Interference No. 106,127

Filed on behalf of Senior Party ToolGen, Inc. 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)

TOOLGEN OPPOSITION 2
(Opposing CVC Motion to Deny ToolGen Accorded Benefit)

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I. INTRODUCTION

CVC's Motion 2 is premised on a single issue: Does ToolGen's P1 describe a codon-optimized nucleic acid encoding Cas9? The answer is "yes" as a factual matter, because ToolGen's P1 describes a successful experiment using a codon-optimized nucleic acid encoding Cas9 to yield a Cas9 protein complex that functions in eukaryotes to cleave DNA. But as a legal matter, the question is immaterial: Count 1 does ***not*** require codon optimization as a matter of law.

As to the facts: CVC claims ToolGen's P1 "does not even mention codon optimization generically." CVC Motion 2 ("Mot."), Paper 364, 2:9. But 11 pages later in its Motion, CVC admits that ToolGen's P1 in fact does describe codon optimization of a nucleic acid encoding Cas9. Mot. 13:10-13.

As to the law: None of this is material, because CVC's half of Count 1 contains no codon-optimization requirement. Apparently recognizing this, CVC's Motion seeks to have the Board use judicial estoppel to ***re-write*** Count 1 so that it requires a codon-optimized nucleic acid encoding Cas9—but only for ToolGen; not for CVC. Count 1 has no such limitation; CVC has not asked to amend Count 1; and CVC's judicial-estoppel arguments are based on misstated facts and incorrect law.

And then there is CVC's expert, Dr. Scott Bailey, who provides the only evidentiary support for CVC's Motion. He admitted he did not analyze ToolGen's P1 as a skilled artisan would—instead, litigation counsel instructed him to apply false assumptions, which he admitted those assumptions to an artisan's understanding that codon optimization was well-known and routine. Dr. Bailey's testimony deserves no weight. The Board should deny CVC's Motion.

II. DESCRIPTION OF APPENDICES

Appendix 1 is a List of Exhibits Cited. Appendix 2 is the Statement of Material Facts (F_).

III. APPLICABLE LEGAL STANDARDS

To challenge accorded benefit, a party must show that the application accorded benefit (here, ToolGen's P1) does not provide a constructive reduction to practice of an embodiment within the count. 37 CFR § 41.208(b); S.O. ¶¶ 121.3, 208.4.2; *see Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (CCPA 1975). To show the written-description requirement—the only one at issue here—is not satisfied, a party must show the application does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This is "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art[]" at the time of filing. *Id*. ToolGen's expert, Dr. Bryan Cullen, explains that such an artisan (or "POSA") would have had a life sciences Ph.D. (such as a Ph.D. in microbiology, genetics, virology, molecular biology, or cell biology) and been actively involved for 1–2 years or more post-Ph.D. in research on manipulating gene expression in eukaryotes. Ex. 1403 (Cullen Decl.), ¶17. CVC's expert, Dr. Bailey, offers a different definition (Ex. 2015 (Bailey Decl.), ¶21), but either definition leads to the same conclusion—ToolGen's P1 shows an embodiment of Count 1. (Dr. Bailey's opinions are nonetheless infirm because they are not offered from the perspective of either Dr. Cullen's or his own artisan definition. *See* pp. 14-15, below.)

IV. TOOLGEN'S P1 PROVIDES A CONSTRUCTIVE REDUCTION TO PRACTICE OF BOTH HALVES OF COUNT 1 AND CVC HAS NOT SHOWN OTHERWISE

The Board has accorded ToolGen benefit of its P1. Paper 1, 10. For CVC's Motion to succeed, it must show that ToolGen's P1 does not provide a constructive reduction to practice of both halves of Count 1. 37 CFR § 41.208(b); S.O. ¶¶ 121.3, 208.4.2; *see Furman v. Cheng*, 59 USPQ2d 1668 (Bd. Pat. App. & Int. 2001). CVC challenges ToolGen's accorded benefit on the ground that ToolGen's P1 does not sufficiently describe a single element—a codon-optimized

nucleic acid encoding Cas9—which is not a limitation of CVC's half of Count 1, but only of ToolGen's half. Mot. 2:15-18, 7:4-9; Paper 1, 5-7; F46-48. (CVC does not dispute that ToolGen's P1 enables Count 1. Mot. *passim*.) But ToolGen's P1 expressly describes the use of a codon-optimized nucleic acid encoding Cas9 to achieve DNA cleavage in a eukaryotic cell, satisfying both halves of Count 1. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196; F49-53. CVC fails to prove otherwise.

A. CVC Does Not Dispute That ToolGen's P1 Discloses An Embodiment Of The CVC Half Of Count 1 As Written

CVC admits that its half of Count 1 "does not require a codon-optimized Cas9 nucleic acid." Mot. 2:16-17; Ex. 1550 (Bailey Tr.), 124:18-125:1 (agreeing that he did not see a "requirement of codon optimization" in CVC's half of Count 1); F47. CVC does not deny that ToolGen's P1 meets every element of the CVC half of Count 1. And its expert "did not analyze CVC's half of the count with respect to the embodiments in ToolGen's P1 in expressing [his] opinions." Ex. 1550 (Bailey Tr.), 125:9-16. CVC's Motion should fail right there.

Yet, despite those concessions, CVC seeks, through allegations of estoppel, to re-write the CVC half of Count 1 to (i) require a codon-optimized nucleic acid encoding Cas9 and (ii) eliminate the alternative limitation of a "Cas9 protein."[1] Mot. 7:4-9, 9:7-9. CVC further argues that the re-written Count 1 should apply to ToolGen, but not to CVC. *Id.* at n.2, 16:22. CVC has neither requested nor been authorized to move to alter Count 1, so this effort fails as well.

[1] CVC does not dispute that ToolGen's P1 describes the use of a Cas9 protein, which CVC's half of Count 1 states as an alternative to a nucleic acid encoding Cas9. Paper 1, 6; F54. ToolGen's P1 describes a CRISPR-Cas system comprising a Cas9 protein. Ex. 1403 (Cullen Decl.), ¶¶187, 194, 207; F55.

