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
Junior Party

(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),

v.

TOOLGEN, INC.,
Senior Party

Application 14/685,510.

Patent Interference No. 106,127 (DK)
(Technology Center 1600)

CVC MOTION 3 (to add the claims of ToolGen patent 10,851,380)

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Cases

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I. INTRODUCTION

The PTAB should add ToolGen's U.S. Patent No. 10,851,380 ("the '380 patent") to this interference and designate all of the patent's claims as corresponding to Count 1 because they recite the same invention as CVC's involved claims and Count 1. Both ToolGen's half of Count 1 and the '380 patent's claims involve systems of cleaving DNA in eukaryotic cells with a CRISPR system comprising a codon-optimized and NLS-tagged Cas9 and a chimeric guide RNA (*i.e.*, a single-guide RNA). The similarity between Count 1 and the claims, combined with the lack of any patentably distinct features in the '380 patent's claims, means that "the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of [each] claim." 37 C.F.R. § 41.207(b)(2); Standing Order, ¶ 208.3.2.

The sole relevant difference between the CRISPR-Cas9 systems of ToolGen's half of Count 1 and the '380 patent is that the '380 patent requires there be two guanines at the 5' end of the guide RNA (a "5'-GG") directly adjacent to the crRNA portion of the guide RNA. But that is not a patentable distinction over Count 1 because including a 5'-GG would have been obvious over Count 1 in view of Jinek 2012 (Ex. 2031). Relying on the combination of Count 1 and Jinek 2012 is appropriate because "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 127, 17-20 (P.T.A.B. Jan. 21, 2014) (holding claims to correspond to the count based on prior art teaching a limitation that was "the difference between" the count and claims).

Jinek 2012 identified the necessary components of a chimeric (*i.e.*, sgRNA) CRISPR-Cas9 system, and taught including a 5'-GG directly adjacent to the crRNA portion of the guide RNA. Jinek 2012 taught making such a guide RNA by performing *in vitro* transcription ("IVT") using T7 RNA polymerase ("T7 RNAP") and the consensus T7 RNAP promoter. A person of ordinary skill in the art ("POSA") would have known that Jinek 2012's IVT method to prepare a guide RNA

necessarily and inevitably results in a 5'-GG directly adjacent to the crRNA portion of the guide RNA. Moreover, a POSA aware of Count 1 as prior art would have been motivated to modify Count 1 to use Jinek 2012's IVT method to make a guide RNA because of the method's low cost, efficiency, and accuracy, and because Jinek 2012 had already used the method to generate RNAs that effectively cleave eukaryotic DNA sequences (*e.g*, GFP) in CRISPR-Cas9 systems. A POSA also would have had a reasonable expectation of success in modifying Count 1 to use a guide RNA having a 5'-GG, as claimed, because making RNA using IVT with T7 RNAP was an established and reliable method. No objective evidence suggests otherwise.

In sum, the '380 patent's claims would have been obvious in view of Count 1 and Jinek 2012. This lack of inventiveness relative to Count 1 justifies adding the patent to this proceeding. Further justification is provided by an interference-in-fact between at least one claim of the '380 patent and at least one CVC involved claim.

II. STATEMENT OF PRECISE RELIEF REQUESTED

CVC requests the PTAB to add ToolGen's '380 patent to this interference and designate all of the patent's claims as corresponding to Count 1 because they would have been obvious in view of Count 1 in view of Jinek 2012.

III. ARGUMENT

A. State of the Art

Count 1 serves as the basis for a POSA's knowledge because it is "treated as prior art to the claim" for the purpose of this motion. 37 C.F.R. § 41.207(b)(2); *N.V. Nutricia v. Mass. Inst. of Tech.*, Interference No. 106,096, Paper 80, 4 (P.T.A.B. Mar. 29, 2019). A POSA's additional prior art knowledge is detailed below. For the purposes of this motion *only*, CVC has treated the filing date of ToolGen's US 61/717,324 (Oct. 23, 2012) as the prior art reference date.

1. The prior art taught making RNAs with T7 RNAP, and that such methods

result in a 5'-GG directly at the end of the transcribed RNA

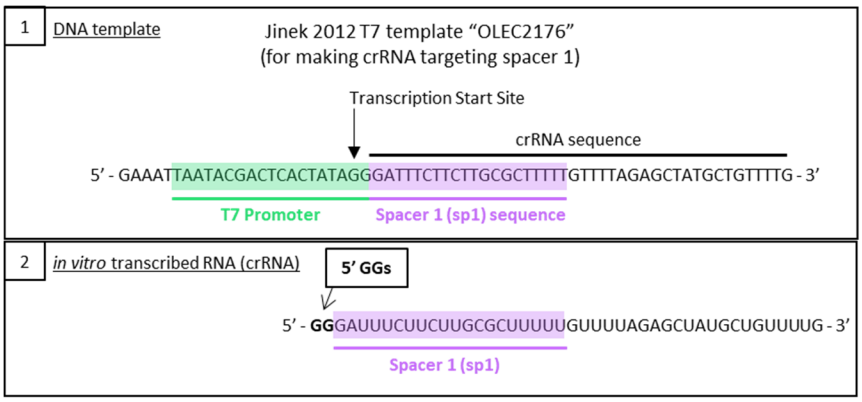
In support of this motion, CVC submits the declaration of Dr. Scott Bailey. He explains that, by October 23, 2012, a POSA would have been aware of numerous disclosures relating to preparing RNA using T7 RNAP. Ex. 2015, ¶72; MF 1. IVT of RNA using T7 RNAP was a "widely used" method of making RNA *for decades* before 2012. Ex. 2064, 59; Ex. 2065, 1229; Ex. 2015, ¶72. The art taught that IVT is a "powerful tool[]" because of "the quite unlimited range of sizes and sequences of the RNA that can be synthesized, as well as the efficiency and accuracy of synthesis." Ex. 2066, 618.

