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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 4 (to Add the Claims of Sigma Patent Nos. 10,731,181 and 10,745,716)

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OPPOSITION TO CVC MOTION 4
(to Add the Claims of Sigma Patent Nos. 10,731,181 and 10,745,716)

I. INTRODUCTION

In CVC Motion 4, CVC applies the incorrect legal analysis for seeking to add an uninvolved patent to an interference, namely, CVC only applies the partial one-way test for determining correspondence to a count, rather than the complete two-way test for determining patentable distinctness. Because of that misapplication of the operative legal standards, CVC fails to address a key issue in this interference, namely, that Count 1's recital of "DNA homology-directed (HDR) repair" would have been non-obvious in view of claims that are silent in that regard.[1] Thus, CVC's Motion 4 is fatally flawed.

CVC's error here is not harmless because the patentable significance of donor integration via HDR in a eukaryotic cell is a fundamental dispute in this interference, and indeed distinguishes this interference from the co-pending interferences that are directed to "cleavage only" in a eukaryotic cell. *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. Moreover, because both the Board and Sigma placed CVC on notice of this important issue in the context of the Board's authorization of the parties' respective motions, CVC's failure here is not justified. Accordingly, CVC fails to carry

[1] In CVC Motion 4, CVC states that "[i]n this motion, 'Count 1' refers to Sigma's half of Count 1 and comparisons are made against Sigma's half of the count, unless otherwise specified." CVC Mot. 4 at 1, n. 1. Moreover, all of CVC's analyses and claim charts are directed to Sigma's part of the 2-part "McKelvey Count," namely, Claim 31 of Sigma's involved '204 application. *E.g., id.* at 4-11, Appx. 3-6.

its burden on this motion, and Sigma thus respectfully requests that the Board exercise its discretion to deny CVC Motion 4.

II. PRECISE RELIEF REQUESTED

Sigma requests that the PTAB deny CVC Motion 4, which requests that the Board grant "CVC's miscellaneous [sic] motion to add Sigma's U.S. Patent No. 10,731,181 ("the '181 patent") and No. 10,745,716 ("the '716 patent") (collectively, "the Sigma Patents") to this interference and designate claims 1-17 of the '181 patent and claims 2-4, 11, 14, and 21-22 of the '716 patent as corresponding to Count 1." CVC Motion 4 at 1.

III. LEGAL STANDARDS

Historically in patent interference proceedings, when an uninvolved patent or application was sought to be added to the interference, the legal standard was articulated as follows:

> During the pendency of an interference, if the administrative patent judge becomes aware of an application or a patent not involved in the interference which claims ***the same patentable invention*** as a count in the interference, the administrative patent judge may add the application or patent to the interference on such terms as may be fair to all parties.

37 C.F.R. § 1.642 (emphasis added) (1998).

The Board defined "the same patentable invention" as a "two-way obviousness test." *See Winter v. Fujita*, 1999 Pat. App. LEXIS 7, *49-50, 53 U.S.P.Q.2D (BNA) 1234, 1248 (BPAI Nov. 16, 1999).

When the interference rules were reformulated in 2004, the USPTO promulgated the same "two-way obviousness" test for evaluating whether to add an uninvolved patent or application to an interference:

> A party may suggest the addition of a patent or application to the interference or the declaration of an additional interference. The suggestion should ***make the showings required under § 41.202(a) of this part***.

37 C.F.R. § 41.203(d) (emphasis added).

> For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and ***show why the claims interfere within the meaning of § 41.203(a)***.

37 C.F.R. § 41.202(a) (emphasis added).

> (a) ***Interfering subject matter.*** An interference exists if ***the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa***.

