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

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I. STATEMENT OF PRECISE RELIEF REQUESTED

CVC respectfully requests that the Board grant CVC's miscellaneous motion to add Sigma's U.S. Patent No. 10,731,181 ("the '181 patent) and No. 10,745,716 ("the '716 patent") (collectively, "Sigma's 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[1] because they would have been obvious over Count 1 and Jinek 2012, in view of Krebber 2000 or Lange 2007.[2]

II. STATEMENT OF MATERIAL FACTS AND EVIDENCE

Appendix 1 is a list of Exhibits cited. Appendix 2 is a Statement of Material Facts.

III. ARGUMENT

Sigma's Patents and Count 1 all encompass methods for modifying a chromosomal sequence in a eukaryotic cell by introducing and integrating a donor sequence via a CRISPR/Cas9 system. They also all encompass using a nuclear localization signal ("NLS")-tagged Cas9 and a guide RNA with a DNA-targeting region. The nominal differences between the Sigma Patents' claims and Count 1 are the recitation of the well-established Cas9 protein (from *S. pyogenes*), a well-known nuclear localization signal (a C-terminal SV40 NLS), and the natural and previously disclosed location for the DNA-targeting region (at the 5' end of the guide RNA). MF 1. These are not patentable differences and all would have been obvious to a skilled artisan, as Dr. Bailey's declaration explains in detail. Ex. 2549, ¶¶9, 29-32. This conclusion is supported by highly similar claims already being involved in this proceeding as part of Sigma's U.S. Application No.

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[1] In 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. However, CVC maintains that the claims in Sigma's patents would have been obvious in view of either half of the count because both halves are directed to the same invention.

[2] Sigma disclaimed claims 1, 5-10, 12, 13, and 15-20 of the '716 patent on Oct. 13, 2020. Ex. 2611; MF 24.

15/456,204 ("the '204 application")—and Sigma has not requested de-designating such claims.

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.

The claims of Sigma's patents would have been obvious because all of the nominal differences between the claims of Sigma's Patents and Count 1 either had been disclosed in Jinek 2012 (Ex. 2031) or had been well known for years. Ex. 2549, ¶¶33-42; MF 2-11. A skilled artisan would have been motivated to apply Jinek 2012's *S. pyogenes* Cas9 and 5' DNA-targeting region in the gene-editing system of Count 1 because Jinek 2012 states that its system offers considerable potential for genome-editing applications. A skilled artisan also would have had reason to tag Cas9 on its C-terminus with an SV40 NLS, as disclosed in Krebber 2000 (Ex. 2023) or Lange 2007 (Ex. 2221), because these NLSs were the most widely used NLSs, and were even part of commercially-available tools for targeting proteins to the nucleus. Finally, a skilled artisan would have had a reasonable expectation of success in modifying Count 1 according to Jinek 2012, Krebber 2000, and Lange 2007 because the modifications involved no more than applying well-known and proven details to the presumptively functional Count 1. Moreover, there are no objective indicia of non-obviousness that would distinguish Sigma's claims from Count 1.

A. State of the Art.

1. Count 1, which is treated as prior art, discloses a method for modifying a chromosomal sequence in eukaryotic cells using a CRISPR-Cas9 system.

By rule, Count 1 is "treated as prior art" to Sigma's patent claims for the purposes of this motion. 37 C.F.R. § 41.207(b)(2); *The Univ. of Calif. v. The Broad Inst., Inc.*, Interference No. 106,115, Paper 877, 43, 66 (P.T.A.B. Sept. 10, 2020); Ex. 2400, 43, 66. Sigma's half of Count 1

recites a method of modifying a chromosomal sequence in a eukaryotic cell by introducing and integrating a donor sequence using a CRISPR/Cas9 system. Ex. 2549, ¶¶44-45. Sigma's half of Count 1 also includes introducing into the eukaryotic cell an NLS-tagged Cas9 protein, a guide RNA comprising a DNA-targeting region and a Cas9-interacting region, and a donor polynucleotide. *Id.* For the purposes of this motion *only*, CVC has treated the filing date of Sigma's US 61/734,256 (December 6, 2012) as the prior art reference date for purposes of establishing other knowledge in the prior art.

2. Jinek 2012 disclosed a CRISPR-Cas9 system using S. pyogenes Cas9 and one of several guide RNA structures with a 5' DNA-targeting region.

Jinek 2012 disclosed in June 2012 for the first time that the DNA cleavage complex of the CRISPR Type II system contained three components: Cas9, crRNA, and tracrRNA. Ex. 2031, Abstract; Ex. 2549, ¶¶33-37; MF 2-4. Jinek 2012 noted that this system "offer[s] considerable potential for gene-targeting and genome-editing applications" because of its ability to "be programmed with guide RNA engineered as a single transcript to target and cleave any [double-stranded DNA] sequence of interest." Ex. 2031, 820; Ex. 2549, ¶¶33; MF 4, 21. Jinek 2012 was indisputably a seminal paper and was considered a "breakthrough" because of the promise of this gene editing system. *See, e.g.*, Ex. 2556; Ex. 2305; Ex. 2549, ¶¶47-48; MF 22.

Jinek 2012's experiments used "Cas9 protein derived from the pathogen *Streptococcus pyogenes* … and test[ed] its ability to cleave a plasmid DNA or an oligonucleotide duplex." Ex. 2031, 816; Ex. 2549, ¶33; MF 2. Jinek 2012's tests included showing *in vitro* DNA cleavage using a complex of *S. pyogenes* Cas9 with a dual guide RNA (dgRNA). Ex. 2031, Figs. 1-4; Ex. 2549, ¶34; MF 2-4. Jinek 2012 also showed that *S. pyogenes* "Cas9 can be programmed using a single engineered RNA molecule combining tracrRNA and crRNA features (*i.e.*, an sgRNA)." Ex. 2031, Fig. 5; Ex. 2549, ¶¶35-37; MF 4. Jinek 2012 further disclosed the structure of the dgRNA and sgRNA, both of which mimicked the naturally occurring structure by placing the DNA-targeting region at the 5' end of the guide RNA. Ex. 2031, Figs. 1E, 3C, 5B; Ex. 2549, ¶¶34; MF 3-4.

3. The prior art taught that the NLS from SV40 large T antigen was the

canonical NLS for targeting proteins to the nucleus.