A well-known and preferred method of T7 RNAP-mediated transcription results in a 5'-GG as part of the transcribed RNA directly adjacent to the remainder of the transcribed RNA. Ex. 2015, ¶¶73-76; MF 3. In this method, T7 RNAP initiates activity by binding to its "consensus" promoter of the DNA template: TAATACGACTCACTATA**G**G. Ex. 2069, 180; Ex. 2064, 59-60; MF 2. When bound to the consensus T7 promoter, "the start point of transcription…is the first G of the final GG sequence [of the T7 promoter; underlined above]." Ex. 2069, 180. The art taught that the consensus promoter was preferred for T7 RNAP because the "two G's are *critical* for transcriptional yield" when using T7 RNAP. Ex. 2070, 30 (emphasis added); Ex. 2064, 60 (the terminal GG sequence is "especially important and significant[]" for T7 RNAP); MF 4.

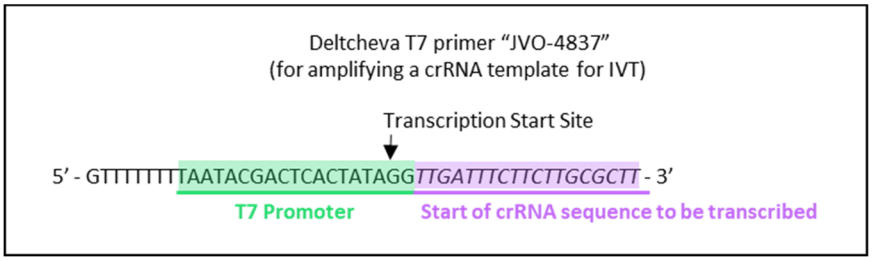
Before 2012, it was generally known in the art that IVT with T7 RNAP was commonly used to make RNA to introduce into eukaryotic cells. Ex. 2015, ¶¶77-80; MF 11. For example, the art taught transfecting 50-70-nucleotide small hairpin RNAs ("shRNAs") transcribed by T7 RNAP into eukaryotic cells to facilitate shRNA-mediated gene silencing in those cells. Ex. 2027, 952; Ex. 2065, 1228-1229; Ex. 2015, ¶¶77-78. Another application of IVT with T7 RNAP was making mRNA that was introduced into eukaryotic cells and organisms to facilitate expression of desired proteins. Ex. 2015, ¶79; Ex. 2067, 487; Ex. 2068, 763.

2. The prior art taught using T7 RNAP to make crRNA, tracrRNA, and sgRNA containing 5'-GG

Before October 2012, the prior art taught using IVT with T7 RNAP to make crRNA, tracrRNA, and sgRNA for use in CRISPR systems using a promoter that necessarily results in a 5'-GG being present on the transcribed RNAs. Ex. 2015, ¶¶81-88; Ex. 2031, Suppl. Methods; Ex. 2029, Suppl. Methods; MF 5, 9. The CVC inventors' Jinek 2012 publication taught making both chimeric RNAs and crRNA with IVT "using T7 Flash in vitro Transcription Kit…and PCR-generated DNA templates carrying a T7 promoter sequence." Ex. 2031, Suppl. Methods., Fig. 5, and Table S3. Jinek 2012 also provided the sequences of the DNA primers used to make crRNAs with T7 RNAP, identifying the T7 RNAP promoter in bold. Ex. 2031, Table S3; MF 6. A POSA would have understood that using those primers results in the transcribed crRNAs having a 5'-GG directly adjacent to the crRNA. Ex. 2015, ¶¶81-86; MF 7. Thus, Jinek 2012 specifically disclosed making such chimeric RNAs and crRNAs with a 5'-GG. Ex. 2015, ¶¶81-86. Jinek 2012 also disclosed using the chimeric RNAs made with IVT and containing a 5'-GG to cleave a eukaryotic DNA sequence from GFP. Ex. 2031, Fig. 5. As shown in the diagram below generated by Dr. Bailey for IVT of crRNA, Jinek 2012's method involves (1) using a DNA template, (2) transcribing that template to make a crRNA with a 5'-GG, and (3) using that crRNA as part of a CRISPR-Cas9 system to cleave target DNA. Ex. 2015, ¶83; Ex. 2013, Table S3.



Deltcheva (Ex. 2029) was part of the general knowledge in the art. And, like Jinek 2012, it taught making crRNAs and tracrRNAs with a 5'-GG using T7 RNAP. Ex. 2029, Suppl. Methods; MF 9. Deltcheva reported using "DNA templates carrying a T7 promoter sequence for in vitro transcription"—and used the same consensus T7 promoter as Jinek 2012, which introduces a 5'-GG directly adjacent to the crRNA and tracrRNA being transcribed. Ex. 2029, Suppl. Methods; Ex. 2015, ¶¶87-88; MF 10. Dr. Bailey's annotated version of one of Deltcheva's primers for IVT of crRNA is shown below. Ex. 2015, ¶88.



Publications dated after October 23, 2012, also "can be relied on for their proper supporting roles, e.g., indicating the level of ordinary skill in the art…." *Yeda Res. v. Mylan Pharms., Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018). The repeated use of T7 RNAP in late 2012 studies provides further evidence that the level of ordinary skill included IVT methods using T7 RNAP with its consensus promoter to make CRISPR-related RNAs, including for use in eukaryotic cells. Ex. 2015, ¶¶89-92; Ex. 2033, 8; Ex. 2028, Suppl. Fig 5. Similarly, patent applications filed starting in May 2012 disclosed using T7 RNAP to make guide RNAs, again reflecting the level of skill in the art. Ex. 2015, ¶¶89-92; Ex. 2001, ¶173; Ex. 2002, Fig 35A; Ex. 2025, ¶49; Ex. 2026, ¶13.