37 C.F.R. § 41.203(a) (second emphasis added).

Thus, the Board may exercise its discretion to add a patent or application that claims the same patentable invention as the count. 37 C.F.R. §§ 41.202(a), 41.203(a), 41.203(d). And likewise, a party may request to add a patent or application to an interference that claims the same patentable invention as the count. *Id.* The proper legal standard to be adopted in evaluating that request is whether the patent or application sought to be added claims the same patentable invention as the count in the ongoing interference proceeding, using the two-way obviousness test. *Id.*; *see Ledenev v. Adest*, 2020 Pat. App. LEXIS 6912, *35-36, Decision on Motions, at 31, 35 (PTAB Mar. 25, 2020) (JTM) (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.").

IV. CVC MOTION 4 WOULD BE MOOT UPON GRANTING OF SIGMA MOTION 1

In the event that the Board grants Sigma Motion 1 (to Substitute Sigma Proposed Count 2), this CVC Motion 4 would be moot. CVC did not address Sigma Proposed Count 2 in CVC Motion 4. Further, CVC did not file any responsive motion to add Sigma's '181 and '716 patents in view of Sigma Proposed Count 2. Accordingly, the Board's grant of Sigma Motion 1 would render moot CVC Motion 4, including the further analysis set forth in this Opposition 4.

V. CVC FAILS TO CARRY ITS BURDEN ON CVC MOTION 4

A. CVC Does Not Apply The Correct Two-Way Obviousness Test, And That Failure Substantively Impacts This Motion

As set forth above, the Board applies a two-way obviousness test to evaluate a request to add an uninvolved patent or application to an existing interference. *See supra* Part III. Thus, CVC's Motion 4 analysis should have been conducted using the two-way obviousness test for evaluating the Sigma Patents, namely, whether each of Sigma's patents contain at least one claim that is patentably indistinct from Count 1. *See Ledenev v. Adest*, 2020 Pat. App. LEXIS 6912, *35-36, Decision on Motions, at 31, 35 (PTAB Mar. 25, 2020) (JTM) (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 its Motion 4, CVC failed to apply the correct ***two-way obviousness test*** for adding an uninvolved patent to the interference:

> Under 37 C.F.R. § 41.207(b)(2), "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." Standing Order, ¶ 208.3.1; 37 C.F.R. § 41.207(b)(2). As part of this analysis, "additional references…may be relied upon to establish the obviousness of the differences between the count and the claims." *Desjardins v. Wax*, Interference No. 105,915, Paper 125, 17-20 (P.T.A.B. Jan. 21, 2014) (granting motion to add claims to the count where the prior art disclosed 'the difference between' the count and claims); Ex. 2558, 19.

CVC Motion 4 at 2.[2]

[2] The authority cited by CVC is directed to the analysis of whether a claim of an ***already involved*** patent or application corresponds to the interference count. 37 C.F.R. § 41.207(b)(2) ("Claim correspondence"); Standing Order ¶ 208.3.1 ("Claim correspondence"); *Desjardins v. Wax*, Interference No. 105,915, Paper 125, 17-20 (PTAB Jan. 21, 2014) ("Wax Motion 2 strives

As shown above, CVC applied a ***one-way obviousness test*** for determining whether a claim of an already involved patent or application corresponds to the count. That subsequent test for claim correspondence only applies ***after*** conducting the initial two-way obviousness test for adding an uninvolved patent to the interference.

CVC's misapplication of the legal standard here is significant because CVC failed to perform half of the legal analysis required to meet its burden on this Motion. For example, as shown below, in evaluating the important "Element 13" for each of the Sigma Patents, CVC only performed the one-way analyses for each of the '181 patent and the '716 patent:

'181 Patent Claim 1 Elements	**Teachings of Count 1, Jinek 2012, and Krebber 2000**
	← **render obvious?**
Element 13: and repair of the double-stranded break by a DNA repair process leads to integration of the exogenous sequence into the chromosomal sequence.	Count: "…**repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.**"

'716 Patent Claim 1 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
	← **render obvious?**
Element 13: and repair of the double-stranded break by a DNA repair process leads to modification of the chromosomal sequence.	Count: "…**repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.**"

CVC Mot. 4, Appx. 3 at 3-3, Appx. 5 at 5-3.

