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 4 (to add Sigma's patents)**

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## I. INTRODUCTION

The PTAB should grant CVC's motion to add Sigma's U.S. Patent Nos. 10,731,181 and 10,745,716 to this interference because their claims are directed to the same invention at issue in this interference. CVC's motion showed that Sigma's patent claims correspond to the count under the *one-way* analysis of 37 C.F.R. § 41.207(b)(2). Sigma's insistence on applying a *two-way* analysis between the count and its claims is contrary to precedent and illogical because CVC merely seeks to add patents to an existing interference that already satisfied the two-way test for an interference-in-fact.

The PTAB applies Rule 207(b)(2) when deciding motions to add a patent to an existing interference. *See, e.g.*, *Ledenev v. Adest*, No. 106,112, Paper 137, Decision on Motions, at 30 (P.T.A.B. Mar. 25, 2020). Under Rule 207(b)(2)'s *one-way* analysis, a claim corresponds to a count if the count, treated as prior art, anticipates or renders obvious the claim. CVC demonstrated that all claims of Sigma's '181 patent (claims 1-17) and the non-disclaimed claims in Sigma's '716 patent (claims 2-4, 11, 14, and 21-22) would have been obvious over Count 1, and therefore correspond to Count 1 under Rule 207(b)(2).

Sigma construes "Element 13" of its claims as including HDR and non-HDR processes for DNA repair. But even under Sigma's construction, its claims correspond to its half of Count 1 under Rule 41.207(b)(2). Sigma admits that Element 13 of its half of Count 1 is limited to HDR. Thus, Element 13 of Sigma's half of Count 1 would have anticipated Element 13 of its claims (which encompasses HDR), and Sigma's half of Count 1 would have rendered obvious its claims for the reasons discussed in CVC's motion.

Sigma does not—and cannot—dispute that Count 1 renders obvious the claims CVC seeks to add, *viz*., that the claims correspond to Count 1 under Rule 207(b)(2). Instead, Sigma advances an improper *two-way* analysis between the count and its claims. Sigma posits that CVC

was required to show that (i) Count 1 renders at least one claim of each of Sigma's patents obvious, *and (ii) at least one claim of each of Sigma's patents renders Count 1 obvious.* But Sigma cites no instance where the PTAB applied a *two-way* analysis between the count and the claims in any context. Neither *Ledenev* nor the other authorities Sigma cites support its position.

Finally, contrary to Sigma's argument, CVC's motion would not be rendered moot if the PTAB were to grant Sigma's Motion 1. Sigma's Proposed Count 2 retains Sigma's half of Count 1 and, as such, Sigma's patent claims (regardless of construction) would also correspond to Proposed Count 2 under Rule 41.207(b)(2) for the same reasons that they correspond to Count 1.

In sum, Sigma has not rebutted CVC's showing that Sigma's patents should be added to this interference given that Sigma's claims—under either party's construction—correspond to Count 1 or Proposed Count 2 under Rule 41.207(b)(2). Sigma's Motion 1 also requires this outcome. There, Sigma argues that an interference with Proposed Count 2 should involve CVC's claims irrespective of whether they are limited to HDR; based on Sigma's assertions, its claims should be added to the interference irrespective of whether they are limited to HDR.

## II. ARGUMENT

### a. CVC correctly applied the one-way analysis set forth in Rule 41.207(b)(2) to demonstrate that claims 1-17 of Sigma's '181 patent and claims 2-4, 11, 14, and 21-22 of Sigma's '716 patent correspond to Count 1.

#### i. A movant must apply a one-way analysis between an existing count and the claims under Rule 41.207(b)(2) to show claim correspondence in a motion to add a patent in an existing interference.

Since the current interference rules were promulgated, the PTAB has applied a one-way analysis to determine claim correspondence when deciding motions to add a patent to an existing interference. 37 C.F.R. § 41.207(b)(2); *Ledenev v. Adest*, Paper 137, at 30, 31; *Ritzberger v. Durschang*, No. 106,012, Paper 210, Decision on Priority and Other Motions, at 17-25 (P.T.A.B.