By December 2012, NLSs were well-known to be useful for their ability to "target a normally nonnuclear protein to the nucleus" of eukaryotic cells when fused to that protein. Ex. 2023, 283-284; Ex. 2549, ¶38; MF 11. The "most commonly used NLS peptide" in NLS-tagged proteins was the NLS from the SV40 large T antigen protein. Ex. 2550, 451-452; Ex. 2120; Ex. 2023, 285; Ex. 2549, ¶¶39-41; MF 9-10. The SV40 NLS was first identified in 1984, and has been used to target proteins to the nucleus in eukaryotic cells ever since. Ex. 2550, 451-452; Ex. 2120; Ex. 2023, 285; MF 9. As a 1991 article put it, "[t]he well-characterized nuclear targeting sequence of SV40 large T antigen, PKKKRKV, [is] *regarded as the model* [for NLSs]." Ex. 2348, 478 (emphasis added); Ex. 2023, 285; Ex. 2549, ¶39; MF 6-7, 10. Moreover, prior art references such as Lange 2007 taught using an alternative version of "the SV40 large T antigen NLS" with the sequence PKKKRRV. Ex. 2221, 3; Ex. 2549, ¶39; MF 8. These two NLS sequences are listed as SEQ ID NOs: 1 and 2 in Sigma's Patents. Ex. 2549, ¶¶44-45; MF 6, 8.

Consistent with its well-known nature, the prior art contained numerous examples of attaching an SV40 NLS to the N- or C-terminus of proteins to successfully target proteins to the nucleus in a variety of cell types. Ex. 2549, ¶¶38-39; Ex. 2564, Fig. 1 (disclosing N-terminal NLS tags on TALE proteins); Ex. 2551, 438, Fig. 8 (disclosing "fusion proteins in which the SV40 NLS [PKKKRKV] has been added to the C-terminus"); Ex. 2118, 24391; Ex. 2117, 42189; Ex. 2564, Fig. 1; Ex. 2552, 100; Ex. 2553, 6375; MF 11. Before December 2012, there were even commercially available vectors for expressing proteins tagged with a C-terminal SV40 NLS. Ex. 2396; Ex. 2587; Ex. 2549, ¶42; MF 11, 15. Skilled artisans routinely attached a SV40 NLS to a wide variety of proteins, including ZFNs, TALENs, RecA, LacZ, meganucleases, and HaloTag™ reporter proteins. *See, e.g.*, Ex. 2555, 12032; Ex. 2564, 17383; Ex. 2138, 8; Ex. 2553, 6375; Ex. 2140, 2; Ex. 2549, ¶¶39-42; MF 9-11. For example, a 2002 publication from Zhang *et al.* disclosed "[a]ddition of an SV40 nuclear localization sequence (NLS)" to the C-terminus of a range of fusion proteins. Ex. 2551, 438; MF 11.

B. Claim 1 of the '181 Patent Corresponds to Count 1.

In view of Count 1 and other prior art, a skilled artisan would have recognized that the '181 patent's claim 1 would have been obvious as "the predictable use of prior art elements according to their established functions," in view of Count 1, Jinek 2012, and Krebber 2000 or Lange 2007. *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); Ex. 2549, ¶¶43-61.

1. A skilled artisan would have been motivated to perform Count 1's method according to Jinek 2012's, Krebber 2000's, and Lange 2007's teachings, arriving at claim 1's method.

Count 1's method is highly similar to that of the '181 patent's claim 1. Ex. 2549, ¶¶44-45. Both Count 1 and claim 1 recite introducing a CRISPR-Cas9 system comprising an NLS-tagged Cas9, a guide RNA that includes a DNA-targeting region, and a donor sequence into eukaryotic cells. *Id.* The difference between Count 1 and claim 1 is that claim 1 provides additional details on the NLS-tagged Cas9 protein and guide RNA. *Id.* In particular, claim 1 specifies which Cas9 protein to use (*S. pyogenes*), where the DNA-targeting region is located within the guide RNA (the 5' end), and which NLS to use (SEQ ID NO: 1 or 2 at the C-terminus of Cas9). *Id.*; MF 1. However, a skilled artisan practicing Count 1's method necessarily would have had to select a Cas9 protein, a guide RNA structure, and an NLS from *some* source to perform the method recited in Count 1. Ex. 2549, ¶¶46-55. As discussed below, a skilled artisan would have had reason to use Jinek 2012, Krebber 2000 and Lange 20007 to fill these gaps, such that Count 1, Jinek 2012, and Krebber 2000 or Lange 2007 teach all elements of claim 1 of the '181 patent. *Id.*; *See* Appendix 3.

In deciding which Cas9 protein to use in the CRISPR-Cas9 system of Count 1, a skilled artisan would have had reason to use the *S. pyogenes* Cas9 protein disclosed in Jinek 2012. Ex. 2549, ¶47. 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; MF 2, 21. Given the revolutionary impact of Jinek 2012 on the gene-editing field, a skilled artisan would have been motivated also to use *S. pyogenes* Cas9 because of its efficiency, versatility, and programmability. Ex. 2549, ¶47; Ex. 2556, Ex. 2305.

In deciding which guide RNA structure to use in the CRISPR-Cas9 system of Count 1, a skilled artisan would have followed Jinek 2012's disclosure to use a guide RNA with the DNA-targeting region at the 5' end. Ex. 2549, ¶¶48-50. All of Jinek 2012's guide RNA structures used guide RNAs with a 5' DNA-targeting region, consistent with the "predicted tracrRNA:crRNA secondary structure" of the natural system. Ex. 2031, 818, Figs. 1E, 3C, 5B; Ex. 2549, ¶¶34-35, 48-50, MF 4-5. For example, Jinek 2012's Figure 5 shows the chimera A guide RNA, with its DNA-targeting region noted on the 5' end. Ex. 2031, Fig. 5B; Ex. 2549, ¶¶48-50; MF 4.

In deciding which NLS to use in the CRISPR-Cas9 system of Count 1, a skilled artisan would have been motivated to use an NLS having SEQ ID NO: 1 (*i.e.*, PKKKRKV) because that sequence was known to be the "most commonly used NLS peptide." Ex. 2550, 451-452; Ex. 2023, 285; Ex. 2549, ¶¶51-53; MF 9-10. Krebber 2000 discloses targeting proteins to the nucleus by attaching the SV40 NLS that matches SEQ ID NO: 1, at either terminus of the targeted protein. Ex. 2023, 285, 289-290; Ex. 2017, 7:63-8:7; Ex. 2549, ¶51; MF 6-7. As an alternative, the skilled artisan likewise would have had reason to use Lange 2007's variant of the SV40 NLS (*i.e.*, SEQ ID NO: 2) because it "exemplified" NLSs. Ex. 2221, 3; Ex. 2549, ¶52; MF 8. Moreover, a skilled artisan would have had reason to place the SV40 NLS on Cas9's C-terminus because the SV40 NLS functions at either terminus of a protein to direct the protein to the nucleus. Ex. 2023, 289-290; Ex. 2549, ¶53; MF 7; *see* § III.A.3 above.