B. The Claims of the '380 Patent Correspond to Count 1

1. Claim 1 of the '380 Patent Would Have Been Obvious In View of Count 1 and Jinek 2012

Treating Count 1 as prior art to the '380 patent, the '380 patent's claim 1 corresponds to Count 1 because claim 1 would have been obvious over Count 1 in view of Jinek 2012's method of making crRNA and sgRNA comprising a 5'-GG with IVT using T7 RNAP. Ex. 2015, ¶¶10, 68-70, 100-117. A POSA would have recognized that the '380 patent's claims are "the predictable use of prior art elements according to their established functions" *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007). Moreover, there are no objective indicia that suggest otherwise.

a) Count 1 and Jinek 2012 teach all elements of claim 1

As laid out in the claim chart in Appendix 3, the ToolGen half of Count 1 and Jinek 2012 teach all elements of the '380 patent's claim 1. Ex. 2015, ¶¶101-105; MF15. While Appendix 3 focuses on ToolGen's half of Count 1, Appendix 4 shows that CVC's half of the count provides equivalent teachings for present purposes. *See infra* § III.C. Count 1's cells comprise a CRISPR-Cas9 system that includes a chimeric guide RNA and polynucleotide encoding Cas9 that are the same as those in claim 1. Appx. 3; Ex. 2015, ¶¶101-102. The ToolGen half of Count 1 and claim 1 recite the same use of that system to cleave target DNA in eukaryotic cells. *Id*., ¶¶101-105. The only element of claim 1 that Count 1 does not recite is element 8: "wherein the guide RNA comprises two guanines at its 5' end, and there are no additional nucleic acid residues between the two guanines at the 5' end and the crRNA portion of the guide RNA" (*i.e.*, a 5'-GG directly adjacent to the crRNA portion of the guide RNA). MF 15. That element is disclosed in Jinek 2012.

Like Count 1, Jinek 2012 disclosed a CRISPR system using Cas9, crRNA, and tracrRNA, where the crRNA and tracrRNA are combined into a chimeric guide RNA, and it suggested using that system for genome editing in eukaryotes. Ex. 2015, ¶¶81-86, 104-105; MF 5-8; *The Broad Inst., Inc. v The Univ. of Calif.*, Interference No. 106,048, Paper 893, 16-17 (P.T.A.B. Sept. 10, 2020). As part of studying CRISPR systems, Jinek 2012 made chimeric guide RNA and crRNA by IVT with T7 RNAP. Ex. 2031, Fig. 5 and Suppl. Materials; MF 5. Moreover, Jinek 2012

disclosed using a T7 promoter with two guanines, which necessarily are transcribed as a 5'-GG directly adjacent to the crRNA portion of the transcribed guide RNA based on how the T7 RNAP enzyme operates. Ex. 2015, ¶¶104-105; Ex. 2031, Table S3; MF 6-7. Jinek 2012 further disclosed using that promoter to prepare crRNAs—which therefore included a 5'-GG. Ex. 2031, Table S3; MF 7. Therefore, Jinek 2012's CRISPR-Cas9 system discloses the only element of claim 1 that Count 1 does not expressly recite (element 8). *Id*., Table S3; Ex. 2015, ¶104; MF 7.

That the '380 patent's claims recite a method does not make them a different invention than Count 1's "isolated mammalian cell." First, CVC has related method claims in this proceeding (*e.g.*, in U.S. Pat. Appl. 15/947,680), reflecting the PTAB's determination that method claims are not separately patentable. Second, the '380 patent's method claims recite no active steps beyond a general instruction to "introduce" a CRIPSR-Cas9 system into cells. MF 18. There is no patentable distinction between such method claims and Count 1's cells "comprising" the same system.

b) A POSA would have been motivated to modify Count 1 by making the cells with a guide RNA comprising a 5'-GG as disclosed in Jinek 2012, arriving at claim 1's method

A POSA would have been motivated to modify Count 1 by using Jinek 2012's method of preparing RNA with a 5'-GG to arrive at claim 1. Jinek 2012's method (*i.e.*, IVT with T7 RNAP using its consensus promoter) was a well-known method that offered several benefits. Ex. 2015, ¶¶106-112; Ex. 2064, 59; Ex. 2066, 618; MF 1-8. T7 RNAP had been "widely used" for decades, resulting in T7 RNAP being known for its "efficiency and accuracy of synthesis." Ex. 2064, 59; Ex. 2066, 618. Moreover, using IVT with T7 RNAP "reduces the cost" of preparing RNA compared to chemically synthesizing RNA. Ex. 2027, 951-952. And as explained above, the T7 RNAP promoter with two G's was preferred for its high efficiency and yield. *See* §III.A.1 *supra*.