Sept. 29, 2016). In *Ledenev*, when assessing a motion to add a patent, the PTAB cited Rule 41.207(b)(2) for the proposition that "[a] claim corresponds to the Count if the subject matter of the Count, treated as prior art to the claims, would have anticipated or rendered obvious the subject matter of the claims. *Bd.R. 207(b)(2).*" *Ledenev*, Paper 137, at 30 (emphasis added). Similarly, the PTAB applied Rule 41.207(b)(2)'s one-way analysis four years earlier in *Ritzberger* when granting a motion to add patents in an existing interference because "the claims of the three additional [] patents would have been obvious in view of the Count." *Ritzberger*, Paper 210, at 20. Thus, the PTAB applies a *one-way* analysis when assessing motions to add a patent in an existing interference. This is for good reason, because if the PTAB enters judgment against the patentee under 35 U.S.C. § 102(g), the earlier invention by another will be prior art to all the patentee's claims. The just, speedy, and inexpensive administration of the interference requires disposition of those patent claims in the interference.

**ii. No authority supports Sigma's position that adding a patent to an existing interference requires a *two-way* analysis between the *existing count* and the *patent's claims*.**

On pg. 4, line 5 to line 8 of the opposition, Sigma incorrectly argues that CVC's motion fails because it did not apply a "*two-way* obviousness test" to show "whether each of Sigma's patents contain *at least one claim* that is patentably indistinct from *Count 1*." *Id.* (emphasis added); *see also id*. at 6:1-5. The response is that Sigma advances the untenable position that a party moving to add a patent to an existing interference must perform a *two-way* analysis between the count and the patent claims, showing each renders the other unpatentable. MF40. This is directly contrary to Rule 41.207(b)(2), which requires only a *one-way* analysis with the count treated as prior art to the claims. The only instance where the PTAB applies a *two-way* analysis is *between the parties' claims* to determine interference-in-fact when *declaring an*

*interference* in the first instance. *See* 37 C.F.R. §§ 41.202(a) and 41.203(a). No authority supports Sigma's position to apply a *two-way* analysis that compares *the count* and *the claims*.

On pg. 2, line 9 to pg. 3, line 19 of the opposition, Sigma cites 37 C.F.R. § 1.642 (2004) (removed), *Winter v. Fujita*, 37 C.F.R. § 41.202(a), 37 C.F.R. § 41.203(a), 37 C.F.R. § 41.203(d), and *Ledenev v. Adest* in alleged support. *See also id*. at 4:4-12. The response is that these authorities do not support a two-way analysis between the count and the claims when adding a patent to an existing interference. Rule 1.642 is an old interference rule that does not have an applicable corresponding current rule. *Winter* does not support the proposition that Sigma argues and it involved the old interferences rules. *Winter v. Fujita*, 53 U.S.P.Q.2d 1234, 1248 (B.P.A.I. Nov. 16, 1999) (Ex. 2657). In recent interferences, the PTAB has expressly refused to apply the old interference rules that are no longer in force. *Ledenev*, at 31 (refusing to apply Rule 1.637 (c)(3)(ii) when deciding a motion to add a patent because it was "an 'old interference rules' rule that [was] outdated . . . is no longer in force.").

Current interference rules 41.202(a), 41.203(a), and 41.203(d) do not support Sigma's *two-way* count vs. claim analysis. No matter what these rules state, *Ledenev* and *Ritzberger* both applied a *one-way* count vs. claim analysis under Rule 41.207(b)(2) when deciding motions to add a patent to an interference. The PTAB's analysis in these cases was correct and dictated by the only logical reading of the rules Sigma cites. Rule 41.203(d) states that a "party may suggest the addition of a patent … to the interference," and that the "suggestion should make the showings required under [Rule] 41.202(a)." Rule 41.202(a) concerns what a suggestion for a new interference requires, and cites Rule 41.203(a) ("41.203 Declaration. (a) Interfering subject matter") only as it applies to determinations of interference-in-fact, *i.e.*, whether an interference should be declared in the first instance. Here, the PTAB has already determined that interfering

subject matter exists under Rule 41.203(a). Where, as here, an interference already exists, a further showing under Rule 41.203(a) is superfluous; rather, the movant need only show, under Rule 41.202(a)(2), that the patent claims correspond to the existing interference count.

Further, Sigma's reliance on Rules 41.202(a), 41.203(a), and 41.203(d) to support its two-way ***count*** vs. *claim* analysis cannot be correct since Rule 41.203(a) sets forth a two-way ***claim*** vs. *claim* analysis. And *Ledenev* expressly rejected a two-way ***claim*** vs. *claim* analysis when assessing whether to add a patent to an existing interference. *Ledenev*, Paper 137, at 35. According to the panel in *Ledenev*: "The standard to be applied is whether the claim is patentably distinct from the *Count*, not other claims. 37 C.F.R. 41.207(b)(2) (2012)." *Id.* at 31 (emphasis in original). In sum, consistent with *Ledenev* and *Ritzberger*, Rule 41.207(b)(2) applies—not Sigma's circuitous path from Rule 41.203(d) to Rule 41.202(a) and back to Rule 41.203(a).