The choices made by other research groups performing CRISPR-Cas9 gene-editing experiments in eukaryotic cells in late 2012 shows the readily apparent nature of using *S. pyogenes* Cas9, a 5' DNA-targeting region, and a C-terminal SV40 NLS. At least three different research groups chose to use all three of these components as part of their eukaryotic gene-editing experiments. Ex. 2033, 7; Ex. 2345, 823 and Fig. 1; Ex. 2154, Fig. 1 and Suppl. p. 2; Ex. 2549, ¶54; MF 23. "Independently made, simultaneous inventions, made within a comparatively short space of time, are persuasive evidence that the claimed apparatus was the product only of ordinary mechanical or engineering skill." *Geo M. Martin Co. v. Alliance Machine Systems Intern. LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (quotations omitted). Moreover, "simultaneous invention

can be compelling evidence of obviousness, because it shows the claimed invention was the product only of ordinary mechanical skill or engineering skill, rather than genuine invention." *Regents of Univ. of California v. Broad Institute*, 903 F. 3d 1286, 1295 (Fed. Cir. 2018).

2. A skilled artisan would have had a reasonable expectation of success in performing claim 1's method in view of Count 1, Jinek 2012, and Krebber 2000 or Lange 2007.

A skilled artisan would have had an expectation of success in performing the method of Count 1 in eukaryotic cells because "whether a CRISPR-Cas9 system would have been expected to work in a eukaryotic cell…is assumed under the framework of 37 C.F.R. § 41.207(b)(2), wherein Count 1 is presumed to be prior art to the…claims." *The Univ. of Calif. v. The Broad Inst., Inc.*, Interference No. 106,115, Paper 877, 66 (P.T.A.B. Sept. 10, 2020); Ex. 2400, 66. From that base, a skilled artisan also would have reasonably expected success in applying the teachings of Jinek 2012, Krebber 2000, and Lange 2007 in the context of Count 1 as claimed, because doing so would have required applying only proven and reliable methods. Ex. 2549, ¶¶56-62.

A skilled artisan would have reasonably expected success in using Jinek 2012's *S. pyogenes* Cas9 and guide RNA structure as part of a CRISPR-Cas9 system because it would have involved no more than applying proven methods and using standard reagents and techniques. Ex. 2549, ¶¶57-58. Jinek 2012's *in vitro* data demonstrated that *S. pyogenes* Cas9 was a reliable enzyme that can target and cleave a variety of DNA sequences adjacent to a PAM. Ex. 2031, Figs. 1-5; Ex. 2549, ¶57; MF 2, 4. Similarly, a skilled artisan would have recognized that Jinek 2012's guide RNA structures with a 5' DNA-targeting region were effective and mimic the natural arrangement in CRISPR systems. Ex. 2031, 818, Figs. 1-5; Ex. 2549, ¶58; MF 3-5. Moreover, suitable methods (*e.g.*, for transfection) and tools (*e.g.*, expression vectors) were readily available to facilitate expressing *S. pyogenes* Cas9 and guide RNAs in eukaryotic cells, which would have necessitated only well-known molecular biology techniques and ordinary skill. *See, e.g.*, Ex. 2577, 3173; Ex. 2396; Ex. 2587. Ex. 2549, ¶60; MF 15, 19-20.

A skilled artisan also would have reasonably expected success in applying Krebber 2000's

or Lange 2007's method of using an SV40 NLS because the SV40 NLS had regularly and successfully delivered non-nuclear proteins to the nucleus, including when the NLS is attached directly to the C-terminus of the tagged protein. *See* § III.A.3 above; Ex. 2549, ¶59; MF 9-11. Moreover, a skilled artisan would have had further expectation of success because of the presumption that Count 1's method, which uses an NLS-tagged Cas9, can operate successfully. Therefore, claim 1 would have been prima facie obvious to a skilled artisan in view of Count 1, Jinek 2012, and Krebber 2000 or Lange 2007.

C. Claims 2-17 of the '181 patent and claims 2-4, 11, 14, and 21-22 of the '716 patent correspond to Count 1.

As discussed below, each of claims 2-17 of the '181 patent and claims 2-4, 11, 14, and 21-22 of the '716 patent would have been obvious over Count 1 and Jinek 2012, in view of Krebber 2000 or Lange 2007. Ex. 2549, ¶¶63-96; Appendix 4 and Appendix 6.

'716 patent claim 1. Each of claims 2-4, 11, 14, and 21-22 of the '716 patent depend from claim 1. Thus, while Sigma has disclaimed claim 1 of the '716 patent, analyzing claims 2-4, 11, 14, and 21-22 necessarily includes analysis of the limitations of claim 1. Claim 1 of the '716 patent recites essentially all of the same features as claim 1 of the '181 patent. The '716 patent's claim 1 is directed to methods "for modifying a chromosomal sequence in a eukaryotic cell," while the '181 patent's claim 1 is directed to a subgenus of the '716 patent's claimed methods in which the chromosomal modification is "integrating an exogenous sequence into a chromosomal sequence of a eukaryotic cell." Essentially, introducing and integrating a donor sequence is "optional[]" in the '716 patent's method but is required by the '181 patent's method. Otherwise, these two method claims are identical. Therefore, the same disclosures and arguments discussed above with respect to the '181 patent also apply to claim 1 of the '716 patent. Ex. 2549, ¶¶84-88; Appendix 5.

'181 patent claim 2 and **'716 patent claim 3.** A skilled artisan would have had reason to use a donor polynucleotide with flanking regions with substantial identity to sequences on either side of the target site because homology-directed repair ("HDR")-based gene editing, which is recited in Count 1, is "driven by the inclusion of extended homologous sequences flanking the

gene of interest." Ex. 2135, 637; Ex. 2549, ¶¶64, 91; MF 12. A skilled artisan would have reasonably expected success in doing so because such donor polynucleotides with flanking regions are part of the standard HDR process. *See, e.g.*, Ex. 2580, 1-2; Ex. 2135, 637; Ex. 2579, 438; Ex. 2549, ¶¶64, 91; MF 12.

'716 patent claims 2 & 11. A skilled artisan would have had reason to use a donor sequence that has at least one nucleotide change because the prior art disclosed HDR-based "genome editing using donor constructs…[to generate mutations] as small as a single-base-pair change." Ex. 2135, 637; Ex. 2031, 816; Ex. 2549, ¶¶90, 93; MF 12. A skilled artisan would have had a reasonable expectation of success in doing so because of prior successes with such donor polynucleotides and because including a nucleotide change would not alter the methods used as part of Count 1. Ex. 2135, 637; Ex. 2549, ¶¶90, 93; MF 13-14.

'181 patent claim 3 and **'716 patent claim 4.** A skilled artisan would have reason to use a donor polynucleotide with a targeted cleavage site that is recognized by the RNA-guided Cas9 because the HDR system relies upon homology with the target sequence and surrounding regions to be cleaved. *See, e.g.*, Ex. 2580, 1; Ex. 2549, ¶¶65, 92; MF 12. A skilled artisan would have had a reasonable expectation of success in doing so because other HDR-based genome editing methods had successfully used such donor polynucleotides. *See, e.g.*, Ex. 2582, 1463-1464, Figs. 1-2; Ex. 2583, 5054; Ex. 2584, 50-51, Fig. 2; Ex. 2549, ¶¶65, 92; MF 13-14.