A POSA also would have viewed Jinek 2012's method of preparing RNA with a 5'-GG as a good choice to make sgRNA for eukaryotic cells *in particular*. Ex. 2015, ¶¶107-111. The prior

art disclosed using IVT with T7 RNAP to make RNAs that were functional in eukaryotic cells, were of similar size to a Jinek 2012's sgRNA (approximately 50-70 nucleotides), and were put to similar use as sgRNA (to hybridize to nucleic acid targets in a cell). *Id*., ¶¶107; MF 1, 11. For example, Paddison disclosed using T7 RNAP to make 50-70 nucleotide shRNAs and subsequently transfecting those shRNAs into human cells and insect cells to alter gene expression. Ex. 2027, 952-953, Fig. 3; Ex. 2031, Fig. 5; Ex. 2015, ¶¶107. A POSA also would have viewed Jinek 2012's method of preparing RNA with a 5'-GG as a good choice because *in vitro* transcribed RNA was favored for microinjection experiments in eukaryotic cells and systems. Ex. 2015, ¶111; MF 17. For example, microinjection of *in vitro* transcribed mRNA was favored in zebrafish experiments because it facilitates "quick and robust assay[s]." Ex. 2071, 1; Ex. 2434, 1; Ex. 2015, ¶111.

Jinek 2012 also demonstrated that crRNA and sgRNA made with its T7 RNAP-based method were effective in facilitating DNA cleavage as part of an *in vitro* CRISPR-Cas9 complex targeting a eukaryotic DNA sequence encoding GFP. Ex. 2015, ¶110; Ex. 2031, Figs. 1-5; *see also*, § III.A *supra*; MF 8. This demonstration of functionality would have provided further reason to use Jinek 2012's method to make the sgRNA recited in Count 1. Ex. 2015, ¶110.

c) A POSA would have had a reasonable expectation of success in performing claim 1's method by using Jinek 2012's guide RNA made with IVT in a CRISPR-Cas9 system of Count 1

A POSA would have reasonably expected success in performing claim 1's method by modifying Count 1 to use Jinek 2012's guide RNA comprising a 5'-GG directly adjacent to the crRNA portion of the guide RNA because doing so would require only application of a proven and reliable method. Ex. 2015, ¶¶113-116; Ex. 2064, 59; MF 1-11. RNA molecules made with IVT using T7 RNA polymerase were regularly and successfully used in eukaryotic cells, and Jinek 2012 and Deltcheva had already tested and proven the method in the context of CRISPR systems. Ex. 2015, ¶¶114-115; Ex. 2031, Figs. 1-5; Ex. 2029, Fig. 3; §III.A *supra*.

ToolGen might argue (as it did when prosecuting the '380 patent) that a POSA would *not* have had a reasonable expectation of success in implementing a CRISPR-Cas9 system *in eukaryotes*. But that argument is irrelevant. Expectation of success in eukaryotes would not be in doubt 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); 37 C.F.R. § 41.207(b)(2).

Therefore, claim 1 would have been prima facie obvious in view of Count 1 and Jinek 2012. And as discussed below, there are no objective indicia that render claim 1 nonobvious.

2. Claims 2-10 of the '380 Patent Would Have Been Obvious In View of Count 1

The '380 patent's claims 3 and 5 recite limitations also recited in Count 1. *See* Appx. 5; MF 15. Count 1 recites that the cell is a mammalian cell (claim 3) and that the polynucleotide encoding Cas9 is codon-optimized for expression in mammalian cells (claim 5). Therefore, claims 3 and 5 would have been obvious for the same reasons as claim 1. Ex. 2015, ¶¶119, 121.

A POSA would have had reason to add the remaining dependent claim limitations because they either relate to well-known features or routinely performed techniques. *Id*., ¶¶117-126; MF 11-14. A POSA would have had reason to add a NLS at the C-terminus of Cas9 (claim 2) because Count 1 specifies that Cas9 comprises an NLS and NLS tags were commonly placed at the C-terminus of proteins. *Id*., ¶95-99, 118; Ex. 2117, 42189; Ex. 2118, 24391; MF 12. A POSA would have had reason to use a human cell (claim 4) because that cell type was often used for genome editing experiments and therapeutic methods. Ex. 2015, ¶120; Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; MF 13. A POSA would have had reason for the target nucleic acid sequence to be a genomic sequence at its endogenous site (claim 6) because a POSA would recognize that targeting

genomic DNA (*i.e.*, the endogenous site of a gene) is how the art taught performing genome editing in a cell. Ex. 2015, ¶122; Ex. 2099-2102, 2106; MF 13. A POSA would have had reason for the polynucleotide encoding Cas9 to be a vector (claim 7) because vectors are a common and reliable method for expressing exogenous proteins within eukaryotic cells. Ex. 2015, ¶123; Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; MF 14. A POSA would have reason to use *Streptococcus pyogenes* Cas9 (claim 8) or a *Streptococcus* Cas9 (claim 10) because Jinek 2012 had successfully used *Streptococcus pyogenes* Cas9 in its experimental demonstrations. Ex. 2015, ¶¶124, 126; Ex. 2031, 816. Finally, a POSA would have reason to introduce the polynucleotide encoding Cas9 before the guide RNA (claim 9) because (1) there are a limited number of orders in which the components can be introduced and (2) introducing a polynucleotide encoding Cas9 first allows time for Cas9 protein expression before introducing the guide RNA. Ex. 2015, ¶125.

Moreover, for each of the limitations in claims 2-10, a POSA would have had a reasonable expectation of success in adding these well–known features or techniques because the literature discloses how to implement each and demonstrated success in doing so. *Id*., ¶¶117-126.

3. No Objective Indicia Support the Patentability of the '380 Patent's Claims

There are no objective indicia that would support the patentability of the '380 patent claims in view of Count 1. Ex. 2015, ¶¶127-131. During prosecution, ToolGen argued that the claims were nonobvious because the claimed guide RNA unexpectedly induced fewer off-target effects—*i.e.*, it had better specificity—relative to prior art zinc finger nucleases ("ZFNs"). *See, e.g.*, Ex. 2120, 8210-8211. Such arguments fail here for at least three reasons.