Finally, Sigma misrepresents *Ledenev*. Sigma's opposition includes the following parenthetical to its citation of *Ledenev*: "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 on upon the movant [is] to compare the claims to the count in the required two-way analysis.'" Paper 709, Sigma Opp. 4, 3:15-19; *see also id*. at 4:8-12. In that parenthetical, Sigma combined quotes from different portions of *Ledenev* and misleadingly presented those portions as though they appeared together. The *Ledenev* statement Sigma quotes in the first half of its parenthetical is from page 31 of *Ledenev*, and the complete statement expressly emphasized Rule 41.207(b)(2) as the applicable analysis for a motion to add a patent to an existing interference, noting: "The standard to be applied is whether the claim is patentably distinct from the *Count*, not other claims. **37 C.F.R. 41.207 (b)(2) (2012)**." *Ledenev*, Paper 137, at 31 (italicized emphasis in original, bold-face emphasis added).

The *Ledenev* statement Sigma quotes in the second half of its parenthetical is from four pages later in the decision (page 35) and is not germane to *Ledenev's* prescribed analysis under Rule 41.207(b)(2) for a motion to add a patent to an existing interference. The statement is unique to the facts in *Ledenev* where the movant had incorrectly proposed a two-way analysis between the parties' claims based on the old interference rules, and the statement simply addresses the movant's flawed analysis. *Id.* at 35.

Thus, Sigma's position[1] is contrary to Rule 41.207(b)(2), *Ledenev*, and *Ritzberger*—all of which require only a one-way analysis between the count and the patent claims when adding a patent to an existing interference.

**iii. CVC showed that Sigma's claims correspond to Count 1 under Rule 41.207(b)(2).**

Supported by Dr. Bailey's opinions, CVC conclusively showed that the '181 and '716 patent claims would have been obvious over Sigma's half of Count 1 in view of Jinek 2012 and Krebber 2000 or Lange 2007. Paper 478, CVC Mot. 4, 1:9-2:21, 4:27-12:22, Appx. 3-6; Ex. 2549, ¶¶ 9, 29-97. Sigma does not challenge CVC's showing. Paper 709, Sigma Opp. 4, 1:5-11, 4:1-9:2; MF41. Dr. Cannon's statements relied upon by Sigma also do not dispute Dr. Bailey's opinion that Sigma's half of Count 1 renders its patent claims obvious. Paper 709, Sigma Opp. 4,

[1] Sigma also applies its improper analysis disingenuously. It does not explain how any of its patent claims fail its analysis with *both* halves of the count. Instead, Sigma compares its claims *only to its half* of the count after construing "Element 13" of its claims as not limited to HDR. In doing so, Sigma ignores CVC's half of the count that is also not limited to HDR and clearly would have undermined Sigma's argument that its patent claims fail its proposed analysis.

6:6-9:2; Ex. 1001, ¶ 100-157; Ex. 1080, ¶¶ 58-75; MF42. Thus, CVC showed that Sigma's patent claims correspond to Count 1 under Rule 41.207(b)(2), and the PTAB should grant CVC's motion.

On pg. 8, lines 7-23 of the opposition, Sigma argues that CVC mischaracterized Jinek 2012 as teaching cleaving eukaryotic DNA. The response is that Sigma's argument is irrelevant and factually incorrect. First, CVC did not rely on Jinek 2012 to meet the eukaryotic limitation of Sigma's claims. Sigma's half of Count 1, which is prior art to its claims under Rule 41.207(b)(2), includes HDR-mediated donor integration in a *eukaryotic cell* and therefore satisfies the eukaryotic limitation of the claims. Thus, Sigma's argument is irrelevant. Second, CVC was factually accurate when describing Jinek 2012. CVC cited Dr. Bailey's opinion that "Jinek 2012's *S. pyogenes* Cas9 protein would have been appealing because that Cas9 protein was successfully used to specifically cleave a eukaryotic DNA sequence (GFP) as part of *in vitro* experiments." Paper 478, CVC Mot. 4, 5:21-27; Ex. 2549, ¶ 47. Jinek 2012 targeted a plasmid vector DNA containing the GFP gene, which is obtained from a eukaryote (*Aequorea*, aka jellyfish) and thus is a eukaryotic DNA. Ex. 2031, Fig. 5D ("Five chimeric RNAs . . . to cleave a GFP gene–containing plasmid."); Ex. 2549, ¶ 47; Ex. 2396, 1; MF43, 44. Thus, Sigma's argument is irrelevant and incorrect.