'181 patent claims 4 & 5. A skilled artisan would have reason to introduce the Cas9 protein as either an mRNA or DNA because those were two established ways to facilitate protein expression in eukaryotic cells. Ex. 2577, Fig 1; Ex. 2549, ¶¶66-68; MF 19. A skilled artisan would have had a reasonable expectation of success with such methods in view of their well known and proven nature. Ex. 2577, Fig 1; Ex. 2549, ¶¶66-68; MF 19.

'181 patent claim 6. A skilled artisan would have had reason to use a human cell because that cell type was often used for genome editing experiments. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; Ex. 2135, 636; Ex. 2549, ¶69; MF 17. A skilled artisan would have had a reasonable expectation of success with such methods in view of the field's extensive experience and successes

with human cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; Ex. 2549, ¶69.

'181 patent claims 7 & 8. A skilled artisan would have had reason to use an *in vitro* or *in vivo* eukaryotic cell because gene editing was useful both "in human cells [*in vitro*] and a number of model organisms." Ex. 2135, 636; Ex. 2549, ¶¶70-71; MF 17. A skilled artisan would have had a reasonable expectation of success with such methods in view of the field's extensive experience and past successes both *in vitro* and *in vivo*. Ex. 2135, 636; Ex. 2549, ¶¶70-71; MF 17.

'181 patent claim 9. A skilled artisan would have had reason to chemically synthesize guide RNA because that was a reliable, common, inexpensive, and commercially available method for preparing RNA, and because Jinek 2012 teaches using "synthetic oligonucleotides and RNAs." Ex. 2031, Suppl. Mats., 1, Table S3; Ex. 2549, ¶72; MF 20. A skilled artisan would have had a reasonable expectation of success in obtaining and using synthetic RNAs given their well known and proven nature, and the availability of commercial synthesis vendors. Ex. 2031, Suppl. Mats., 1, Table S3; Ex. 2549, ¶72; MF 20.

'181 patent claim 10. A skilled artisan would have had reason to use MGAS15252 Cas9 with an appended SV40 NLS (i.e., SEQ ID NO: 9) because MGAS15252 was a known *S. pyogenes* "reference genome sequence." Ex. 2554, 650; Ex. 2549, ¶73; MF 18. A skilled artisan also would have reasonably expected success with this Cas9 given MGAS15252's status as a *S. pyogenes* reference sequence, Jinek 2012's demonstration of the efficacy of *S. pyogenes* Cas9, and the established positive track record of SV40 NLS. Ex. 2549, ¶73; MF 4, 9, 20.

'181 patent claims 11 & 12. As explained above in §§ III.A.3 and III.B.1-2, a skilled artisan would have had a reason to select an SV40 NLS listed as SEQ ID NO: 1 or SEQ ID NO: 2, with a reasonable expectation of success. Ex. 2549, ¶¶74-75.

'181 patent claims 13-15. These claims recite introducing mRNA or DNA encoding Cas9, when the guide RNA is either two non-covalently bound RNA molecules or a single RNA molecule. A skilled artisan would have reason to introduce the Cas9 protein as either a mRNA or DNA because those were two established ways to introduce a nucleic acid encoding a protein into eukaryotic cells, and would have had reason to use either two non-covalently bound RNA

molecules or a single RNA molecule as the guide RNA because those were the principal options disclosed in the art for a guide RNA. Ex. 2031, Figs. 1 and 5; Ex. 2549, ¶¶76-81; MF 4, 19. A skilled artisan would have had a reasonable expectation of success in performing these methods in view of the standard nature of introducing DNA and mRNA into cells, and in view of Jinek 2012's success in using both dgRNA and sgRNA to cleave target DNA. Ex. 2031, Figs. 1 and 5; Ex. 2577, Fig 1; Ex. 2549, ¶¶76-81; MF 4, 19.

'716 patent claim 14. A skilled artisan would have had reason to perform claim 14's method, with a reasonable expectation of success, for the same reasons as discussed for claim 1 because claim 14 differs only in making the donor DNA non-optional. Ex. 2549, ¶94.

'181 patent claims 16 & 17 and **'716 patent claims 21 & 22**. A skilled artisan would have had reason to use either double stranded DNA or single stranded DNA as a donor polynucleotide because HDR was known to use either as a repair template. Ex. 2578, 5560; Ex. 2549, ¶¶82-83, 95-96; MF 13. A skilled artisan would have had a reasonable expectation of success with either type of DNA because both "can promote efficient introduction of desired insertions, deletions or substitutions." Ex. 2578, 5560; Ex. 2549, ¶¶82-83, 95-96; MF 13, 21.

D. No Objective Indicia Support the Patentability of Sigma's Patents.

There are no objective indicia of non-obviousness that would distinguish the additional limitations of Sigma's claims from Count 1. Ex. 2549, ¶97. Sigma did not present evidence of objective indicia during prosecution of the '181 or '716 patents. Thus, each of the Sigma Patent claims identified above would have been obvious over Count 1 in view of the art.

E. Claims that are highly similar to those in Sigma's Patents are *already* part of this proceeding without contest

The Board has already decided that all claims in Sigma's involved '204 application correspond to Count 1, and Sigma has not argued for the separate patentability of any of the '204 patent claims. This status is relevant to this motion because the '204 application's claims contain limitations that are highly similar or identical to limitations in the claims in Sigma's Patents. Two of the nominal differences between Count 1 and the independent claims in Sigma's Patents are

that the claims recite using *S. pyogenes* Cas9 and that the Cas9 is tagged with an NLS consisting of SEQ ID NO: 1 or 2. But claims in Sigma's involved '204 application that correspond to Count 1 also specify using *S. pyogenes* Cas9 (claim 39) and SEQ ID NO: 1 or 2 (claims 42 and 43). And the remaining differences (the 5' DNA-targeting region and the C-terminal NLS location) were well established in the art. *See* § III.B.3 above. Similarly, most of the dependent claims in Sigma's Patents contain limitations essentially identical to claims in Sigma's involved '204 application, as shown below. The Board should treat these analogous claims no differently than the involved claims and designate them as corresponding to Count 1.