First, ToolGen's results are not unexpected when "compared with the closest prior art" as required. *Millennium Pharmaceuticals, Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017); MF 16. The closest prior art can be identified by "[a] comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common

with each reference, bearing in mind the relative importance of particular limitations." *In re Merchant*, 575 F.2d 865, 868 (CCPA 1978). The closest prior art for the purposes of this motion is ToolGen's half of Count 1 because it is identical to the '380 patent claims, except for the 5'-GG limitation. Ex. 2015, ¶129. Thus, ToolGen's past assertions regarding superiority are irrelevant. Rather, the pertinent inquiry is whether the claimed method with the 5'-GG limitation provides unexpected results relative to the mammalian cell and system of Count 1—which it does not. ToolGen cannot attribute the alleged unexpected increase in specificity to the 5'-GG, because ToolGen argued that the same allegedly unexpected increase in specificity is obtained with systems that did not include the 5' GG. During prosecution of its Application No. 14/685,510 ("the '510 application"), ToolGen relied on the same data to allege that the claimed invention in the '510 application, *which did not require a 5' GG,* also showed an unexpected increase in specificity. ToolGen's arguments included claim 85, which is the same as ToolGen's half of Count 1, and ToolGen argued its claims were "commensurate in scope" with the allegedly unexpected increase in specificity. Ex. 2012, 6774-6775, 6910-6914, 6939-6940; MF 16. Thus, there can be no unexpectedly superior results when the closest prior art (*i.e.*, Count 1) has the *same* results as the claimed method. *Millennium Pharmaceuticals*, 862 F.3d at 1368.

Second, the *prima facie* case here is extraordinarily strong and would not be outweighed by data showing increased specificity of the '380 patent's claimed method. "[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions, as here, evidence of secondary indicia are frequently deemed inadequate to establish nonobviousness." *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013); *see also*, *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) ("weak secondary considerations generally do not overcome a strong *prima facie* case").

Just as the objective indicia in *Ohio Willow Wood* were insufficient to show nonobviousness of the predictable use of prior art elements, any unexpectedly superior results with the '380 patent's claimed invention cannot overcome the prima facie obviousness of applying a well-known method of making RNA in the context of Count 1's CRISPR system to arrive at the claimed invention.

Third, discovering the effect of including a 5'-GG does not render the *prima facie* obvious combination of Count 1 and Jinek 2012 patentable. The Federal Circuit has held that simply measuring the results of an obvious method does not render that method patentable. In *In re Huai-Hung Kao*, 639 F.3d 1057 (Fed. Cir. 2011), the Federal Circuit held that a "previously-unknown, yet inherent, food-effect property" did not make the claims patentable because "merely discovering and claiming a new benefit of an old process cannot render the process again patentable." *In re Huai-Hung Kao*, 639 F.3d at 1072; *see also*, *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). As in *Kao*, any alleged unexpected result relating to lower off-target effects would not confer patentability. The '380 patent's claimed process was obvious, and any improved specificity also would have been a property of Jinek 2012's CRISPR-Cas9 system, which has the same components and the same structure. Ex. 2015, ¶130.

C. The Claims of the '380 Patent Interfere In Fact with CVC Claims Involved in the Interference

The necessity, and appropriateness, of adding the '380 patent's claims to the interference is reinforced by their interference-in-fact with CVC's involved claims. Claims interfere in fact "if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa." 37 CFR § 41.203; *Regents of Univ. of Calif. v. Broad Inst.*, 903 F.3d 1286, 1291 (Fed. Cir 2018). As discussed below, this "two way test" is met between at least one claim in the '380 patent and at least one involved CVC claim. Therefore, failure to add the '380 patent claims that interfere with CVC's involved claims would

only lead to another interference.

The ’380 patent’s claim 1 would have been obvious in view of at least claim 156 of CVC’s involved application No. 15/981,807 (*i.e.*, CVC’s half of Count 1). Ex. 2015, ¶¶11, 71, 132-139; MF 15. The only relevant differences between these claims are codon optimization of the Cas9 polynucleotide, the NLS-tag on Cas9, and including a 5’-GG on the guide RNA. Appx. 4. CVC involved claim 184 (’807 application) also recites specific NLSs. POSA would have had reason to include all of these elements as part of a CRISPR-Cas9 system because they are the results of well-known techniques for performing experiments in eukaryotic cells, and a “combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007); MF 1, 11; Ex. 2015, ¶¶81-99; § III.B *supra*. And a POSA would have had a reasonable expectation of success in doing so because such techniques were regularly successful. MF 1, 11; § III.A *supra*.

For the other half of the two-way test, the ’380 patent’s claim 1 teaches all elements of claim 156 arranged as claimed, and therefore anticipates CVC’s claim 156, assuming claim 1 to be prior art. Ex. 2015, ¶¶140-142; Appx. 6; MF 15, 19. In declaring the interference, the PTAB has already determined that claim 1’s chimeric RNA is the same invention as the single-molecule DNA-targeting RNA of CVC’s claim 156. Moreover, a POSA would have understood that the term chimeric RNA is used in the the ’380 patent to refer to crRNA and tracrRNA covalently linked with intervening nucleotides. Ex. 2011, 1:60-64; Ex. 2031, Fig. 5; Ex. 2015, ¶¶37, 140-142.

IV. CONCLUSION

For the reasons set forth above, the PTAB should designate all the ’380 patent’s claims as corresponding to Count 1. There are no adequate alternative remedies because leaving the ’380 patent out of this proceeding risks the inefficiency and expense of another interference proceeding involving CVC and ToolGen.