B. Judicial Estoppel Cannot Apply As A Matter Of Fact And Law

CVC argues that ToolGen's P1 should be denied accorded benefit on the ground of judicial estoppel, because ToolGen, in the appeal reversing the Examiner's obviousness rejections, told the Board that a codon-optimized nucleic acid encoding Cas9 is required for CRISPR/Cas9 to work in eukaryotes. Mot. 2:18-20. This argument is factually and legally without support. Judicial estoppel is an equitable doctrine that prevents a party from taking clearly inconsistent positions before different tribunals. *See Zedner v. United States*, 547 U.S. 489, 491, 504 (2006) (citing *New Hampshire v. Maine*, 532 U.S. 742, 749 (2001)). It requires that the party to be estopped have succeeded in one tribunal by advancing a particular legal position, and then offered a clearly inconsistent position before a second tribunal to gain for itself "an unfair advantage or impos[ing] an unfair detriment on the opposing party if not estopped." *Id*. None of these is present here.

1. CVC's Judicial Estoppel Theory Fails Because It Relies On A Misrepresentation Of The Prosecution History

Pointing to the prosecution history of ToolGen's involved application, CVC argues that ToolGen is estopped from arguing an embodiment without a codon-optimized nucleic acid encoding Cas9. Mot. 9:7-9. This is not what the prosecution record says.

a) ToolGen Argued, And The Board Found, That ToolGen's Claims Were Not Obvious Over The Prior Art Because There Was No Reasonable Expectation of Successfully Using CRISPR/Cas9 In Eukaryotic Cells

CVC argues that ToolGen obtained allowability of its involved application because of codon optimization. That is demonstrably wrong. To overcome the Examiner's obviousness rejection, ToolGen explained that the transition from using CRISPR/Cas9 in prokaryotic cells to eukaryotic cells was unpredictable at the time, but that ToolGen had succeeded and should be allowed its then-pending claims, directed to the use of CRISPR/Cas9 for genome editing in mammalian cells. Codon optimization and nuclear localization signals ("NLS") were two claim

elements, and aspects of how ToolGen succeeded over the then-prevailing unpredictability and pessimism. ToolGen's P1, in fact, provided three working examples of the successful use of CRISPR/Cas9 in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶¶183-194; F56. ToolGen consistently argued that its "claimed invention is ***not obvious*** at least because one of ordinary skill in the art would have doubted whether a Type II CRISPR/Cas9 system could be introduced into a eukaryotic/mammalian cell without toxicity and whether, once introduced, could successfully bring about site-specific double-stranded breaks in a target nucleic acid sequence of the cell." Ex. 2012, 6769 (emphasis in original), 6883, 6896, 8529-8530; F57.

The Examiner mistakenly focused on codon optimization, not unpredictability of CRISPR/Cas9 in eukaryotic cells as a whole. That is the issue on which ToolGen appealed and prevailed. ToolGen explained that the Examiner offered "only conclusory statements regarding reasonable expectation of success that incorrectly focus[ed] on whether one of ordinary skill in the art would have expected to successfully codon-optimize Cas9 and/or add an NLS to it[,]" which "fail as a matter of law." Ex. 2012, 6769; F58. Despite this—and notwithstanding the Board's decision in the '048 Interference—the Examiner's misunderstanding of the prior art led her to continuously reject ToolGen's pending claims.

ToolGen argued to the Board that applying CRISPR/Cas9 in eukaryotic cells as a whole was unpredictable. The Board agreed, overruling the Examiner and finding ToolGen's claims nonobvious. In doing so, the Board found that even though codon optimization had been a known technique, it did "not allay the concerns of those of skill in the art concerning transitioning the use of CRISPR/Cas9 from prokaryotic cells to eukaryotic cells [because] the evidence of record supports that there was a ***high level of uncertainty and unpredictability in the art*** and that ***the skilled artisan would not have had a reasonable expectation of successfully transitioning the***

CRISPR/Cas9 technology to eukaryotic cells, e.g., mammalian cells as claimed." Ex. 2012, 8645 (Decision on Appeal) (emphasis added); F80.

b)CVC Misrepresents ToolGen's Prosecution Arguments

CVC's Motion uses the prosecution history (Mot. 3:16-6:27) selectively and inaccurately. Its Motion relies on contextual fragments of arguments, statements with omitted words, and disparate questions and answers, all stitched together like Frankenstein's monster, to assemble a false narrative that ToolGen achieved patentability by focusing on codon optimization, not the unpredictability in prokaryote-to-eukaryote translation.

(1) ToolGen Never Argued That Codon Optimization Was Required For CRISPR/Cas9 Functionality In Eukaryotic Cells

As apparent support for writing a nonexistent limitation into the CVC half of Count 1, CVC contends that ToolGen argued that "a codon-optimized Cas9 nucleic acid is required for CRISPR-Cas9 to function in eukaryotic cells" (Mot. 1:5-6, 3:8-10, 10:8-12, 15:17-20, 16:22-17:16, n.2) and that CRISPR/Cas9 "required" codon optimization. Mot. 1:16-17, 4:6-10, 8:11-13. Neither is true. CVC's narrative is not just inaccurate, but inconsistent with the understanding of an ordinary artisan. Without the benefit of ToolGen's P1, that artisan would not have known what was required for CRISPR/Cas9 functionality in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶206; F60, 62. The ToolGen statements cited by CVC were about its pending claims that included, *inter alia*, a codon optimization limitation, not about CRISPR/Cas9 use in eukaryotes generally. Mot. 1:5-6. This flunks the "straight-face" test.

CVC next says that ToolGen argued codon optimization was essential to patentability. Mot. 3:8-10, 4:3-4, n.2. The Board will search the record in vain for such a statement. CVC takes a question asked by Judge Flax, and staples onto ToolGen's counsel's answer to a ***different question from a different Judge***. Mot. 4:10-5:2; Ex. 2012, 8604:24-8605:25. When Judge Flax

asked "What is it that you claimed here that's the secret sauce?" ToolGen did not—as CVC represents—respond "codon optimization." Mot. 4:10-5:2. ToolGen's answer ***never even mentioned codon optimization***:

> JUDGE FLAX: So what is it that's specifically different about this claimed method, that is different from more generalized disclosure of CRISPR in the prior art that allows you to do it in a mammalian -- even say, eukaryotic cell? What is it that you claimed here that's the secret sauce?
>
> MR. INSOGNA: So, several different things. I think one, the right way to look at it is if you look at the Jinek paper, or the Doudna provisionals, and what it discloses and teaches to one of skill in the art, does it teach them how to take that system and put into the mammalian cells to operate? And the answer is no. It doesn't -- so if you took the CRISPR/CAS9 using the reagents in the way it was used, for example, in Jinek where they had high concentrations of the components.
>
> They had purified everything, they added magnesium, if you follow that recipe, if you will, it would not function in the -- well, I should say at the time, people didn't know if it would function in mammalian cell or eukaryotic cells. So, there really wasn't any discussion of how to do that.