ALIGNMENT OF SIGMA'S PATENT DEPENDENT CLAIMS WITH INVOLVED CLAIMS

Claims Compared	Limitation in Common
'181 claim 4 → '204 claim 37	The nucleic acid encoding Cas9 is mRNA
'181 claim 5 → '204 claim 38	The nucleic acid encoding Cas9 is DNA
'181 claim 6 → '204 claim 44	The eukaryotic cell is a human cell, a nonhuman mammalian cell, or a plant cell
'181 claim 9 → '204 claim 36	The guide RNA is chemically synthesized
'181 claim 10 → '204 claim 40	The Cas9 protein is from *S. pyogenes* strain MGAS15252 and comprises SEQ ID NO: 9
'181 claim 11 → '204 claim 42	The NLS consists of SEQ ID NO: 1
'181 claim 12 → '204 claim 43	The NLS consists of SEQ ID NO: 2
'181 claim 13 → '204 claims 34/37	The nucleic acid encoding Cas9 is mRNA and the guide RNA is comprised of two non-covalently bound RNA molecules
'181 claim 14 → '204 claims 33/37	The nucleic acid encoding Cas9 is mRNA and the guide RNA is comprised of a single RNA molecule
'181 claim 15 → '204 claims 33/37	The nucleic acid encoding Cas9 is mRNA, the guide RNA is encoded by DNA, and the guide RNA is comprised of a single RNA molecule
'181 claim 16 and '716 claim 21 → '204 claim 45	The donor polynucleotide is double stranded DNA
'181 claim 17 and '716 claim 22 → '204 claim 46	The donor polynucleotide is single stranded DNA

F. CVC will prevail on priority relative to Sigma's Patents.

Sigma's related patents are members of the same family as Sigma's involved application and claim the same December 6, 2012, priority date. Accordingly, the priority case asserted as part of CVC's other pleadings is applicable here as well. Briefly, CVC's P1 and P2 were filed before

the earliest claimed priority date of Sigma's involved patent family. Each of these applications describes and enables embodiments within the scope of Count 1, in that they describe using eukaryotic cells (*e.g.*, a fish cell, a human cell, or a fruit fly cell) comprising a Type II CRISPR-Cas9 system as recited in Count 1. These embodiments include a sgRNA and *S. pyogenes* Cas9. Moreover, during the priority phase CVC will provide proofs to show earlier conception and diligence to a reduction to practice.

IV. CONCLUSION

For the reasons set forth above, claims 1-17 of the '181 patent and claims 2-4, 11, 14, and 21-22 of the '716 patent are directed to the same invention as Count 1. Therefore, the Board should designate these claims as corresponding to Count 1. There are no adequate alternative remedies because leaving Sigma's patents out of this proceeding risks the inefficiency and expense of duplicative interference proceedings involving CVC and Sigma.

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Appendix 1: List of Exhibits

Exhibit No.	Description
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)
2120	Kalderon, D., *et al*., "A Short Amino Acid Sequence Able to Specify Nuclear Location," *Cell* 39:499-509 (1984)
2135	Urnov, F.D., *et al*., "Genome editing with engineered zinc finger nucleases," *Nat Rev Genet* 11:636-646 (2010)
2138	Meng, X., *et al*., "Targeted gene inactivation in zebrafish using engineered zinc finger nucleases," *Nat. Biotechnol*. 26(6):695-701 (2008)
2140	Foley, J.E., *et al*., "Rapid Mutation of Endogenous Zebrafish Genes Using Zinc Finger Nucleases Made by Oligomerized Pool Engineering (OPEN)," *PLoS ONE* 4(2):e4348, pp. 1-13 (2009)
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)
2221	Lange, A., *et al*., "Classical Nuclear Localization Signals: Definition, Function, and Interaction with Importin α," *J. Biol. Chem.* 282(8): 5101–5105 (2007)
2305	The Nobel Prize in Chemistry 2020 Press Release, The Royal Swedish Academy of Sciences, 1 page, October 7, 2020

Exhibit No.	Description
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)
2400	Decision on Motions 37 C.F.R. § 41.125(a), *The Regents of the University of California v. The Broad Institute, Inc.,* Patent Interference No. 106,115, Paper 877, (September 10, 2020)
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 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 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)
2555	Zhang, F., *et al*., "High frequency targeted mutagenesis in *Arabidopsis thaliana* using zinc finger nucleases," *PNAS* 107(26): 12028-12033 (2010)
2556	Genomic Cruise Missiles, *Science* 338:1526-1527 (2012)
2564	Carlson, D.F., *et al*., "Targeting DNA With Fingers and TALENs," *Molecular Therapy-Nucleic Acids* 1:e3 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)
2579	Porteus, M.H., "Mammalian Gene Targeting with Designed Zinc Finger Nucleases," *Molecular Therapy* 13(2): 438 – 446 (2006)
2580	Liu, J. and Morrical, S.W., "Assembly and dynamics of the bacteriophage T4 homologous recombination machinery," *Virology Journal* 7:357 (2010)
2582	Carroll, D., "Progress and prospects: Zinc-finger nucleases as gene therapy agents," *Gene Therapy* 15: 1463–1468 (2008)

Exhibit No.	Description
2583	Gordley, R.M., *et al*., "Synthesis of programmable integrases," *PNAS* 106(13): 5053–5058 (2009)
2584	Joung, J.K. and Sander, J.D., "TALENs: a widely applicable technology for targeted genome editing," *Nat Rev Mol Cell Biol.* 14(1): 49–55 (2013)
2587	pShooter™ Vector Information, Life Technologies (2012)

Appendix 2: 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.

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.

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.

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.

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.

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

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.

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

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.

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

2549, ¶39.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

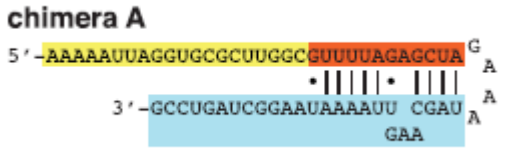
22. Before December 2012, Jinek 2012 was considered a "breakthrough" because of the promise of its disclosed CRISPR-Cas9 gene editing system. Ex. 2556; Ex. 2549, ¶¶47-48.

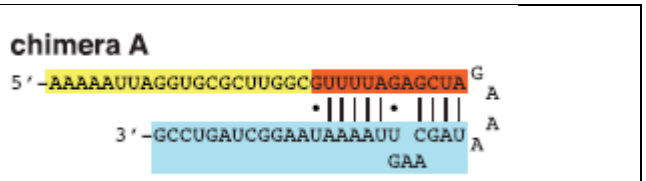
23. In late 2012, at least three different research groups were performing CRISPR-Cas9 gene-editing experiments in eukaryotic cells using *S. pyogenes* Cas9, a 5' DNA-targeting region, and a C-terminal SV40 NLS. Ex. 2033, 7; Ex. 2345, 823 and Fig. 1; Ex. 2154, Fig. 1 and Suppl. p. 2; Ex. 2549, ¶54.