Respectfully submitted,

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APPENDIX 1 – LIST OF EXHIBITS

Exhibit No.	Description
2001	Prov. Appl. No. 61/652,086, filed May 25, 2012
2002	Prov. Appl. No. 61/716,256, filed October 19, 2012
2011	U.S. Patent No. 10,851,380
2012	U.S. Appl. No. 14/685,510
2015	Declaration of Scott Bailey, Ph.D.
2025	Broad P1 – Prov. Appl. No. 61/736,527 - PCT/US2013/074819
2026	Sigma P1 – 61/734,256
2027	Paddison, P.J., *et al*., "Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells," *Genes & Development* 16:948–958 (2002)
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APPENDIX 2 – STATEMENT OF MATERIAL FACTS

1. By Oct. 23, 2012, methods of preparing RNA using *in vitro* transcription ("IVT") with T7 RNA polymerase were known in the art. Ex. 2064, 59; Ex. 2065, 1229.

2. By Oct. 23, 2012, a POSA would have known that the consensus promoter for T7 RNA polymerase ("T7 RNAP") is TAATACGACTCACTATAGG. Ex. 2069, 180; Ex. 2064, 59-60.

3. Using T7 RNAP and the T7 RNAP promoter TAATACGACTCACTATAGG to transcribe RNA results in a 5'-GG on the transcribed RNA. Ex. 2069, 180; Ex. 2064, 59-60.

4. By Oct. 23, 2012, a POSA would have known that including the terminal GG sequence in the T7 RNA polymerase promoter is critical for transcriptional yield with T7 RNAP. Ex. 2070, 30 Ex. 2064, 60; Ex. 2027, 952

5. Jinek 2012 discloses making sgRNA and crRNA with IVT using T7 RNA polymerase. Ex. 2031, Fig. 5 and Suppl. Methods.

6. Jinek 2012 discloses using TAATACGACTCACTATAGG as the promoter for making RNA with IVT using T7 RNAP. Ex. 2031, Table S3.

7. Jinek 2012 discloses making crRNA with primers that, when used for IVT with T7 RNAP, would have resulted in a 5'-GG directly adjacent to the targeting region of the crRNA. Ex. 2031, Table S3; Ex. 2069, 180; Ex. 2064, 59-60.

8. Jinek 2012 demonstrated that RNA made with IVT using T7 RNAP and the consensus T7 RNAP promoter was functional in a CRISPR-Cas9 system, including in cleaving eukaryotic DNA sequences. Ex. 2031, Figs. 1-5.

9. Deltcheva (Ex. 2029) discloses making crRNA and tracrRNA with IVT using T7 RNA polymerase. Ex. 2029, Suppl. Methods.

10. Deltcheva discloses making crRNA and tracrRNA with promoters that, when used for IVT

with T7 RNAP, would have resulted in a 5'-GG on the transcribed RNAs. Ex. 2029, Suppl. Table 10; Ex. 2069, 180; Ex. 2064, 59-60.

11. By Oct. 23, 2012, a POSA would have known that IVT of RNA with T7 RNAP had been used to make RNA that was subsequently introduced into eukaryotic cells. Ex. 2027, 952; Ex. 2065, 1228-1229; Ex. 2067, 487; Ex. 2068, 763.

12. By Oct. 23, 2012, NLS tags were commonly placed at the C-terminus of proteins to obtain nuclear localization. Ex. 2117, 42189; Ex. 2118, 24391.

13. By Oct. 23, 2012, human cells were used for genome editing experiments with ZFN and TALEN systems. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4.

14. By Oct. 23, 2012, using vectors was a known method for expressing exogenous proteins within eukaryotic cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4.

15. The only difference between the CRISPR-Cas9 system in '380 patent's claims and Count 1 is the presence of a 5'-GG on the guide RNA. Ex. 2011, 179:18-38.

16. During prosecution of the '510 patent, ToolGen argued that the claims that would become Count 1 were commensurate in scope with an unexpected increase in specificity. Ex. 2012, 6774-6775, 6910-6914, 6939-6940.

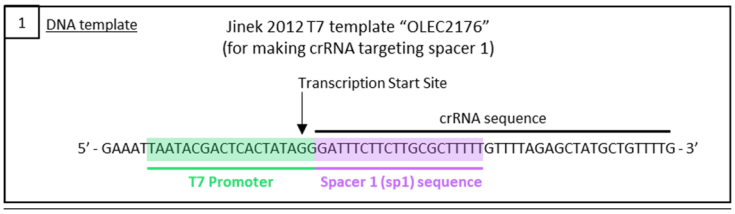
17. By Oct. 23, 2012, injection of *in vitro* transcribed RNA was known as an essential quick and robust tool for exploring gene function in the zebrafish embryos. Ex. 2071, 1.

18. The '380 patent's method claims recite no active steps beyond a general instruction to "introduce" a CRIPSR-Cas9 system into cells. Ex. 2011, 179:18-180:38.

19. By Oct. 23, 2012, a POSA would understand a chimeric guide RNA to comprise a crRNA and a tracrRNA linked together with intervening nucleotides. Ex. 2031, Fig. 5.