**iv. Even under Sigma's proposed construction, the '181 and '716 patent claims correspond to Count 1 under Rule 41.207(b)(2).**

Sigma does not argue that its patent claims, as construed by CVC, fail Sigma's proposed two-way analysis with Count 1. MF45. Instead, on pg. 6, line 6 to pg. 9, line 2 of the opposition, Sigma argues that all of its patent claims are not limited to HDR-mediated repair of the DNA cleaved by CRISPR-Cas9. According to Sigma, its claims broadly recite "repair of the double-stranded break by a DNA repair process." Paper 709, Sigma Opp. 4, 7:1-6. In alleged support of

this position, Sigma points to its P1 and argues that "Element 13" of its claims includes both HDR and non-HDR processes that lead to DNA repair, including NHEJ ligation repair processes for integration of an exogenous sequence (recited in claim 1 of the '181 patent) and modification of a chromosomal sequence (recited in claim 1 of the '716 patent). *Id*. at 4, 6:6-8:6. Thus, Sigma concludes that its claims include both HDR and non-HDR processes that lead to DNA repair. Sigma does not dispute CVC's construction of any other element of Sigma's claims or Sigma's half of Count 1.[2]

The response is that even accepting Sigma's proposed construction, Sigma's claims still would have been obvious over Count 1. Briefly, Sigma admits that Element 13 of Sigma's half of Count 1 is limited to HDR-mediated DNA repair, noting that it "specifically recites: repair of the double-stranded break ***by a DNA homology-directed repair (HDR) process*** leads to integration . . . into the chromosomal sequence." Paper 709, Sigma Opp. 4, 6:9-15 (emphasis in original). As explained above, Sigma also argues that Element 13 of its claims encompasses

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[2] Sigma misrepresents CVC's position, arguing that CVC did not "emphasize [] 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." Paper 709, Sigma Opp. 4, 6:16-18. To the contrary, CVC's claim charts treated Element 13 of Sigma's claims as they treated other elements that CVC considered were the same between Sigma's claims and its half of Count 1, such as Elements 1 and 2. Paper 478, CVC Mot. 4, Appx. 3-6. CVC argued that Sigma's claims and Sigma's half of Count 1 both require HDR and that the two differ only by three non-patentable aspects: recitation of *S. pyogenes* Cas9; C-terminal SV40 NLS; and DNA-targeting region at the 5' end of the guide RNA. *Id.*, 1:10-18.

HDR-mediated DNA repair. Thus, Element 13 of Count 1 would have anticipated Element 13 of Sigma's claims. Sigma does not challenge CVC's analysis of any other claim element in view of Count 1. Paper 478, CVC Mot. 4, 1:9-2:21, 4:27-12:22, Appx. 3-6. Accordingly, for reasons presented in CVC's motion, Sigma's half of Count 1 would have also rendered Sigma's claims obvious even under Sigma's proposed construction.

As discussed in CVC's motion, Sigma's patent claims are also similar to Sigma's claims that are already in the interference, and they are similar to CVC's claims that are not limited to HDR and already in the interference. Paper 478, CVC Mot. 4, 11:21-12:22; Paper 4, Jr. Party's Clean Copy of Claims. As such, even under Sigma's construction, its patent claims correspond to Count 1 under Rule 41.207(b)(2) and its patents should be added to the interference.

**b. Granting Sigma's motion 1 would not render CVC's motion to add Sigma's '181 and '716 patents moot.**

On pg. 3, lines 20-25 of the opposition, Sigma argues that CVC's motion would be moot upon granting of Sigma Motion 1. The response is that if the PTAB redeclares the interference with Proposed Count 2, for the reasons in CVC's motion, Sigma's patents should be included in the redeclared interference with all claims of its '181 patent and claims 2-4, 11, 14, and 21-22 of its '716 patent corresponding to Proposed Count 2. CVC's motion showed that Sigma's patent claims correspond to Sigma's half of the Count 1 under the one-way analysis of Rule 41.207(b)(2). Paper 478, CVC Mot. 4, 1:9-2:21, 4:27-12:22; *see also* Section II.a.iii above. Even under Sigma's construction, its patent claims correspond to its half of Count 1. *See* Section II.a.iv above. Sigma's half of Proposed Count 2 is the same as that of Count 1. Thus, CVC's arguments for correspondence of Sigma's patent claims to Sigma's half of Count 1 also support their correspondence to Sigma's half of Proposed Count 2 (under either party's construction).