Ex. 2012, 8604:24-8605:13 (Oral Hearing Tr.); F61.

When ToolGen ***did*** reference codon optimization, the question ToolGen was ***actually answering*** was Judge Schneider's subsequent inquiry whether one of ToolGen's pending claims contained limitaitons as to "amounts or levels of different things" that would distinguish ToolGen's claims from prior art—what was done in prokaryotic cells. Unremarkably, those distinctions were found in the claim limitations, including the "main distinction" of using CRISPR/Cas9 in mammalaian cells, as well as NLS and a codon-optimized nucleic acid encoding Cas9:

> JUDGE SCHNEIDER: I'm looking at your claim 66, and I don't see anything that talks about amounts or levels of different things, all the things you've said, or that you -- from being able to apply the eukaryotic cells? How's what's in claims 66 distinguishable from what was done in the prokaryotic cells?
>
> MR. INSOGNA: Well, the main distinction is recited in Section A, where we are providing a nucleic acid into the mammalian cell, and that nucleic acid has been engineered with both the nuclear localization signal and codon optimization. So, in order to express a protein in the mammals of prokaryotic protein or bacterial protein in a eukaryotic cell, number one, there's lots of evidence in the record from Dr. Cullen (phonetic) that that's not an easy task. It doesn't always work.
>
> And even if you get an expression, then you also have to have it actually function as I said. So what our inventors had determined and were able to do, was to figure out how did Cullen optimize input in NLS, express it in the mammalian cell, and get double-stranded breaks.

Ex. 2012, 8605:14-8606:4 (Oral Hearing Tr.).

ToolGen's answer was about a specific pending claim (66), not whether an artisan understood CRISPR/Cas9 in eukaryotic cells generally. ToolGen never wavered from the position that its claims were directed to CRISPR/Cas9 in mammalian cells, and that the inventors got there using codon optimization and NLS. Its working examples—entirely consistent with ToolGen's answer here—used a Cas9-coding sequence reconstituted using the human codon usage table—i.e., a codon-optimized nucleic acid—to express the Cas9 protein. Ex. 2008, 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196, 207; F53, 55-56; 63, 88.

(2) ToolGen Never Argued That Codon Optimizing A Nucleic Acid Encoding Cas9 Was Unpredictable

CVC claims ToolGen argued that "codon-optimizing the Cas9 nucleic acid was unpredictable[.]" Mot. 2:3-5, 15:4-7, 17:18-20; Ex. 2015 (Bailey Decl.), ¶¶ 50-54. The prosecution history shows this to be another mischaracterization. On October 23, 2012, without

the benefit of ToolGen's P1, there were multiple reasons—including the effect of codon optimization—why an ordinary artisan would have had no reasonable expectation of successfully transitioning prokaryotic CRISPR/Cas9 to eukaryotic cells. ToolGen's P1, however, alleviated that unpredictability with an actual demonstration of a CRISPR/Cas9 system that successfully introduced site-specific double-stranded breaks in a target nucleic acid sequence within a eukaryotic cell using a codon-optimized nucleic acid encoding Cas9. Ex. 2008, 5-13; Ex. 2012, 5646, ¶18 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶¶164, 176-196; F65.

ToolGen consistently maintained in prosecution that it "was the first to engineer a Type II CRISPR/Cas system to successfully introduce site-specific, double-stranded breaks in target sequences of mammalian cells." Ex. 2012, 6868 (Appeal Brief); F66. ToolGen's appeal Reply Brief explained that "***[p]rior to Appellant's claimed invention***, CRISPR/Cas9 had never been shown to introduce site-specific double-stranded breaks in target sequences in mammalian cells, and a POSA ***would have had*** no idea what the outcome may have been ***even if*** one were to apply codon optimization and NLS addition to CRISPR/Cas9." Ex. 2012, 8531 (emphasis added); F67. CVC provides only the last part of this quote, and even then omits the qualifying "***even if***" to create the false impression that ToolGen argued a POSA would have no idea what the outcome of codon optimization would be. Mot. 1:6-7, n.1. The "outcome" ToolGen was referring to was use of CRISPR/Cas9 in mammalian cells.

In its appeal, ToolGen argued, among other reasons, "[t]he Examiner either summarily dismissed or failed to address the evidence presented by Applicant in the Cullen Declaration, showing that one of ordinary skill in the art would not have had a reasonable expectation of success, based on [CVC's] '797 Pl/P2, Gustafsson and Chiu, for a method of introducing a site-specific, double-stranded break at a target nucleic acid sequence in a mammalian cell using a Type

II CRISPR/Cas system." Ex. 2012, 6893; F68. ToolGen explained how the "Cullen Declaration discussed numerous reasons why one of ordinary skill in the art, as of October 23, 2012, would not have had and, in fact, did not have a reasonable expectation of success for the claimed method . . . ." *Id*. at 6894; F69. Dr. Cullen explained that the unpredictability stems from transitioning a bacterial system to a eukaryotic system:

> [T]he intracellular environment of a eukaryotic cell is wholly incomparable to the controlled, artificial environment afforded by a test tube, and as such, the *in vitro* data in Jinek 2012 and '797 P1/P2 would have provided nothing to one of ordinary skill in the art as of October 23, 2012 that would have contributed to a reasonable expectation of success in eukaryotic cells.

Ex. 2012, 5646, ¶17 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶¶200-201; F70. ToolGen explained that one (of nine) of the reasons for that unpredictability was "bacterial proteins may not fold properly in mammalian cells" and therefore could lack activity. Ex. 2012, 6895-96; F71.