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to have some of Desjardins' non-corresponding claims designated as corresponding to Count 1 and the remainder designated as corresponding to Count 2.").

For this claim element, the Sigma Patents' claims are broader than Count 1, so the one-way analyses are incomplete to evaluate patentable distinctness. The second half of the proper two-way inquiry is critically important, namely, ***does the broader claim render obvious the narrower Count***? In CVC Motion 4, CVC entirely ignores the second half of the two-way test, and thus CVC fails to carry its burden on this Motion.

B. CVC Fails To Address That Donor Integration Via HDR (Count 1) Would Have Been Non-Obvious In View Of NHEJ Repair/End Ligation (The Sigma Patents' Claims)

In its Motion 4, CVC fails to address that Count 1's recital of the "homology-directed repair (HDR) process" would have been non-obvious in view of Element 13 of Sigma's '181 and '716 patents. In particular, Count 1 specifically recites:

> repair of the double-stranded break ***by a DNA homology-directed repair (HDR) process*** leads to integration or exchange of the donor sequence into the chromosomal sequence.

Declaration (Paper 1) at 6-7 (June 21, 2021) (emphasis added).

Notably, CVC does not emphasize this key claim language ("by a DNA homology-directed repair (HDR) process") in its claim charts, implicitly acknowledging that the Sigma Patents' claims do not recite a counterpart limitation:

'181 Patent Claim 1 Elements	**Teachings of Count 1, Jinek 2012, and Krebber 2000**
Element 13: and repair of the double-stranded break by a DNA repair process leads to integration of the exogenous sequence into the chromosomal sequence.	Count: "…**repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.**"

'716 Patent Claim 1 Elements	Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007
Element 13: and repair of the double-stranded break by a DNA repair process leads to modification of the chromosomal sequence.	Count: "…**repair of the double-stranded break** by a DNA homology-directed repair (HDR) process **leads to integration or exchange of the donor sequence into the chromosomal sequence.**"

CVC Mot. 4, Appx. 3 at 3-3, Appx. 5 at 5-3.

Importantly, none of the Sigma Patents claims recite a ***homology-directed repair (HDR)*** process. Instead, the Sigma Patents only recite more broadly "repair of the double-stranded break by a DNA repair process." As explained in detail in Sigma Motion 1, in the early December 2012 time frame, the CRISPR-Cas9 technology was in its infancy, and whether integration of a donor polynucleotide via HDR in a eukaryotic cell could be accomplished in that bacteria-derived system was uncertain. *See* Sigma Mot. 1 at 6-24; Ex. 1001 (Cannon Decl.) ¶¶ 100-157, Summary; Ex. 1080 (Cannon Supp'l Decl.) ¶¶ 58-75. Indeed, in Sigma P1, in addition to describing HDR processes that result in integration of a donor polynucleotide, Sigma P1 also discusses ***non-HDR*** processes that lead to DNA repair, including NHEJ ligation repair processes for integration of an exogenous sequence and modification of a chromosomal sequence:

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

Ex. 1003 (Sigma P1) ¶ [0042] (emphases added); Ex. 1080 (Cannon Supp'l Decl.) ¶ 82.

> [0043] Lastly, in embodiments in which a linear donor polynucleotide comprising a short donor sequence is introduced into the cell, the short donor sequence can be integrated into the chromosomal sequence at the site of the

> double-stranded break via a NHEJ process. The integration can proceed via the ligation of blunt ends between the short donor sequence and the double stranded break in the chromosomal sequence. Alternatively, the integration can proceed via the ligation of sticky ends (i.e., having 5′ or 3′ overhangs) between the short donor sequence and the cleaved chromosomal sequence.

Id. (Sigma P1) ¶ [0043] (emphases added); Ex. 1080 (Cannon Supp'l Decl.) ¶ 82.

Further, in CVC Motion 4, CVC endeavors to rewrite history by mischaracterizing the teachings of Jinek (2012):

> Jinek 2012 teaches that *S. pyogenes* Cas9 is "efficient, versatile, and programmable" in cleaving eukaryotic DNA, and "could offer considerable potential for gene-targeting and genome-editing applications."
>
> * * *
>
> . . . Jinek 2012's success in using both dgRNA and sgRNA to cleave target DNA.