The PTAB should include Sigma's patents in any redeclared interference with their identified claims corresponding to Proposed Count 2 in view of Sigma's arguments.

## III. CONCLUSION

Because all claims (claims 1-17) of Sigma's '181 patent and claims 2-4, 11, 14, and 21-22 of Sigma's '716 patent (as construed by either party) correspond to Count 1 or Proposed Count 2 under the one-way analysis set forth in 37 C.F.R. § 41.207(b)(2), the PTAB should grant CVC's motion and add Sigma's patents in this interference with the identified claims corresponding to Count 1 or Proposed Count 2.

Respectfully submitted,

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# APPENDIX 1: LIST OF EXHIBITS

| Exhibit No. | Description |
|---|---|
| 1001 | Cannon Decl. |
| 1080 | Cannon Supp'l Decl. |
| 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) |
| 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) |
| 2033 | Jinek, M., *et al*., "RNA-programmed genome editing in human cells," *eLife* 2:e00471, 1-9 (2013) |
| 2110 | Holt, N., *et al*., "Zinc finger nuclease-mediated CCR5 knockout hematopoietic stem cell transplantation controls HIV-1 in vivo," *Nat Biotechnol.* 28(8):839-847 (2010) |
| 2111 | Mussolino, C., *et al*., "A novel TALE nuclease scaffold enables high genome editing activity in combination with low toxicity," *Nucleic Acids Research* 39(21):9283-9293 (2011) |
| 2112 | Reiss, B., *et al*., "RecA protein stimulates homologous recombination in plants," *Proc. Natl. Acad. Sci*. 93:3094-3098 (1996) |
| 2117 | Planey, S.L., *et al*., "Inhibition of Glucocorticoid-induced Apoptosis in 697 Pre-B Lymphocytes by the Mineralocorticoid Receptor N-terminal Domain," *J. Biol. Chem*. 277(44): 42188-42196 (2002) |
| 2118 | Dai, Y-S., *et al*., The Transcription Factors GATA4 and dHAND Physically Interact to Synergistically Activate Cardiac Gene Expression through ap300-dependent Mechanism, *J. Biol. Chem*. 277(27): 24390 – 24398 (2002) |
| 2135 | Urnov, F.D., *et al*., "Genome editing with engineered zinc finger nucleases," *Nat Rev Genet* 11:636-646 (2010) |
| 2154 | Cho, S.W., *et al*., "Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease," *Nature Biotechnol*. 31(3):230-232, Supplementary Information (2013) |

| Exhibit No. | Description |
|---|---|
| 2221 | Lange, A., *et al*., "Classical Nuclear Localization Signals: Definition, Function, and Interaction with Importin α," *J. Biol. Chem.* 282(8): 5101–5105 (2007) |
| 2345 | Mali, P. *et al*., "RNA-Guided Human Genome Engineering via Cas9," *Science* 339(6121): 823-826 (2013) |
| 2348 | Dingwall, C. and Laskey, R.A., "Nuclear targeting sequences-a consensus?" *TIBS* 16:478-481 (1991) |
| 2396 | pAcGFP1-Nuc Vector Information, Clontech (2003) |
| 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) |
| 2551 | Zhang, Y.A., *et al*., "Regulated Nuclear Trafficking of the Homeodomain Protein Otx1 in Cortical Neurons," *Molecular and Cellular Neuroscience* 19:430-446 (2002) |
| 2552 | Lee, C.M., *et al*., "Correction of the ΔF508 Mutation in the Cystic Fibrosis<br>Transmembrane Conductance Regulator Gene by Zinc-Finger Nuclease Homology-Directed Repair," *BioResearch Open Access* 1(3): 99-108 2012 |
| 2553 | Greenwald, D.L., *et al*., "Engineered Zinc Finger Nuclease–Mediated Homologous<br>Recombination of the Human Rhodopsin Gene," *IOVS* 51(12): 6374-6380 (2010) |
| 2554 | Fittipaldi, N., *et al*., "Genomic Analysis of *emm*59 Group A *Streptococcus* Invasive Strains, United States," *Emerging Infectious Diseases* 18(4): 650-652 (2012) |
| 2556 | Genomic Cruise Missiles, *Science* 338:1526-1527 (2012) |
| 2564 | Carlson, D.F., *et al*., "Efficient TALEN-mediated gene knockout in livestock," *PNAS* 109(43): 17382 – 17387 (2012) |
| 2577 | Kim, T.K., and Eberwine, J.H., "Mammalian cell transfection: the present and the future," *Anal Bioanl Chem* 397:3173-3178 (2010) |
| 2578 | Ramirez, C.L., *et al*., "Engineered zinc finger nickases induce homology-directed repair with reduced mutagenic effects," *Nucleic Acids Research* 40(12): 5560–5568 (2012) |
| 2587 | pShooter™ Vector Information, Life Technologies (2012) |