While Dr. Cullen's primary concerns were related to the differences between the prokaryotic and eukaryotic environment, he also noted that codon optimization can affect protein folding: "[T]he importance of native codon organization to proper folding was known by one of ordinary skill in the art by October 23, 2012." Ex. 2012, 5653-5654, ¶39-40 (2016 Cullen Decl.); F72. "Because it was unknown ***as of October 23, 2012*** whether particular codons encoding Cas9 are essential for its proper folding and function in a bacterial background, for example, in *S. pyogenes*, it would have been unpredictable what the possible effects of eukaryotic cell codon optimization might be on the activity Cas9 polypeptide expressed from a codon-optimized sequence in a eukaryotic cell." *Id*. (emphasis added); Ex. 1403 (Cullen Decl.), ¶201; F73. Dr. Cullen further explained that an artisan would have appreciated that "codon optimization of a nucleic acid encoding Cas9 could result in a Cas9 exhibiting inactive or aberrant function, likely due to inappropriate Cas9 folding. So, the failure to successfully use a Type II CRISPR/Cas9 in a

eukaryotic cell [and] the expectation of success at the time would have been diminished even further." Ex. 2012, 5654 ¶40; Ex. 1403 (Cullen Decl.), ¶201; F74.

Dr. Cullen agreed that the references used by the Examiner to show codon optimization "serve as verifications that . . . the technique of codon optimization [was] known by October 23, 2012." Ex. 2012, 5646, ¶17 (2016 Cullen Decl.); F75. He then explained:

> [T]he only thing that would have alleviated the unpredictability in the art as of October 23, 2012 and allayed the concerns one of ordinary skill in the art would have been ***the actual demonstration*** of a Type II CRISPR/Cas9 system successfully introducing site-specific double-stranded breaks in a target nucleic acid sequence within a eukaryotic cell. ***[ToolGen's P1], filed on October 23, 2012, does just this***, by demonstrating successful site specific cleavage in human cells of the genomic DNA of not only one, but two, endogenous human genes (CCR5 and C4BPB) as well as successful cleavage of a gene (green fluorescent protein) present on a plasmid.

Id. at 5646, ¶18 (emphasis added); Ex. 1403 (Cullen Decl.), ¶199; F76.

The "unpredictability" ToolGen referred to in prosecution was about successful use of CRISPR/Cas9 in eukaryotes, not—as CVC now tries to claim—about codon optimization. Mot. 1:6-7, n.1, 6:13-15, 12:15-13:2; Ex. 1403 (Cullen Decl.), ¶¶198, 205. Before ToolGen's P1, the outcome of using CRISPR/Cas9 in mammalian cells was not known, but the technique of codon optimization was. Ex. 1403 (Cullen Decl.), ¶¶202-205; F62, 77. The Board acknowledged all of this:

- "Dr. Cullen opined that even though the technique of codon optimization … [was] known in the prior art, a skilled artisan would not have reasonably expected the Type II CRISPR/Cas system to function in eukaryotic cells." Ex. 2012, 8638; F78.

- "[ToolGen] argues that [the references in evidence] may verify that NLSs and codon-optimization were known techniques, but they do not allay the concerns of those of skill in the art concerning transitioning the use of CRISPR/Cas9 from prokaryotic cells to eukaryotic cells." Ex. 2012, 8645; F80.

ToolGen's arguments reflected the uncertainty of protein folding due to codon optimization

as one of many factors in applying CRISPR-Cas9 in eukaryotic cells before ToolGen's P1. But that says nothing about the written description in ToolGen's P1, whose adequacy must take into account ***the working examples*** set forth there. Those examples demonstrated that ToolGen overcame the uncertainty, and successfully designed a CRISPR/Cas9 system introducing site-specific double-stranded breaks in a target nucleic acid sequence within a eukaryotic cell using a codon-optimized nucleic acid encoding Cas9. Ex. 2008, 5-6, 11; Ex. 2012, 5646, ¶18 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶¶164, 176-196; F53, 55-56; 63, 88.

2. CVC's Judicial-Estoppel Theory Fails As A Matter Of Law

CVC's judicial-estoppel theory (Mot. 7:4-9, 9:7-9) fails because ToolGen took no position in prosecution inconsistent with ToolGen's P1 showing a constructive reduction to practice of Count 1, with or without codon optimization. The Decision on Appeal contains no indication that the Board understood ToolGen to be making any of the arguments CVC contends ToolGen made there. The only "unfair advantage" or "unfair detriment" that could arise here would be if this Board were to embrace CVC's misguided judicial-estoppel argument.

a) ToolGen's Prosecution Arguments Are Completely Consistent With ToolGen's Accorded Benefit Of Its P1

ToolGen's prosecution arguments were about an ordinary artisan's expectation of success in using CRISPR/Cas9 to successfully induce genomic editing in eukaryotic cells. Both the Board (in the ToolGen-involved application prosecution and the 048 and 115 Interferences) and the Federal Circuit's 048 Interference affirmance recognized this. The prior art contained no working examples, nor did it otherwise disclose successful application of CRISPR/Cas9 in eukaryotic cells. The arguments were all about the absence of an expectation of success in this unpredictable art before ToolGen's P1.

The dispute in CVC's Motion, though, is about priority. The Board has already accorded

benefit to ToolGen's P1, which describes three working examples of the successful application of CRISPR/Cas9 to cleave DNA in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶¶183-194; F56. ToolGen's P1 alleviated the unpredictability in the art. ToolGen's arguments during prosecution were to nonobviousness, not written description. The issues now are fundamentally different, and CVC's Motion does not prove otherwise.

b)ToolGen Did Not Prevail Because Of The Mischaracterized Arguments CVC Attributes To ToolGen

The Board should not credit CVC's mischaracterizations of ToolGen's prosecution arguments. But even if ToolGen had made every single one of those arguments in prosecution, judicial estoppel still would not apply. Why? Because the Board's decision does not reflect that it embraced any such argument—it did not say, or even imply, that an ordinary artisan would have thought codon optimization unpredictable or required for function or patentability. In fact, the Board's decision does not cite to the hearing transcript at all—the only source for CVC's claim that ToolGen argued codon optimization was required for function. The Board's silence shouts loudly, for judicial estoppel requires a "strong" showing "that the court adopted and relied on the represented position." *Egenera, Inc. v. Cisco Systems, Inc.*, 972 F.3d 1367, 1379 (Fed. Cir. 2020). Judicial estoppel is unavailable here as a matter of law. *Zedner*, 547 U.S. at 504.