CVC Mot. 4 at 5, 11.

Contrary to CVC's arguments, Jinek (2012) contains no teachings about cleaving eukaryotic DNA. Ex. 1080 (Cannon Supp'l Decl.) ¶¶ 83-84. Jinek used recombinant protein and RNAs that were assembled in vitro into an RNP complex, and used in vitro to cleave short oligonucleotide or plasmid targets.[3] *Id.* ¶ 84. Jinek (2012) has no teachings about whether such RNPs work in a eukaryotic cell. *Id.* Additionally, Jinek has no teachings if separately introducing the two components (Cas9 protein and gRNA), or nucleic acid precursors of the Cas9 protein (mRNA or DNA expression vector) or gRNA (DNA expression vector), could result in the assembly and function of a CRISPR-Cas9 RNP complex in a eukaryotic cell. *Id.*

Accordingly, for all of the reasons set forth in Sigma Motion 1, in early December 2012, donor integration via HDR (as recited in Count 1) would not have been obvious in view of

[3] "Eukaryotic DNA" is not simply a 20bp target that may comprise a eukaryotic sequence, but reflects that such a target sequence exists in the context of a chromatinized genome in a nucleus in a eukaryotic cell. Ex. 1080 (Cannon Supp'l Decl.) ¶ 84 n.2.

alternative non-homology driven integration mechanisms that depend on NHEJ repair, such as NHEJ ligation. *See* Sigma Mot. 1 at 6-24.

C. Sigma And The Board Placed CVC On Notice Of This Important Issue Of Donor Integration via HDR

In its List of Proposed Motions, Sigma made clear that cleavage plus integration via HDR was patentably distinct from "cleavage only":

> In contrast [to CVC's claim of the 2-part "McKelvey count"], Sigma's claim of the count (Sigma 26 Application 15/456,204, claim 31) is directed solely to cleavage plus integration (namely, "the CRISPR-Cas type II protein introduces a double-stranded break at the target site, and repair of the double-stranded break by a DNA homology directed repair (HDR) process leads to integration or exchange of the donor sequence into the chromosomal sequence.").

Sigma List of Proposed Motions (Paper 26) at 3 (Aug. 10, 2021) (highlighting added; emphasis omitted).

Similarly, in its Order Authorizing Motions, the Board authorized Sigma to file Sigma Motion to Substitute Sigma Proposed Count 2 for Count 1:

> Sigma indicates that if the motion is authorized, it will argue that proposed Count 2 will be limited to incorporation, integration, or exchange of a donor sequence, thus encompassing only the patentably distinct invention commonly claimed by both parties.
>
> * * *
>
> Authorization for this motion is GRANTED for Sigma to file a motion arguing that the count should be changed to its proposed Count 2, with the CVC portion of the count expressed as claim 164 of CVC application 15/947,680.

Order Authorizing Motions (Paper 30) at 7-8 (Sept. 20, 2021).

Both CVC Claim 164 and Sigma Claim 31 of Sigma Proposed Count 2 expressly recite this limitation directed to cleavage plus integration via HDR:

CVC Claim 164	Sigma Claim 31
. . . creation of a double strand break in the target DNA molecule which is repaired by a homology-directed repair mechanism which incorporates a sequence of a donor polynucleotide into the target DNA molecule,	. . . introduces a double-stranded break at the target site, and repair of the double-stranded break by a DNA homology-directed repair (HDR) process leads to integration or exchange of the donor sequence into the

thereby editing the target DNA molecule.	chromosomal sequence.

Sigma Mot. 1 at 5-6; Declaration (Paper 1) at 6-7 (June 21, 2021) (highlighting added).

Accordingly, CVC was on notice that the patentable distinction of donor integration via HDR is a key issue in this interference. CVC has no justifiable excuse for failing to address that fundamental issue in its CVC Motion 4.