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

Appendix 3: Claim Chart Comparing the '181 Patent's Claim 1 to Count 1, Jinek 2012, Krebber 2000, and Lange 2007

'181 Patent Claim 1 Elements	**Teachings of Count 1, Jinek 2012, and Krebber 2000**
Element 1: A method for integrating an exogenous sequence into a chromosomal sequence of a eukaryotic cell,	Count 1: "A method for modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence…"
Element 2: the method comprising: introducing into the eukaryotic cell:	Count 1: "…the method comprising **introducing into the eukaryotic cell**…"
Element 3: (i) at least one RNA-guided endonuclease or nucleic acid encoding at least one RNA-guided endonuclease, wherein the at least one RNA-guided endonuclease is a clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR associated (Cas) (CRISPR-Cas) type II system protein,	Count 1: "…**a Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR-Cas) type II protein** linked to only one nuclear localization signal (NLS) **or a nucleic acid encoding the CRISPR-Cas type II protein** linked to only one NLS…"
Element 4: wherein the nucleic acid encoding the CRISPR-Cas type II system protein is codon optimized for expression in the eukaryotic cell,	Count 1: "…the **nucleic acid encoding the CRISPR-Cas type II protein is codon optimized for expression in the eukaryotic cell**…"
Element 5: wherein the CRISPR-Cas type II system protein is a *Streptococcus pyogenes* Cas9 protein	Count 1: "…wherein the CRISPR-Cas type II protein is **a Cas9 protein**…" Jinek 2012: "[W]e used an overexpression system to purify **Cas9 protein derived from the pathogen *Streptococcus pyogenes*** (fig. S2, see supplementary materials and methods) and tested its ability to cleave a plasmid DNA or an oligonucleotide duplex bearing a protospacer sequence complementary to a mature crRNA, and a bona fide PAM."
Element 6: including at least one	Count 1: "…a Clustered Regularly Interspersed Short

nuclear localization signal consisting of SEQ ID NO: 1 or SEQ ID NO: 2 covalently attached to the C-terminal amino acid of the Cas9 protein sequence;	Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR-Cas) type II protein **linked to only one nuclear localization signal (NLS)** or a nucleic acid encoding the CRISPR-Cas type II protein **linked to only one NLS**…" Krebber 2000: "The classic NLS consists of basic amino acid residues that are either continuous (monopartite) or interrupted by several nonbasic residues (bipartite). **The canonical short NLS** from the simian virus 40 (sv40) large T antigen **is the 7-amino acid stretch PKKKRKV**." p. 285 Lange 2007: "Monopartite cNLSs are exemplified by the SV40 large T antigen NLS (**^{126}PKKKRRV^{132}**)…." p. 3
Element 7: and (ii) at least one engineered guide RNA or DNA encoding at least one engineered guide RNA	Count 1: "…(ii) **a guide RNA or DNA encoding the guide RNA**…"
Element 8: each guide RNA comprising (1) a first region at the 5′ end that base pairs with a target site in the chromosomal sequence,	Count 1: "…wherein the guide RNA comprises a **first region that is complementary to a target site in the chromosomal sequence**…" Jinek 2012: "Sequences of chimeric RNAs A and B are shown with DNA-targeting (yellow), crRNA repeat-derived sequences (orange), and tracrRNA-derived (light blue) sequences." Figure 5 
Element 9: and (2) a second region that forms a secondary structure which interacts with the at least one RNA-guided endonuclease;	Count 1: "…and a **second region that interacts with the CRISPR-Cas type II protein**…" Jinek 2012: "Sequences of chimeric RNAs A and B are shown with DNA-targeting (yellow), crRNA repeat-derived sequences (orange), and tracrRNA-derived (light blue) sequences." Figure 5

	
Element 10: and (iii) at least one donor polynucleotide comprising the exogenous sequence;	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…"
Element 11: whereby the at least one guide RNA guides the at least one RNA-guided endonuclease to the target site in the chromosomal sequence where the RNA-guided endonuclease introduces a double-stranded break,	Count: "…wherein the **guide RNA guides the CRISPR-Cas type II protein to the target site** in the chromosomal sequence, 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."
Element 12: the target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM),	Count: "…which **target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM)**…"
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**."

Appendix 4: Claim Chart Comparing the '181 Patent's Claims 2-17 to Count 1, Jinek 2012, Krebber 2000, and Lange 2007

'181 Patent Claim 2 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the exogenous sequence in the donor polynucleotide is flanked by sequences having substantial sequence identity to sequences on either side of the target site in the chromosomal sequence.	Count 1: "…a donor polynucleotide comprising **the donor sequence and upstream and downstream sequences**…" Count 1: "…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." General knowledge in the art: homologous recombination-based gene editing is "driven by the inclusion of **extended homologous sequences flanking the gene of interest**…." Ex. 2135, 637.

'181 Patent Claim 3 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the exogenous sequence in the donor polynucleotide further comprises a targeted cleavage site that is recognized by the at least one RNA-guided endonuclease.	Count 1: "…wherein the guide RNA comprises a first **region that is complementary to a target site in the chromosomal sequence**…" Count 1: "…wherein the **guide RNA guides the CRISPR-Cas type II protein to the target site** in the chromosomal sequence… General knowledge in the art: "Homologous recombination (HR) is a conserved biological process in which **DNA strands are physically exchanged between DNA molecules of identical or nearly identical**

	sequence." Ex. 2580, 1

'181 Patent Claim 4 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the at least one RNA-guided endonuclease is mRNA.	Count 1: "…a **nucleic acid encoding the CRISPR-Cas type II protein**…" General knowledge in the art: "Schematic diagrams of two different transfections…Foreign **mRNA (blue wave) is also delivered into the cytosol, where it is translated**." Ex. 2577, 3174, Fig. 1.

'181 Patent Claim 5 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the at least one RNA-guided endonuclease is DNA.	Count 1: "…a **nucleic acid encoding the CRISPR-Cas type II protein**…" General knowledge in the art: "Schematic diagrams of two different transfections…Foreign **mRNA (blue wave) is also delivered into the cytosol, where it is translated**." Ex. 2577, 3174, Fig. 1.

'181 Patent Claim 6 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the eukaryotic cell is a human cell, a nonhuman mammalian cell, or a plant cell.	Count 1: "A method for modifying a chromosomal sequence **in a eukaryotic cell**…"

'181 Patent Claim 7 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the eukaryotic cell is in vitro.	Count 1: "A method for modifying a chromosomal sequence **in a eukaryotic cell**…" General knowledge in the art: gene editing had been performed *in vitro*, *e.g.*, in cells such as "human embryonic stem and induced pluripotent stem cells … [and human] immune cells." Ex. 2135, 636.

'181 Patent Claim 8 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the eukaryotic cell is in vivo.	Count 1: "A method for modifying a chromosomal sequence **in a eukaryotic cell**…" General knowledge in the art: gene editing had been performed *in vivo*, *e.g.*, "in model organisms such as *Drosophila melanogaster*, *Arabidopsis thaliana*, zebrafish and rats." Ex. 2135, 636.