Yet CVC persists in claiming that "it is beyond reasonable dispute that ToolGen's codon-optimization requirement argument was necessary to the PTAB's decision reversing the obviousness rejection and the examiner's indication of allowance that led to this interference." Mot. 10:13-15. Saying that does not make it so. The Board recognized that codon optimization was "known" but would not have allayed an ordinary artisan's concerns about unpredictability:

> [ToolGen] argues that, like the evidence discussed above, Chen, Close, Gustafsson, and Chiu may verify that NLSs and codon-optimization were known techniques, but they ***do not allay the concerns of those of skill in the art concerning transitioning the use of CRISPR/Cas9 from***

> ***prokaryotic cells to eukaryotic cells***. *Id*. We are again persuaded by [ToolGen's] arguments and evidence. As discussed above, the evidence of record supports that there ***was a high level of uncertainty and unpredictability in the art and that the skilled artisan would not have had a reasonable expectation of successfully transitioning the CRISPR/Cas9 technology to eukaryotic cells***, e.g., mammalian cells as claimed. This evidence, on the whole, supports [ToolGen's] contentions that the claims would not have been obvious.

Ex. 2012, 8645 (emphasis added); F80.

c) Prosecution History Estoppel Is Inapplicable

CVC also cites to several prosecution-history-estoppel cases. Mot. 7:11-24. None apply here. Prosecution history estoppel applies when a patentee tries to assert infringement beyond the scope of its claims, construed in light of the prosecution history. The scope of ToolGen's claims is not at issue here—the only question is whether ToolGen's P1 discloses an embodiment of Count 1. *See Furman,* 59 USPQ2d 1668 ("Benefit is accorded with respect to a count, not claims corresponding to a count.")

C. CVC Does Not Dispute That ToolGen's P1 Discloses An Embodiment Of The ToolGen Half Of Count 1

CVC argues that ToolGen's P1 does not adequately describe a codon-optimized nucleic acid encoding Cas9. Mot. 11:14-20, 16:5-7, 16:16-18. That is untrue. P1 describes exactly this limitation. CVC can only offer this argument by taking liberties with the perspective of the ordinary artisan. Mot. 11:19-20, 13:14-15; Ex. 2015 (Bailey Decl.), ¶¶50-54. CVC's lawyers instructed their expert, Dr. Bailey, to analyze P1 ***not*** as an ordinary artisan would, but instead to start with certain assumptions provided by CVC's lawyers. Mot. 11:19-20; Ex. 2015 (Bailey Decl.), ¶38; Ex. 1550 (Bailey Tr.), 102:11-105:7; F81-82. CVC's untenable position violates two requirements of the written-description requirement—the disclosure is analyzed from the perspective of an ordinary artisan at the time of filing, and it is limited to the four corners of the specification. *Ariad*, 598 F.3d at 1351.

Aside from these improper assumptions, CVC does not dispute that ToolGen's P1 discloses an embodiment of ToolGen's half of Count 1 as read by an ordinary artisan. The analysis should end there, in ToolGen's favor, because the assumptions are, as shown above, based on a demonstrably incorrect recounting of the prosecution history. ToolGen's P1 describes a codon-optimized nucleic acid encoding Cas9 to an ordinary artisan. Ex. 1403 (Cullen Decl.), ¶¶176-182; F53, 55-56; 63, 88.

1. CVC's Expert, Dr. Bailey, Applies The Wrong Standard

Dr. Bailey was instructed to not provide his opinion from the perspective of an ordinarily skilled artisan, but rather to assume that an ordinary artisan would believe to be true certain statements about codon optimization provided to him by CVC's counsel. Ex. 2015 (Bailey Decl.), ¶38; Ex. 1550 (Bailey Tr.), 102:11-105:7; F81-82. These are the same mischaracterizations of ToolGen's prosecution arguments addressed above in connection with judicial estoppel (and CVC's counsel instructed Dr. Bailey not to answer questions about the basis for any of these assumptions). *Id*. That is reason enough for the Board to discount Dr. Bailey's testimony to zero.

Dr. Bailey assumed that an artisan would believe codon optimization to be (i) required for CRISPR/Cas9 functionality, (ii) unpredictable, and (iii) unlikely to lead to a functional Cas9 protein. Ex. 2015 (Bailey Decl.), ¶¶ 50-54; F83. But even he did not believe those assumptions: He stated that an ordinary artisan would know "codon-optimization was a well-known, routine technique that was used frequently and successfully in the field to achieve enhanced protein expression of a foreign gene." Ex. 2015 (Bailey Decl.), ¶63, n.1. Dr. Bailey did no objective inquiry into the four corners of the specification from the perspective of an ordinary artisan at the time of filing. The law requires that, though. *Ariad*, 598 F.3d at 1351. His opinions should therefore be disregarded as both irrelevant and unreliable. *Id.*; *see AAT Bioquest, Inc. v. Texas Fluorescence Laboratories, Inc.*, 2015 WL 1738402, *5-*7 (N.D. Cal. 2015).

2. An Ordinary Artisan Would Understand The Inventors Possessed A Codon-Optimized Nucleic Acid Encoding Cas9 And A Cas9 Protein

CVC repeatedly argues that ToolGen's P1 does not disclose codon optimization. Mot. 2:7-10, 13:6-9. Again, untrue. ToolGen's P1 describes codon optimization expressly and utilizes a codon-optimized nucleic acid encoding Cas9 in its working examples, which describes CRISPR/Cas9 successfully cleaving target DNA in a eukaryotic cell. Ex. 2008, 11; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196; F53, 55-56; 63, 88. Further, codon optimization was—again, quoting CVC's Dr. Bailey himself—"a well-known, routine technique that was used frequently and successfully in the field." Ex. 2015 (Bailey Decl.), ¶63, n.1; F84. An ordinary artisan therefore would have had no reason to doubt that the inventors possessed a codon-optimized nucleic acid encoding Cas9 as described in the specification. Ex. 1403 (Cullen Decl.), ¶¶196, 175, 208-211; F85.

a) An Ordinary Artisan Would Understand Reconstituting A Nucleic Acid Sequence Using A Codon Usage Table To Be Codon Optimization

CVC argues that ToolGen's P1 "fails to describe the supposedly required codon-optimization of a Cas9 nucleic acid," "does not even mention codon optimization generically," and "never even mentions 'codon optimization.'" Mot. 2:7-10, 13:6-9. But on page 13 of its 17-page Motion, CVC finally concedes that ToolGen's P1 does in fact describe codon optimization, just not in CVC's quoted words. Indeed, Dr. Bailey admitted this at deposition, before later trying to walk his admission back. Ex. 1550 (Bailey Tr.), 108:7-10; F86.