D. The PTAB May Exercise Its Discretion To Deny CVC Motion 4

Finally, the PTAB may exercise its discretion to deny CVC Motion 4. As the former interference rules set forth, "the administrative patent judge ***may*** add the application or patent to the interference on such terms as may be fair to all parties." 37 C.F.R. § 1.642 (emphasis added) (1998). As the Board has explained, "[t]he operative word in the above-quoted section is 'may' – a discretionary term." *Louis v. Okada*, 2001 Pat. App. LEXIS 154, *16 (BPAI Jan. 9, 2001) (informative); *Winter v. Fujita*, 2000 Pat. App. LEXIS 3, *22 (BPAI Jan. 5, 2000) ("Action under Rule 642 is discretionary."). Here, CVC was on notice of the key issue in this interference, namely, the patentable distinct invention of cleavage plus integration via HDR, as recited in both CVC Claim 164 and Sigma Claim 31. CVC's failure to address that issue in CVC Motion 4 is more than a sufficient basis for the Board to deny this motion.

Moreover, Patent Examiner Jennifer Dunston issued a Notice of Allowance for the '181 patent (Application No. 15/188,911) and the '716 patent (Application No. 15/188,924) on April 21, 2020, and May 5, 2020, respectively. Ex. 1112; Ex. 1113. At that time, Examiner Dunston was well aware of Sigma's efforts to provoke an interference with the CVC applications. *See, e.g.*, Ex. 1114 at 1 (Petition to the Director and Chief APJ to Declare an Interference, dated July 19, 2019); Ex. 1115 at 1, 7 (Renewed Petition to the Director and Chief APJ to Declare an Interference, including Rule 202 Statement, dated October 17, 2019); Ex. 1116 at 1, 10 (Partial Withdrawal and Supplementation of Renewed Petition, including Supplemental Rule 202

Statement, dated April 6, 2020).[4] The Examiner nonetheless determined that the '181 patent the '716 patent were patentably distinct from CVC's applications. Thus, for that additional reason, the Board may reasonably exercise its discretion to deny CVC Motion 4 here. *See Winter v. Fujita*, 2000 Pat. App. LEXIS at *23 ("[I]f the examiner determines that no interference exists, then there is no reason to declare a second interference or add the second reissue to an existing interference."). As the Board has explained in a similar context:

> [Even a]ssuming that the claims of Kanzaki's Patent Nos. 5,950,500 and 5,473,964, are drawn to the same patentable invention as the count in this interference, we nonetheless exercise our ***discretion*** not to add either patent to this on-going interference, to keep this interference simple, as one solely between junior party Sauer's Patent No. 5,513,717 and senior party Kanzaki's application 08/818,964. This interference can be conducted in a more speedy and inexpensive manner without the addition of Kanzaki's issued patents . . . .
>
> In this interference, we are addressing the conflict between Sauer's Patent No. 5,513,717 and Kanzaki's application 08/818,964, nothing more. The Sauer patent stands in the way of issuance of the Kanzaki application. An interference has been declared in order to provide an answer as to whether the Sauer patent precludes the issuance of the Kanzaki application. The proposed addition of Kanzaki patents into this interference does not help in any way in resolving the bar which Sauer may provide to the allowance of the Kanzaki application.

Louis v. Okada, 2001 Pat. App. LEXIS at *18-20 (emphasis in original).

Accordingly, even assuming that the Sigma Patents are drawn to the same patentable invention as Count 1 (which Sigma does not concede), this interference "can be conducted in a more speedy and inexpensive manner without the addition of [Sigma's] issued patents." *See id.*; s*ee also* 37 C.F.R. § 41.1(b) (setting forth the Board's responsibility "to secure the just, speedy, and inexpensive resolution of every proceeding"). Further, CVC's proposed addition of the Sigma Patents to this interference "does not help in any way in resolving the bar which [CVC]

[4] With respect to this interference, Sigma filed the operative Second Amended Supplemental Rule 202 Statement on October 13, 2020 (Ex. 1117).

may provide to the allowance of the [Sigma] application." *See id.* Accordingly, for these additional reasons, the Board may reasonably exercise its discretion to deny CVC Motion 4.