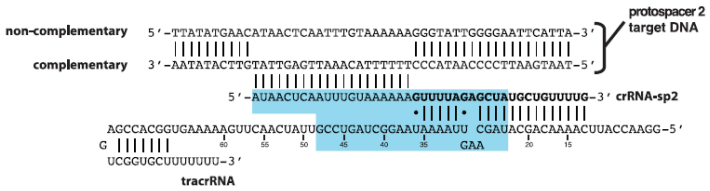
'181 Patent Claim 9 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the at least one guide RNA is at least partially chemically synthesized.	Jinek 2012: "VBC-Biotech Services, Sigma-Aldrich and Integrated DNA Technologies supplied the synthetic oligonucleotides and RNAs listed in Table S3." Suppl. Materials and Methods, p. 1

'181 Patent Claim 10 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the Cas9 protein is from Streptococcus pyogenes strain MGAS15252 and comprises SEQ ID NO: 9.	Count 1: "…wherein the CRISPR-Cas type II protein is **a Cas9 protein**…" General knowledge in the art: "The **reference genome sequence** … was that of the emm59 Canadian strain **MGAS15252** (GenBank accession no. CP003116)." Ex. 2554, 650.

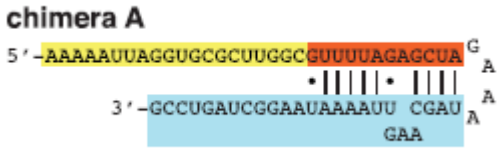
'181 Patent Claim 11 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the at least one nuclear localization signal covalently attached to the C-terminal amino acid of the Cas9 protein sequence consists of SEQ ID NO: 1.	Krebber 2000: "The classic NLS consists of basic amino acid residues that are either continuous (monopartite) or interrupted by several nonbasic residues (bipartite). **The canonical short NLS** from the simian virus 40 (sv40) large T antigen **is the 7-amino acid stretch PKKKRKV**." p. 285

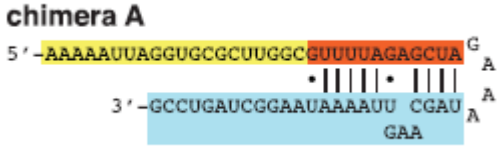
'181 Patent Claim 12 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the at least one nuclear localization signal covalently attached to the C-terminal amino acid of the Cas9 protein sequence consists of SEQ ID NO: 2.	Lange 2007: "Monopartite cNLSs are exemplified by the SV40 large T antigen NLS (^{126}**PKKKRRV**^{132})…." p. 3

'181 Patent	**Teachings of Count 1, Jinek 2012, Krebber 2000, and**

Claim 13 Elements	**Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the at least one RNA-guided endonuclease is mRNA and the at least one guide RNA is comprised of two non-covalently bound RNA molecules.	Count 1: "…a **nucleic acid encoding the CRISPR-Cas type II protein**…" Jinek 2012: "We show here that in a subset of these systems, the mature crRNA that is base-paired to trans-activating crRNA (tracrRNA) **forms a two-RNA structure** that directs the CRISPR-associated protein Cas9 to introduce double-stranded (ds) breaks in target DNA." Abstract Jinek 2012:  Figure 3 General knowledge in the art: "Schematic diagrams of two different transfections…Foreign **mRNA (blue wave) is also delivered into the cytosol, where it is translated**." Ex. 2577, 3174, Fig. 1.

'181 Patent Claim 14 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the at least one RNA-guided endonuclease is mRNA and the at least one guide RNA is comprised of a single RNA molecule.	Count 1: "…a **nucleic acid encoding the CRISPR-Cas type II protein**…" Jinek 2012: "The dual-tracrRNA:crRNA, when **engineered as a single RNA chimera**, also directs sequence-specific Cas9 dsDNA cleavage.." Abstract

	Jinek 2012:  Figure 5 General knowledge in the art: "Schematic diagrams of two different transfections…Foreign **mRNA (blue wave) is also delivered into the cytosol, where it is translated**." Ex. 2577, 3174, Fig. 1.

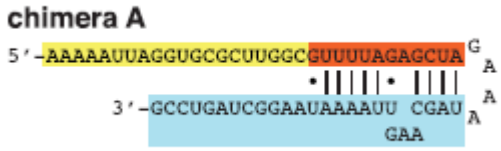
'181 Patent Claim 15 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the at least one RNA-guided endonuclease is DNA, the at least one guide RNA is encoded by DNA, and the at least one guide RNA is comprised of a single RNA molecule.	Count 1: "…a **nucleic acid encoding the CRISPR-Cas type II protein**…" Jinek 2012: "The dual-tracrRNA:crRNA, when **engineered as a single RNA chimera**, also directs sequence-specific Cas9 dsDNA cleavage.." Abstract Jinek 2012:  Figure 5 General knowledge in the art: "Schematic diagrams of two different transfections…**Foreign DNA (red wave) is delivered into the nucleus**." Ex. 2577, 3174, Fig. 1.

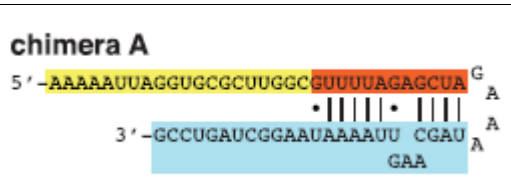
'181 Patent Claim 16 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the at least one donor polynucleotide is double stranded DNA.	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…" Count 1: "…repair of the double-stranded break by a **DNA** homology-directed repair (HDR) process…" General knowledge in the art: "[B]reaks at specific recognition sequences and can promote efficient introduction of desired insertions, deletions or substitutions at or near the cut site via homology-directed repair (HDR) **with a double-** and/or single-**stranded donor DNA template**." Ex. 2578, 5560.

'181 Patent Claim 17 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	See Appendix 3
Element 2: wherein the at least one donor polynucleotide is single stranded DNA.	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…" Count 1: "…repair of the double-stranded break by a **DNA** homology-directed repair (HDR) process…" General knowledge in the art: "[B]reaks at specific recognition sequences and can promote efficient introduction of desired insertions, deletions or substitutions at or near the cut site via homology-directed repair (HDR) **with a** double- and/or **single-stranded donor DNA template**." Ex. 2578, 5560.

Appendix 5: Claim Chart Comparing the '716 Patent's Claim 1 to Count 1, Jinek 2012, Krebber 2000, and Lange 2007

'716 Patent Claim 1 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: A method for modifying a chromosomal sequence in a eukaryotic cell,	Count 1: "A method for modifying a chromosomal sequence in a eukaryotic cell by integrating a donor sequence…"
Element 2: the method comprising: introducing into the eukaryotic cell	Count 1: "…the method comprising **introducing into the eukaryotic cell**…"
Element 3: (i) at least one RNA-guided endonuclease or nucleic acid encoding at least one RNA-guided endonuclease, wherein the at least one RNA-guided endonuclease is a clustered regularly interspersed short palindromic repeats (CRISPR)/CRISPR associated (Cas) (CRISPR-Cas) type II system protein,	Count 1: "…**a Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR-Cas) type II protein** linked to only one nuclear localization signal (NLS) **or a nucleic acid encoding the CRISPR-Cas type II protein** linked to only one NLS…"
Element 4: wherein the nucleic acid encoding the CRISPR-Cas type II system protein is codon optimized for expression in the eukaryotic cell,	Count 1: "…the **nucleic acid encoding the CRISPR-Cas type II protein is codon optimized for expression in the eukaryotic cell**…"
Element 5: wherein the CRISPR-Cas type II system protein is a *Streptococcus pyogenes* Cas9 protein	Count 1: "…wherein the CRISPR-Cas type II protein is **a Cas9 protein**…" Jinek 2012: "[W]e used an overexpression system to purify **Cas9 protein derived from the pathogen *Streptococcus pyogenes*** (fig. S2, see supplementary materials and methods) and tested its ability to cleave a plasmid DNA or an oligonucleotide duplex bearing a protospacer sequence complementary to a mature crRNA, and a bona fide PAM."