It was well-known to an ordinary artisan (without a lawyer demanding contrary assumptions) that nucleic acids were routinely codon-optimized through the use of codon usage tables, which involved replacing codons in the wild type gene sequence with codons that code for the same amino acids but more closely reflect the codon usage of the host cell. Ex. 1403 (Cullen

Decl.), ¶¶171-74; Ex. 2096, 3-4; Ex. 2449; Ex. 2075; Ex. 2015 (Bailey Decl.), ¶39; F87. ToolGen's P1 expressly discloses that the nucleic acid encoding Cas9 that was used in its working examples was codon-optimized using such a table:

> The Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain M1 GAS (NC_002737.1), was ***reconstituted using the human codon usage table*** and synthesized using oligonucleotides.

Ex. 2008, 11 (emphasis added); F88.

Both side's experts agree that the artisan would understand that reconstitution of a sequence using a human codon usage table is codon optimization. Ex. 1403 (Cullen Decl.), ¶176; Ex. 1550 (Bailey Tr.), 108:7-10 (agreeing "this is the section where P1, Exhibit 2008, discloses the codon optimization of the Cas9-encoding plasmids."); F79, 86. At the time of filing, codon-usage tables were widely known and used to codon-optimize proteins for expression in human cells. Ex. 1403 (Cullen Decl.), ¶173; Ex. 2015 (Bailey Decl.) ¶¶38-49; F79. ToolGen's P1 also discloses the well-known *S. pyogenes* Cas9 sequence as the sequence being codon-optimized. Ex. 1403 (Cullen Decl.), ¶¶176-182; Ex. 2008, 11; F31, 64. CVC agrees that ToolGen's P1 discloses the native *S. pyogenes* Cas9 nucleic acid sequence. *See* F31 (referring to "the native *S. pyogenes* Cas9 nucleic acid (NC_002737.1) disclosed in ToolGen's P1"). An ordinary artisan would have understood the specific Cas9 sequence based on ToolGen's P1 in view of the references known to an artisan. Ex. 1403 (Cullen Decl.), ¶¶176-182; *see also* CVC Substantive Motion 1, Paper 368, 23:24-24:1 ("[t]he sequence of the *S. pyogenes* Cas9 gene, and methods for obtaining it, were in the art by May 25, 2012"); Ex. 2013 (Doyon Decl.), ¶150 (same); F64. That artisan would understand that ToolGen's P1 described a codon-optimized nucleic acid sequence encoding Cas9 and expressed a Cas9 protein. Ex. 1403 (Cullen Decl.), ¶¶176-182; F53, 55.

b)An Ordinary Artisan Would Have No Reason To Doubt That The Inventors Possessed A Codon-Optimized Nucleic Acid Encoding Cas9 As They Describe In The Specification

Reading ToolGen's P1, an ordinary artisan would have no reason to doubt that the inventors possessed a codon-optimized nucleic acid encoding Cas9 as they describe. Ex. 1403 (Cullen Decl.), ¶¶175, 196, 208-211; F85. Dr. Bailey claims that an ordinary artisan would have required both a sequence listing and a showing of enhanced Cas9 expression compared to the wild type to understand possession. Ex. 2015 (Bailey Decl.), ¶¶57, 64. Dr. Bailey's opinions should be disregarded because they are based entirely on the assumptions provided by CVC's lawyers, not based upon what an ordinary artisan would understand. As explained below, neither of these requirements is justified, even crediting CVC's mischaracterizations of the prosecution history.

(1) An Ordinary Artisan Would Not Have Required A Sequence Listing To Understand Possession

An ordinary artisan would not have required a specific sequence listing to understand that the ToolGen inventors possessed a codon-optimized nucleic acid encoding Cas9. Ex. 1403 (Cullen Decl.), ¶211; F59. The specification identifies a specific, known *S. pyogenes* Cas9 sequence as the starting point, and the specification explains that a human codon-usage table was used to reconstitute the sequence—*i.e.*, it was codon-optimized. Ex. 2008, 11; F88. The law does not require more. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (holding "where . . . accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences . . . satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences."). Codon optimization was routine, and an ordinary artisan would know of the "widely used" Kazusa human codon-usage table or another acceptable human codon-usage table or program. Ex. 1403 (Cullen Decl.), ¶¶171-175; Ex. 1550 (Bailey Tr.), 120:6-16; F87. CVC has not challenged

enablement, and there is no evidence that the artisan would have doubted that the inventors successfully codon-optimized the *S. pyogenes* Cas9 sequence as they describe. To the extent there was any uncertainty, ToolGen's successful cleavage results confirm that the inventors possessed a codon-optimized nucleic acid encoding Cas9. Ex. 1403 (Cullen Decl.), ¶¶183-196; F85.

(2) An Ordinary Artisan Would Not Understand A Codon-Optimized Nucleic Acid Encoding Cas9 To Require Enhanced Expression Compared To Wild Type

ToolGen's P1 also describes codon optimization of a nucleic acid encoding Cas9. So CVC tries a different tack and asks this Board to put yet another unwritten limitation on Count 1, to be applied only to ToolGen. CVC argues that ToolGen's P1 cannot show a constructive reduction to practice because it does not show that the codon-optimized nucleic acid encoding Cas9 results in "enhanced" expression of the Cas9 protein compared to the wild type. Mot. 16:1-5. CVC has no basis for this new limitation. Ex. 1403 (Cullen Decl.), ¶¶208-210; Paper 1, 5-7; F48, 52. While codon optimization may lead to enhanced Cas9 protein expression compared to wild type *S. pyogenes* Cas9 (Ex. 1403 (Cullen Decl.), ¶¶208-210), Count 1 contains no such limitation (Paper 1, 5-7; F48, 84) and CVC has made no claim construction or other argument to justify adding such a limitation to Count 1.

V. CONCLUSION

ToolGen is entitled to accorded benefit of its P1. CVC's Motion should be denied.