VI. 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 4.

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
1080	Cannon Supp'l Decl.
1112	15188911 (NOA) (2020-04-21)
1113	15188924 (NOA) (2020-05-05)
1114	15456204 (Petition) (2019-07-19)
1115	15456204 (Petition) (2019-10-17)
1116	15456204 (Petition) (2020-04-06)
1117	15456204 (202 Statement) (2020-10-13)

APPENDIX 2

RESPONSE TO CVC'S STATEMENT OF MATERIAL FACTS

1. 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

2. 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

3. 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: Admitted

4. Jinek 2012 showed that Cas9 can be programmed with dual-molecule guide RNA or single-guide RNA to target and cleave target DNA. Ex. 2031, 820, Figs. 1-5; Ex. 2549, ¶¶34-37.

Response: Denied

5. 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

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

Response: Denied

7. 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

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

Response: Denied

9. 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

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

Response: Denied

11. The prior art contained multiple examples of attaching the SV40 NLS either to the N-terminus or C-terminus of proteins to target them to the nucleus in a variety of eukaryotic cell types. Ex. 2551, Fig. 8; Ex. 2118, 24391; Ex. 2112, 3095; Ex. 2111, Fig. 1; Ex. 2117, 42189; Ex. 2564, Fig. 1; Ex. 2552, 100; Ex. 2553, 6375; Ex. 2396; Ex. 2587; ; Ex. 2549, ¶¶38-39.

Response: Denied

12. HDR is a natural cellular process that integrates DNA into a chromosomal sequence using flanking regions within a donor sequence with substantial identity to sequences on either side of a break as part of its repair mechanism. Ex. 2135, 637; Ex. 2549, ¶64.

Response: Admitted

13. HDR uses a single-stranded oligonucleotide, double-stranded oligonucleotide, or a double-stranded DNA plasmid as the donor sequence. Ex. 2578, 5560; Ex. 2549, ¶82.

Response: Denied

14. Before December 2012, HDR-based genome editing had used donor constructs to generate mutations as small as a single-base-pair change. Ex. 2135, 637; Ex. 2549, ¶90.

Response: Denied

15. Before December 2012, the C-terminal SV40 NLS was used as part of commercially available vectors. Ex. 2396; Ex. 2587; Ex. 2549, ¶¶42, 60.

Response: Denied

16. Before December 2012, HDR-based gene editing methods had used a donor sequence that has at least one nucleotide change relative to the target DNA. Ex. 2135, 637; Ex. 2549, ¶90.

Response: Denied

17. Before December 2012, gene-editing experiments had been performed both *in vitro* and *in vivo*, including in human cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; Ex. 2135, 636; Ex. 2549, ¶¶69-71.

Response: Denied

18. Before December 2012, MGAS15252 was a known *S. pyogenes* strain that the prior art disclosed as a "reference genome sequence." Ex. 2554; Ex. 2549, ¶73.

Response: Admitted

19. The prior art taught methods of introducing mRNA or DNA into eukaryotic cells to facilitate protein expression. Ex. 2577, Fig 1; Ex. 2549, ¶¶76-81.

Response: Denied

20. Chemical synthesis of RNA was a reliable, common, inexpensive, and commercially available method for preparing RNA before December 2012. Ex. 2031, Suppl. Materials and Methods, 1, Table S3; Ex. 2549, ¶72.

Response: Denied

21. Jinek 2012 teaches that *S. pyogenes* Cas9 is "efficient, versatile, and programmable" in cleaving eukaryotic DNA, and "could offer considerable potential for gene-targeting and genome-editing applications." Ex. 2031, 820, Figs 1-5; Ex. 2549, ¶47.

Response: Denied

22. Before December 2012, Jinek 2012 was considered a "breakthrough" because of the promise of its disclosed CRISPR-Cas9 gene editing system. Ex. 2556; Ex. 2549, ¶¶47-48.