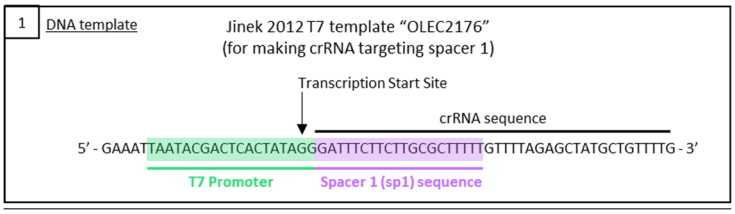
APPENDIX 3 – CLAIM CHART COMPARING THE '380 PATENT'S CLAIM 1 TO TOOLGEN'S HALF OF THE COUNT 1 AND JINEK 2012

Claim 1 Elements	Teachings of Count 1 and Jinek 2012
Element 1: A method of introducing a site-specific, double-stranded break at a target nucleic acid sequence	Count 1: "a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas **system for site-specific, cleavage of a double-stranded target nucleic acid sequence**"
Element 2: in a eukaryotic cell	Count 1: "**An isolated mammalian cell** comprising a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system for site-specific, cleavage of a double-stranded target nucleic acid sequence **in the isolated mammalian cell**…"
Element 3: the method comprising introducing into the eukaryotic cell a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system,	Count 1: "An isolated mammalian cell comprising **a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system** for site-specific, cleavage of a double-stranded target nucleic acid sequence in the isolated mammalian cell…"
Element 4: wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a Cas9 polypeptide comprising a nuclear localization signal,	Count 1: "…wherein the CRISPR/Cas system comprises: a) **a nucleic acid encoding a Cas9 polypeptide, wherein the Cas9 polypeptide comprises a nuclear localization signal**…"
Element 5: wherein the nucleic acid is codon-optimized for expression in eukaryotic cells,	Count 1: "…wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a Cas9 polypeptide, wherein the Cas9 polypeptide comprises a nuclear localization signal and wherein said **nucleic acid is codon-optimized for expression in mammalian cells**…"
Element 6: and b) a guide RNA that hybridizes to the target nucleic acid,	Count 1: "…b) a chimeric guide RNA comprising a CRISPR RNA (crRNA) portion and a transactivating crRNA (tracrRNA) portion, wherein **the target nucleic acid sequence comprises a first strand having a region complementary to the crRNA portion** of the chimeric guide RNA…"
Element 7: wherein the guide RNA is a chimeric guide RNA comprising a CRISPR RNA (crRNA) portion fused to a trans	Count 1: "…b) **a chimeric guide RNA comprising a CRISPR RNA (crRNA) portion and a transactivating crRNA (tracrRNA) portion**, wherein the target nucleic acid sequence comprises a first strand having a region

activating crRNA (tracrRNA) portion,	complementary to the crRNA portion of the chimeric guide RNA…"
Element 8: wherein the guide RNA comprises two guanines at its 5' end, and there are no additional nucleic acid residues between the two guanines at the 5' end and the crRNA portion of the guide RNA;	Jinek 2012: "A plasmid … was subjected to cleavage by Cas9 programmed with … **in vitro–transcribed chimeric RNAs**…." Ex. 2031, 820: Fig. 5 Jinek 2012: Ex. 2031, Supplemental Materials, 9 and Table S3 
Element 9: whereby a site-specific, double stranded break at the target nucleic acid sequence is introduced.	Count 1: "wherein the Cas9 polypeptide and the chimeric guide RNA form a Cas9/RNA complex in the isolated mammalian cell and **mediate double stranded cleavage at the target sequence**"

APPENDIX 4 – CLAIM CHART COMPARING THE '380 PATENT'S CLAIM 1 TO THE CVC HALF OF COUNT 1 AND JINEK 2012

Claim 1 Elements	Teachings of Count 1 and Jinek 2012
Element 1: A method of introducing a site-specific, double-stranded break at a target nucleic acid sequence	Count 1: "…whereby said **system is capable of cleaving or editing the target DNA molecule** or modulating transcription of at least one gene encoded by the **target DNA molecule**"
Element 2: in a eukaryotic cell	Count 1: "A **eukaryotic cell** comprising a target DNA molecule and an engineered and/or non-naturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system…
Element 3: the method comprising introducing into the eukaryotic cell a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system,	Count 1: "A eukaryotic cell comprising a target DNA molecule and an engineered and/or non-naturally occurring **Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system**…"
Element 4: wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a Cas9 polypeptide comprising a nuclear localization signal,	Count 1: "…comprising a) a Cas9 protein, or a nucleic acid comprising a **nucleotide sequence encoding said Cas9 protein**"
Element 5: wherein the nucleic acid is codon-optimized for expression in eukaryotic cells,	A POSA would have considered a codon-optimized nucleic acid to be a standard technique in the field. Ex. 2015, ¶¶93-94, 134-137.
Element 6: and b) a guide RNA that hybridizes to the target nucleic acid,	Count 1: "comprising…a targeter-RNA that is capable of **hybridizing with a target sequence** in the target DNA molecule…" "…wherein the **single molecule DNA-targeting RNA** is capable of forming a complex with the Cas9 protein, thereby targeting the Cas9 protein to **the target DNA molecule** …"
Element 7: wherein the guide RNA is a chimeric guide RNA comprising a CRISPR RNA (crRNA) portion fused to a trans	Count 1: wherein the **single molecule DNA-targeting RNA comprises**: i) **a targeter-RNA** that is capable of hybridizing with a target sequence in the target DNA molecule, and ii) **an activator-RNA** that is capable of

activating crRNA (tracrRNA) portion,	hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, **wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides**
Element 8: wherein the guide RNA comprises two guanines at its 5' end, and there are no additional nucleic acid residues between the two guanines at the 5' end and the crRNA portion of the guide RNA;	Jinek 2012: "A plasmid … was subjected to cleavage by Cas9 programmed with … **in vitro–transcribed chimeric RNAs**…." p. 820: Fig. 5 Jinek 2012: Supplemental Materials, p. 9 and Table S3 
Element 9: whereby a site-specific, double stranded break at the target nucleic acid sequence is introduced.	Count 1: "…whereby said **system is capable of cleaving or editing the target DNA molecule** or modulating transcription of at least one gene encoded by the **target DNA molecule**"

APPENDIX 5 – CLAIM CHARTS COMPARING '380 PATENT DEPENDENT CLAIMS TO COUNT 1 AND JINEK 2012

Claim 2 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nuclear localization signal is located at the C terminus of the Cas9 polypeptide.	Count 1: "…wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a Cas9 polypeptide, wherein the **Cas9 polypeptide comprises a nuclear localization signal**…" The commercially available pShooter vector from Invitrogen contained three tandem nuclear localization sequences downstream of the multiple cloning site, which would produce a protein that contained three carboxy-terminal tandem NLSs. Ex. 2117, 42189; Ex. 2118, 24391; Ex. 2015, ¶118.