Respectfully submitted,

Dated: July 15, 2021

/Timothy J. Heverin/
Timothy J. Heverin
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JONES DAY
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APPENDIX 1: LIST OF EXHIBITS CITED

Ex. No.	Title
1001	U.S. Provisional Application No. 61/717,324, filed October 23, 2012.
1403	July 15, 2021 Declaration of Bryan R. Cullen, Ph.D.
1550	Deposition Transcript of Scott Bailey, Ph.D., The Regents of the University of California v. ToolGen, Inc., Interference No. 106, 127, June 25, 2021.
2008	Prov. Appl. No. 61/717,324, filed October 23, 2012.
2012	File History for U.S. Appl. No. 14/685,510.
2013	Declaration of Yannick Doyon, Ph.D.
2015	Declaration of Scott Bailey, Ph.D.
2075	Sandhu, K., et al., GASCO: Genetic Algorithm Simulation for Codon Optimization, *In Silico Biology* 8: 187–192 (2008).
2096	Gustafsson et al., Codon bias and heterologous protein expression, *TRENDS in Biotechnology*, 22, 346–353 (2004).
2449	Codon Usage Table Homo sapiens [gbpri]: 93487 CDS's (40662582 codons), available at https://www.kazusa.or.jp/codon/cgi-bin/showcodon.cgi?species=9606 (last visited July 13, 2021).

APPENDIX 2: STATEMENT OF MATERIAL FACTS

Junior Party's Alleged Facts 1-45

1. ToolGen's involved claims all require a Cas9 nucleic acid that "is codon-optimized for expression in mammalian cells." Paper 6.

Response: Admitted only to the extent that ToolGen's involved claims require "a nucleic acid encoding a Cas9 polypeptide, . . . wherein said nucleic acid is codon-optimized for expression in mammalian cells."

2. During prosecution, ToolGen narrowed the claims to require that a Cas9 "nucleic acid is codon-optimized for expression in mammalian cells" to distinguish the prior art and to overcome rejections under 35 U.S.C. §§ 102 and 103. Ex. 2012, 510 Appl. Pros. History,6745-6749 (Resp., Mar. 3, 2017).

Response: Denied.

3. The examiner withdrew the anticipation rejection in view of ToolGen's claim amendment requiring that a Cas9 "nucleic acid is codon-optimized for expression in mammalian cells." *Id.*, 6783 (Office Action, Jun. 14, 2017).

Response: Admitted only to the extent that the examiner withdrew the anticipation rejection on June 14, 2017.

4. ToolGen argued during prosecution that a skilled artisan "would ***not*** have reasonably expected that a Type II CRISPR/Cas9 system could successfully have been used . . . in eukaryotic (*e.g.*, mammalian) cells. The reasons . . . include . . . challenges presented bymodification (*e.g.*, tagging and codon-optimization) of nucleic acids to be expressed in eukaryotic/mammalian cells." *Id.*, 6758 (Resp., Mar. 3, 2017) (emphasis in original) (internal citations omitted).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page response to an office action supported by a multi-page declaration.

5. ToolGen argued during prosecution that a skilled artisan would not have reasonably expected the Cas9 protein expressed from a codon-optimized nucleic acid to be functional in "eukaryotic/mammalian cells" because a skilled artisan would have "(i) questioned whether Cas9 could properly fold when expressed in eukaryotic cells . . . ; (ii) recognized that modification of Cas9, *e.g.*, by tagging it with a NLS and/or optimizing itscodon sequence, could have rendered [Cas9] inactive upon expression in a eukaryotic cell. . . ; and (iii) understood the importance of native codon optimization to proper proteinfolding " *Id*., 6761-6762 (Resp., Mar. 3, 2017).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page response to an office action supported by a multi-page declaration.

6. On appeal, ToolGen argued as follows: "Bacterial proteins may not fold properly in mammalian cells, and alteration of codons (which occurs as a result of codon optimization) can result in altered translation kinetics leading to misfolding. Since improperly folded proteins can lack activity, exhibit aberrant function or be degraded in cells, it would not have been predictable, whether a bacterial protein such as Cas9 and, inparticular, codon-optimized Cas9 would fold in a mammalian cell in a way that would preserve its functionality." *Id*., 6895-6896 (Appeal Br., June 13, 2018) (internal citations omitted).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page appeal brief supported by a multi-page declaration submitted during prosecution.

7. On appeal, ToolGen argued as follows: "it was not known or reasonably expected in theart that a prokaryotic Type II CRISPR/Cas system with codon-optimized Cas9 would successfully function in mammalian cells." *Id*., 6899 (Appeal Br., Jun. 13, 2018).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page appeal brief supported by a multi-page declaration submitted during prosecution.

8. On appeal, ToolGen argued that "a POSA would have had no idea what the outcome mayhave been even if one were to apply codon optimization and NLS addition to CRISPR/Cas9." *Id*., 8531 (Reply Br., Jan. 8, 2019).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page appeal brief supported by a multi-page declaration submitted during prosecution..

9. During oral argument, ToolGen stated: "So, you have to introduce the nucleic acid [encoding Cas9] into the mammalian cell, and then in our case, we're explicitly claiming it has to have a nuclear localization signal, and it has to be codon optimized." *Id*., 8604:1-3 (Oral Hr., Mar. 11, 2020).

Response: Admitted only to the extent those words appear in the Oral Hearing transcript.

10. During oral argument, ToolGen told the PTAB that in its claimed invention the "nucleicacid [that] has been engineered withcodon optimization" is the "main distinction" from the prior art. *Id.*, 8604:24-8605:25 (Oral Hr., Mar. 11, 2020).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page Oral Hearing transcript. .

11. During oral argument, ToolGen argued that codon optimization of Cas9 nucleic acid is "required in the science to get [CRISPR-Cas9] to work." *Id.*, 8606:5-11 (Oral Hr., Mar.11, 2020).

Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page Oral Hearing transcript.

12. Relying on ToolGen's representations and accepting its arguments, the PTAB reversed the examiner's obviousness rejection of ToolGen's involved claims. *Id*., 8638, 8642, 8643, 8645, 8646 (PTAB Decision, Jun. 22, 2020).

Response: Denied. The PTAB's basis for its Decision is set forth in that decision.

13. On remand, the examiner found ToolGen's claims to be in condition for allowance. Id., 8651 (Office Comm., Oct. 23, 2020).

Response: Admitted.

14. ToolGen's P1 does not provide a single codon-optimized Cas9 nucleic acid sequence. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶56.

Response: Denied.

15. ToolGen's P1 never mentions "codon optimization" at all. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶56.

Response: Denied.