23. In late 2012, at least three different research groups were performing CRISPR-Cas9 gene-editing experiments in eukaryotic cells using *S. pyogenes* Cas9, a 5' DNA-targeting region, and a C-terminal SV40 NLS. Ex. 2033, 7; Ex. 2345, 823 and Fig. 1; Ex. 2154, Fig. 1 and Suppl. p. 2; Ex. 2549, ¶54.

Response: Denied

24. Sigma has disclaimed claims 1, 5-10, 12, 13, and 15-20 of the '716 patent. Ex. 2611.

Response: Admitted

SIGMA'S STATEMENT OF MATERIAL FACTS

25. In CVC Motion 4, CVC's analysis was not conducted using the two-way obviousness test for evaluating the Sigma Patents, namely, whether each of Sigma's patents contain at least one claim that is patentably indistinct from Count 1. *Ledenev v. Adest*, 2020 Pat. App. LEXIS 6912, *35-36, Decision on Motions, at 31, 35 (PTAB Mar. 25, 2020) (JTM).

26. In CVC Motion 4, CVC states that "[i]n this motion, 'Count 1' refers to Sigma's half of Count 1 and comparisons are made against Sigma's half of the count, unless otherwise specified." CVC Mot. 4 at 1, n. 1.

27. In CVC Motion 4, all of CVC's analyses and claim charts are directed to Sigma's part of the 2-part "McKelvey Count," namely, Claim 31 of Sigma's involved '204 application. CVC Mot. 1.

28. In CVC Motion 4, CVC did not address Sigma Proposed Count 2.

29. CVC did not file any responsive motion to add Sigma's '181 and '716 patents in view of Sigma Proposed Count 2.

31. In CVC Motion 4, with respect to claim "Element 13", the Sigma '181 and '716 patents' claims are broader than Count 1. CVC Mot. 4, Appx. 3 at 3-3, Appx. 5 at 5-3.

32. None of the Sigma '181 and '716 patents' claims recite a homology-directed repair (HDR) process. CVC Mot. 4, Appx. 3-6.

33. In the early December 2012 time frame, the CRISPR-Cas9 technology was in its infancy. Ex. 1001 ¶ 100; Ex. 1080 ¶ 82.

34. In the early December 2012 time frame, whether integration of a donor polynucleotide via HDR in a eukaryotic cell could be accomplished in that the bacteria-derived CRISPR-Cas9 system was unpredictable and uncertain. Ex. 1001 ¶¶ 100-157, Summary; Ex.

1080 ¶¶ 58-75.

35. Sigma P1 discusses non-HDR processes that lead to DNA repair, including NHEJ ligation repair processes for integration of an exogenous sequence and modification of a chromosomal sequence. Ex. 1080 ¶ 82.

36. CVC does not substantively address whether Count 1's recital of the "homology-directed repair (HDR) process" would have been non-obvious in view of "Element 13" of the Sigma '181 and '716 patents.

37. Jinek (2012) contains no teachings about cleaving eukaryotic DNA. Ex. 1080 ¶¶ 83-84.

38. Before filing CVC Motion 4, CVC was on notice that Sigma contended that the invention of CRISPR-Cas9 cleavage plus integration via HDR in a eukaryotic cell, as recited in both CVC Claim 164 and Sigma Claim 31, is patentably distinct from CRISPR-Cas9 cleavage alone in a eukaryotic cell. Sigma List of Proposed Motions (Paper 26) at 3 (Aug. 10, 2021); Order Authorizing Motions (Paper 30) at 7-8 (Sept. 20, 2021).

39. Count 1's recital of "DNA homology-directed (HDR) repair" would have been non-obvious in view of claims that are silent in that regard. Ex. 1001 ¶¶ 100-157, Summary; Ex. 1080 ¶¶ 58-75.

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 4
(to Add the Claims of Sigma Patent Nos. 10,731,181 and 10,745,716)

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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