| Exhibit No. | Description |
|---|---|
| 2611 | Statutory Disclaimer, dated October 13, 2020, filed in U.S. Patent No. 10, 745,716 (U.S. Appl. No. 15/188,924) |
| 2657 | *Winter v. Fujita*, 53 U.S.P.Q.2d 1234 (B.P.A.I. Nov. 16, 1999) |

# APPENDIX 2: STATEMENT OF MATERIAL FACTS

**CVC's Material Facts 1-24 (with Sigma's Responses)**

**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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's Response: Denied.**

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

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

**10.** Before December 2012, the SV40 NLS was "the model" for NLSs. Ex. 2348, 478; Ex. 2549, ¶39. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's 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. **Sigma's Response: Not provided. Therefore admitted by Sigma under SO ¶41.122.**

**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. **Sigma's Response: Denied.**

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

**Sigma's Response: Admitted.**

**Sigma's Material Facts 25-39 (with CVC's Responses)**

**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). **CVC's Response: Admitted that CVC did not conduct a two-way obviousness test between at least one claim and Count 1 in its Motion 4. Denied that *Ledenev v. Adest* adopts a two-way obviousness test between at least one claim and Count 1 for evaluating a motion to add a patent to an existing interference.**

**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. **CVC's Response: Admitted.**

**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. **CVC's Response: Admitted.**

**28.** In CVC Motion 4, CVC did not address Sigma Proposed Count 2. **CVC's Response: Denied.**

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

**30. Material Fact 30 absent from Sigma's Statement of Material Facts.**

**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. **CVC's Response: Denied.**

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

**33.** In the early December 2012 time frame, the CRISPR-Cas9 technology was in its infancy. Ex. 1001 ¶ 100; Ex. 1080 ¶ 82. **CVC’s Response: Denied.**

**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. **CVC’s Response: Denied.**

**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. **CVC’s Response: Denied.**

**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. **CVC’s Response: Admitted that “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”; denied that such an analysis is required.**

**37.** Jinek (2012) contains no teachings about cleaving eukaryotic DNA. Ex. 1080 ¶¶ 83-84. **CVC’s Response: Denied.**

**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). **CVC's Response: Denied.**

**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. **CVC's Response: Denied.**

**CVC's Additional Material Facts 40-45**

**40.** Sigma argues that a movant requesting to add a patent to an existing interference must apply a two-way analysis between the count and the patent claims. Paper 709, Sigma Opp. 4, 4:5-8, 6:1-5.

**41.** Sigma does not challenge CVC's showing that claims 1-17 of the '181 patent and claims 2-4, 11, 14, and 21-22 of the '716 patent would have been obvious over Sigma's half of Count 1 in view of Jinek 2012 and Krebber 2000 or Lange 2007. Paper 709, Sigma Opp. 4, 1:5-11, 4:13-5:18.

**42.** Dr. Cannon does not dispute Dr. Bailey's opinion that Sigma's half of Count 1 renders obvious claims 1-17 of its '181 patent and claims 2-4, 11, 14, and 21-22 of its '716 patent. Ex. 1001, ¶ 100-157; Ex. 1080, ¶¶ 58-75.

**43.** GFP DNA is from a eukaryote (*Aequorea*, aka jellyfish). Ex. 2549, ¶ 47; Ex. 2396, 1.

**44.** Jinek 2012 targeted a plasmid vector DNA containing the GFP gene. Ex. 2031, Fig. 5D.

**45.** Sigma does not argue that its patent claims, as construed by CVC, do not meet Sigma's proposed two-way analysis with Count 1. Paper 709, Sigma Opp. 4.

## CERTIFICATE OF SERVICE

I hereby certify that the foregoing **CVC REPLY 4** was 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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