Element 6: including at least one nuclear localization signal consisting of SEQ ID NO:1 or SEQ ID NO:2 covalently attached to the C-terminal amino acid of the Cas9 protein sequence;	Count 1: "…a Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas) (CRISPR-Cas) type II protein **linked to only one nuclear localization signal (NLS)** or a nucleic acid encoding the CRISPR-Cas type II protein **linked to only one NLS**…" Krebber 2000: "The classic NLS consists of basic amino acid residues that are either continuous (monopartite) or interrupted by several nonbasic residues (bipartite). **The canonical short NLS** from the simian virus 40 (sv40) large T antigen **is the 7-amino acid stretch PKKKRKV**." p. 285 Lange 2007: "Monopartite cNLSs are exemplified by the SV40 large T antigen NLS (**^{126}PKKKRRV^{132}**)…." p. 3
Element 7: and (ii) at least one engineered guide RNA or DNA encoding at least one engineered guide RNA,	Count 1: "…(ii) **a guide RNA or DNA encoding the guide RNA**…"
Element 8: each guide RNA comprising (1) a first region at the 5′ end that base pairs with a target site in the chromosomal sequence,	Count 1: "…wherein the guide RNA comprises a **first region that is complementary to a target site in the chromosomal sequence**…" Jinek 2012: "Sequences of chimeric RNAs A and B are shown with DNA-targeting (yellow), crRNA repeat-derived sequences (orange), and tracrRNA-derived (light blue) sequences." Figure 5 
Element 9: and (2) a second region that forms a secondary structure which interacts with the at least one RNA-guided endonuclease;	Count 1: "…and a **second region that interacts with the CRISPR-Cas type II protein**…" Jinek 2012: "Sequences of chimeric RNAs A and B are shown with DNA-targeting (yellow), crRNA repeat-derived sequences (orange), and tracrRNA-derived (light blue) sequences." Figure 5

	
Element 10: and, optionally, (iii) at least one donor polynucleotide;	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…"
Element 11: whereby the at least one guide RNA guides the at least one RNA-guided endonuclease to the target site in the chromosomal sequence where the RNA-guided endonuclease introduces a double-stranded break,	Count: "…wherein the **guide RNA guides the CRISPR-Cas type II protein to the target site** in the chromosomal sequence, 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."
Element 12: the target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM),	Count: "…which **target site in the chromosomal sequence is immediately followed by a protospacer adjacent motif (PAM)**…"
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**."

Appendix 6: Claim Chart Comparing the '716 Patent's Claims 2-4, 11, 14, and 21-22 to Count 1, Jinek 2012, Krebber 2000, and Lange 2007

'716 Patent Claim 2 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 5
Element 2: wherein the optional donor polynucleotide comprises a donor sequence that has at least one nucleotide change relative to the chromosomal sequence near the target site in the chromosomal sequence.	Count 1: "A method for modifying a chromosomal sequence in a eukaryotic cell by **integrating a donor sequence**" Jinek 2012: "Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for **RNA-programmable genome editing.**" General knowledge in the art: researchers prior to 2012 were successfully using "genome editing using donor constructs…[to generate mutations] as small as **a single-base-pair change**." Ex. 2135, 637.

'716 Patent Claim 3 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 2,	*See* Appendix 5
Element 2: wherein the donor sequence is flanked by sequences having substantial sequence identity to sequences on either side of the target site in the chromosomal sequence.	Count 1: "…a donor polynucleotide comprising **the donor sequence and upstream and downstream sequences**…" Count 1: "…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." General knowledge in the art: homologous recombination-based gene editing is "driven by the inclusion of **extended homologous sequences flanking**

	the gene of interest….” Ex. 2135, 637.

’716 Patent Claim 4 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 2,	*See* Appendix 5
Element 2: wherein the donor sequence further comprises a targeted cleavage site that is recognized by the at least one RNA-guided endonuclease.	Count 1: “…a donor polynucleotide comprising **the donor sequence and upstream and downstream sequences**…” General knowledge in the art: “Homologous recombination (HR) is a conserved biological process in which **DNA strands are physically exchanged between DNA molecules of identical or nearly identical sequence**.” Ex. 2580, 1

’716 Patent Claim 11 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 5
Element 2: wherein the optional donor polynucleotide is introduced into the eukaryotic cell, and repair of the double-stranded break results in a change of at least one nucleotide in the chromosomal sequence.	Count 1: “A method for modifying a chromosomal sequence in a eukaryotic cell by **integrating a donor sequence**” Jinek 2012: “Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for **RNA-programmable genome editing.**” General knowledge in the art: researchers prior to 2012 were successfully using “genome editing using donor constructs…[to generate mutations] as small as **a single-base-pair change**.” Ex. 2135, 637.

’716 Patent Claim 14 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**

Element 1: The method of claim 1,	*See* Appendix 5
Element 2: wherein (i), (ii), and (iii) are introduced into the eukaryotic cell.	*See* Appendix 5

'716 Patent Claim 21 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 5
Element 2: wherein the optional donor polynucleotide is double stranded DNA.	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…" Count 1: "…repair of the double-stranded break by a **DNA** homology-directed repair (HDR) process…" General knowledge in the art: "[B]reaks at specific recognition sequences and can promote efficient introduction of desired insertions, deletions or substitutions at or near the cut site via homology-directed repair (HDR) **with a double-** and/or single-**stranded donor DNA template**." Ex. 2578, 5560.

'716 Patent Claim 22 Elements	**Teachings of Count 1, Jinek 2012, Krebber 2000, and Lange 2007**
Element 1: The method of claim 1,	*See* Appendix 5
Element 2: wherein the optional donor polynucleotide is single stranded DNA.	Count 1: "…(iii) **a donor polynucleotide** comprising the donor sequence and upstream and downstream sequences…" Count 1: "…repair of the double-stranded break by a **DNA** homology-directed repair (HDR) process…" General knowledge in the art: "[B]reaks at specific recognition sequences and can promote efficient introduction of desired insertions, deletions or

	substitutions at or near the cut site via homology-directed repair (HDR) **with a** double- and/or **single-stranded donor DNA template**." Ex. 2578, 5560.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **CVC SUBSTANTIVE MOTION 4 (To Add the Claims of Sigma Patent Nos. 10,731,181 and 10,745,716)** was filed via the Interference Web Portal by 8:00 PM Eastern Time on November 19, 2021, 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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