?
>
> A. Treatments A through D all contain Cas9, an RNA, and donor DNA.
>
> Q. All right. And then for treatment A, it used a pre-annealed crRNA-tracrRNA ***duplex***; correct?
>
> A. Treatment A states they use pre-annealed tracrRNA -- sorry -- pre-annealed CRISPR RNA-tracrRNA ***duplex***.
>
> Q. Okay. And treatment B through D use a ***chimeric*** guide RNA; correct?

> A. Treatments B and C use a ***chimeric*** RNA. Treatment D uses a U6-***chimeric*** RNA plasmid DNA.

Ex. 1082 at 105:15 – 106:3 (emphases added; objections omitted).

Accordingly, notwithstanding CVC's selective quotations of Sigma P1, and in view of the express teachings of that provisional application, Sigma's claimed "guide RNA" is generic and encompasses both sgRNA and dgRNA. And that understanding is fully supported by the disclosure of Sigma P1.

E. CVC's So-Called "Consistency" Rationale Is Entirely Unsupported

CVC's novel "efficiency, uniformity, and clarity" rationale (*e.g.*, CVC Mot. 3 at 2-5) is crafted from whole cloth for this motion. Sigma is unaware of any authority supporting such a facially broad-brush theory divorced from the unique sets of facts typically attributable to different interferences involving different parties and different priority applications.

CVC's sole reliance on *In re Vivint*, a case involving parallel *inter partes* review and *ex parte* reexamination proceedings, is entirely unavailing:

> Whatever action the PTAB takes across similar interferences must not be arbitrary or capricious. *In re Vivint, Inc*., 14 F.4th 1342, 1351 (Fed. Cir. 2021) (noting that '[a]' action is an abuse of discretion when it '(1) is clearly unreasonable, arbitrary, or fanciful') (quoting *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto.* 11 Ins. Co., 463 U.S. 29, 43 (1983)).

Mot. 3 at 2.

> If there are multiple, related interferences where the parties and involved claims overlap, and where each count is directed to the same patentable invention, it is reasonable to expect the Board will ensure that the scope of all the interference counts is the same. *See Vivint*, 14 F.4th at 1351.

Id. at 5.

In re Vivint is not a patent interference case, and thus not surprisingly does not address interference counts in any way. Instead, in that case, the Federal Circuit evaluated a challenge to the Board's decision to grant an *ex parte* reexamination request after the Board had denied an

essentially identical *inter partes* review petition under § 325(d). *In re Vivint*, 14 F.4th at 1350-54. The Federal Circuit determined that the Board should have also denied the substantively identical *ex parte* reexamination request under § 325(d):

> It was, therefore, arbitrary for the Patent Office to grant reexamination after denying institution of the '091 IPR based on § 325(d). . . . Thus, the Patent Office, when applying § 325(d), cannot deny institution of IPR based on abusive filing practices then grant a nearly identical reexamination request that is even more abusive.

Id. at 1354-54.

Thus, the *In re Vivint* case has no relevance to the issues raised in CVC Motion 3. Moreover, CVC's argument is based on the false premise that in each of the other CRISPR-Cas9-related interferences "each count is directed to the same patentable invention". As discussed in Sigma Motion 1, however, three of the co-pending interference are directed to the patentably distinct invention of 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. The parties are *not* contesting the further technological advance of integrating a donor polynucleotide into the cleaved target DNA via HDR, which integration is a nonobvious and technically challenging process. 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.

Sigma Mot. 1 at 4.

And with respect to the co-pending *Broad v. Sigma* case, Int'f No. 106,133, the count is not directed to "cleavage only" in a eukaryotic cell, but instead to the patentably distinct inventions of cleavage plus donor integration via HDR (Sigma) or cleavage plus altering gene product expression (Broad). Thus, because this interference (and Interference No. 106,133) are

not directed to CRISPR-Cas9 "cleavage only" in a eukaryotic cell, there is no legitimate reason to attempt to conform the count in this interference to the counts in those other interferences. Accordingly, in these circumstances, the Board may exercise its discretion to deny CVC Motion 3.

F. CVC P1 And CVC P2 Do Not Provide A Constructive Reduction To Practice Of An Embodiment Within The Scope Of CVC Proposed Count 2

CVC argues that it is entitled to the priority benefit of CVC P1 and P2 for CVC Proposed Count 2. CVC Mot. 3 at 12-17. There is no dispute that CVC Proposed Count 2, like current Count 1, is directed to using CRISPR-Cas9 to successfully cleave a target DNA ***in a eukaryotic cell***. The parties are in the process of extensively briefing this identical issue in the context of CVC Motion 1. Indeed, in Sigma's opposition to CVC Motion 1, Sigma explains in detail why neither CVC P1 nor CVC P2 provide a constructive reduction to practice of current Count 1 (and hence CVC Proposed Count 2). Sigma Opp'n 1 (filed concurrently herewith). In particular, neither of those CVC provisional applications provide a described and enabled embodiment within the scope of Count 1 because they do not demonstrate that the CVC inventors possessed a CRISPR-Cas9 system ***in a eukaryotic cell***. *Id.* 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 CVC Motion 1. *Id.*; *see* S.O. at 10 ("The parties are encouraged to find ways to consolidate arguments when briefing the authorized motions.").

VII. CONCLUSION

For the foregoing reasons, because CVC has failed to carry its burden on this motion, Sigma respectfully requests that the Board exercise its discretion and deny CVC Motion 3.

Respectfully submitted,

Dated: February 18, 2022

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APPENDIX 1

LIST OF EXHIBITS CITED

Exhibit No.	Description
1001	Cannon Decl.
1003	Sigma P1
1013	CVC P3
1082	Bailey Tr. 01/24/22
1084	Doyon Tr. 02/03/22
1085	EPO Opposition of EP 3138911 B1 (Schlich)
1086	In re Schlich (SDNY 2017)
1087	Broad P1
1088	ToolGen P1

APPENDIX 2

RESPONSE TO CVC'S STATEMENT OF MATERIAL FACTS

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

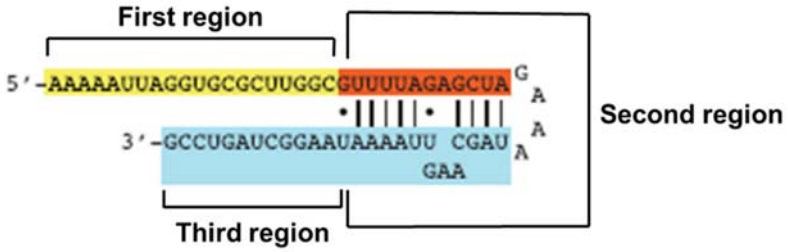
7. The PTAB construed the term "guide RNA" in the '115 Interference to refer to sgRNA. Ex. 2400, 31-33.

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.

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

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.

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

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.

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.*

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.

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.*

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

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

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

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

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.*

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

CERTIFICATE OF FILING AND SERVICE

I hereby certify that:

I. The following paper was filed February 18, 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 REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER.

SIGMA OPPOSITION TO CVC MOTION 3
(to Change the Count)

II. A courtesy copy of the above paper is being sent to counsel for Junior Party THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER at the address(es) below on February 18, 2022, via e-mail:

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