Claim 3 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the eukaryotic cell is a mammalian cell.	Count 1: "An isolated **mammalian cell** comprising a Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system…"

Claim 4 Elements	**Teachings of the Art**
Element 1: The method of claim 3,	*See* Appendix 3 and Claim 3 Chart
Element 2: wherein the mammalian cell is a human cell.	Genomic cleavage experiments using ZFNs or TALENs were routinely tested in human cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; Ex. 2015, ¶120.

Claim 5 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid	Count 1: "…wherein the CRISPR/Cas system

encoding the Cas 9 polypeptide is codon-optimized for expression in mammalian cells.	comprises: a) a nucleic acid encoding a Cas9 polypeptide, wherein the Cas9 polypeptide comprises a nuclear localization signal and wherein said **nucleic acid is codon-optimized for expression in mammalian cells**…"

Claim 6 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the target nucleic acid sequence is a genomic sequence located at its endogenous site in the genome of the eukaryotic cell.	Count 1: "…wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a Cas9 polypeptide, wherein the **Cas9 polypeptide comprises a nuclear localization signal**…" Adding one or more NLS sequences increases protein localization in the nucleus. Ex. 2099-2102, 2106; Ex. 2015, ¶122.

Claim 7 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the Cas9 polypeptide is a vector.	Count 1: "…wherein the CRISPR/Cas system comprises: a) a **nucleic acid encoding a Cas9 polypeptide**…" Vectors are a method for expressing exogenous proteins within eukaryotic cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4; ; Ex. 2015, ¶123.

Claim 8 Elements	**Teachings of the Art**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the Cas9 polypeptide is a *Streptococcus pyogenes* Cas9 polypeptide.	Jinek 2012: "Cas9 protein [was] derived from the pathogen *Streptococcus pyogenes*." Ex. 2031, 816, Fig. S2.

Claim 9 Elements	**Teachings of Count 1 and Jinek 2012**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the nucleic acid encoding the Cas9 polypeptide is introduced into the eukaryotic cell before introducing the guide RNA into the eukaryotic cell.	There are a limited number of orders in which the components can be introduced. ; Ex. 2015, ¶125.

Claim 10 Elements	**Teachings of Count 1 and Jinek 2012**
Element 1: The method of claim 1,	*See* Appendix 3
Element 2: wherein the Cas9 polypeptide is a *Streptococcus* Cas9 polypeptide.	Jinek 2012: "Cas9 protein [was] derived from the pathogen *Streptococcus pyogenes*." Ex. 2031, 816, Fig. S2.

APPENDIX 6 - CLAIM CHART COMPARING CVC's CLAIM 156 OF US APPL. NO. 15/981,807 TO THE '380 PATENT'S CLAIM 1

'807 App. Claim 156 Elements	Teachings of Claim 1 of the '380 patent
Element 1: A eukaryotic cell	"…in a eukaryotic cell…"
Element 2: comprising a target DNA molecule and	"A method of introducing a site-specific, double-stranded break at **a target nucleic acid** sequence …"
Element 3: an engineered and/or non-naturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising	"…the method comprising introducing into the eukaryotic cell a **Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas system**…"
Element 4: a) a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein; and	"…wherein the CRISPR/Cas system comprises: a) a **nucleic acid encoding a Cas9 polypeptide**…"
Element 5: b) a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises:	"…and b) a **guide RNA** that hybridizes to the target nucleic acid…"
Element 6: i) a targeter-RNA that is capable of hybridizing with a target sequence in the target DNA molecule, and	"…and b) a guide RNA that **hybridizes to the target nucleic acid,** wherein the guide RNA is a chimeric guide RNA comprising a **CRISPR RNA (crRNA)** portion fused to…"
Element 7: ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,	"…comprising a **CRISPR RNA (crRNA)** portion fused to a **trans activating crRNA (tracrRNA)** portion…"
Element 8: wherein the activator-RNA and the targeter-RNA are	"…a guide RNA that hybridizes to the target nucleic acid, wherein the guide RNA is **a chimeric guide RNA**

covalently linked to one another with intervening nucleotides; and	**comprising a CRISPR RNA (crRNA) portion fused to a trans activating crRNA (tracrRNA) portion**…"
Element 9: wherein the single molecule DNA-targeting RNA is capable of forming a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule.	"…wherein the CRISPR/Cas system comprises: a) a nucleic acid encoding a **Cas9 polypeptide** comprising a nuclear localization signal,… and b) **a guide RNA** that hybridizes to the target nucleic acid,… whereby a **site-specific, double stranded break** at the target nucleic acid sequence is introduced."

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **CVC MOTION 3 (to add the claims of ToolGen patent 10,851,380)** was filed via the Interference Web Portal by 8:00 PM Eastern Time on May 20, 2021, pursuant to an agreement between the parties, and thereby served on the attorney of record for the Senior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to the agreement between the parties, the foregoing was also served via email by 11:00 PM Eastern Time on counsel for the Senior Party at:

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