16. ToolGen's P1 states that "[t]he Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain M1 GAS (NC_002737.1), was reconstituted using the human codon usage table and synthesized using oligonucleotides." Ex. 2008, ToolGen'sP1, 11; Ex. 2015, Bailey Decl., ¶56.

Response: Admitted only to the extent the quoted words appear in ToolGen's P1, Exs. 1001 and 2008.

17. NC_002737.1 is the accession number for the nucleic acid sequence record of the complete

genome of M1 GAS strain of *S. pyogenes* in the NCBI database, which at bestincludes the nucleotide range of the location of the Cas9 gene in the genome. Ex. 2015, Bailey Decl., ¶59; Ex. 2447; Ex. 2448.

Response: Admitted only to the extent that NC_002737.1 is the accession number for the nucleic acid sequence record of the complete genome of M1 GAS strain of *S. pyogenes* in the NCBI database.

18. ToolGen's P1 does not disclose a single human codon-usage table. Ex. 2008, ToolGen'sP1; Ex. 2015, Bailey Decl., ¶60.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

19. Without knowing the specific codon-usage table or the process or set of rules for selecting codons from the table, numerous sequences could be reconstituted from acodon-usage table. Ex. 2015, Bailey Decl., ¶¶60, 64.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

20. In ToolGen's P1, there is no disclosure of what the sequence was or that the reconstituted sequence was in fact optimized vis-à-vis the wild-type *Streptococcus pyogenes* strain. Ex.2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶57.

Response: Denied.

21. Multiple human codon-usage tables were known in the art by October 23, 2012. Ex. 2015; Bailey Decl., ¶¶41-46, 61; Ex. 2449, Kazusa 2007; Ex. 2077, Jorgensen 2005, Table 8; Ex. 2078, Alff-Steinberger 1987, Table 1.

Response: Admitted.

22. Different human codon-usage tables known in the art by October 23, 2012 identified adifferent codon as the most frequent codon for certain amino acids. Ex. 2015, Bailey Decl., ¶¶41-46, 61; Ex. 2449, Kazusa 2007; Ex. 2077, Jorgensen 2005, Table 8; Ex. 2078, Alff-Steinberger 1987, Table 1.

Response: Denied as the statement is incomplete, vague as to "most frequent" and "certain amino acids" and to the extent it implies codon optimization could not be completed without undue experimentation.

23. ToolGen's P1 does not provide any human codon-usage information to reconstitute theCas9 sequence. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶60.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

24. ToolGen's P1 does not indicate which human codon-usage table should be used to reconstitute the Cas9 sequence. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶60.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

25. The codon-usage frequencies for as many as 12 of the 20 possible amino acids differedfrom table to table. Ex. 2015, Bailey Decl., ¶¶39-46, 61.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

26. If the most frequent codon for each amino acid were picked from multiple possible human codon-usage tables, ToolGen's P1 reconstituted myriad different Cas9 nucleic acids from the native *S. pyogenes* nucleic acid sequence. Ex. 2015, Bailey Decl., ¶¶39-46,60-61, 63-65.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

27. ToolGen's P1 does not identify a particular codon-optimization program. Ex. 2008,ToolGen's P1; Ex. 2015, Bailey Decl., ¶62.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

28. Several human codon-optimization programs were known in the art by October 23, 2012. Ex. 2015, Bailey Decl., ¶¶47-49, 62; Ex. 2084; Ex. 2088; Ex. 2094; Ex. 2089; Ex. 2087; Ex. 2085; Ex. 2086; Ex. 2091; Ex. 2074; Ex. 2073.

Response: Admitted.

29. The codon-optimization programs known by October 23, 2012 relied on codon-usagedata from different tables. Ex. 2015, Bailey Decl., ¶¶47-49.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

30. The codon-optimization programs known by October 23, 2012 applied different criteriato select codons to generate a codon-optimized nucleic acid sequence. Ex. 2015, Bailey Decl., ¶¶47-49, 62.

Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

31. Different codon-optimization programs known in the art by October 23, 2012 would have generated myriad different codon-optimized Cas9 nucleic acid sequences from the native *S. pyogenes* Cas9 nucleic acid (NC_002737.1) disclosed in ToolGen's P1. Ex. 2015, Bailey Decl., ¶¶47-49, 62-64; Ex. 2008, ToolGen's P1.

Response: Admitted that a POSA could have made "codon-optimized Cas9 nucleic acid sequences from the native *S. pyogenes* Cas9 nucleic acid (NC_002737.1) disclosed in ToolGen's P1" but otherwise denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.

32. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is requiredfor CRISPR-Cas9 to function in eukaryotic cells. Ex. 2012, 510 Appl. Pros. History, 8606:5-11 (Oral Hr., Mar. 11, 2020).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.

33. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is requiredfor CRISPR-Cas9 to function in mammalian cells. *Id*., 8606:5-11 (Oral Hr., Mar. 11, 2020).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.

34. ToolGen argued during prosecution that a codon-optimization is unpredictable. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531 (Reply Br., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.

35. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in eukaryotic cells due to alleged unpredictability in protein folding. *See, e.g., id*., 6895-6896 (Appeal Br., Jun. 13, 2018) *see also id.*, 6761-6762 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief and response to an office action.

36. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in eukaryotic cells due to unpredictability in codon optimization. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531 (ReplyBr., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.

37. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in mammalian cells due to unpredictability in proteinfolding. *See, e.g., id*., 6895-6896 (Appeal Br., Jun. 13, 2018) *see also id.*, 6761-6762 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief and response to an office action.

38. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in mammalian cells due to unpredictability in codon optimization. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531 (ReplyBr., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.

39. ToolGen's P1 does not disclose a single Cas9 nucleic acid sequence from among the myriad different Cas9 sequences that can be reconstituted using different codon usage tables or different codon optimization algorithms. Ex. 2015, Bailey Decl., ¶¶55-65; Ex.2008, ToolGen's P1.

Response: Denied.

40. A skilled artisan reading its P1 would not have been able to know or predict which of the myriad Cas9 nucleic acid sequences reconstituted using human codon-usage tables known by

October 23, 2012 would express a functional Cas9 protein in eukaryotic cells.Ex. 2015, Bailey Decl., ¶¶60-61, 63-65; Ex. 2008, ToolGen's P1.

Response: Denied.

41. A skilled artisan reading its P1 would not have been able to know or predict which of the myriad Cas9 nucleic acid sequences reconstituted using human codon-optimization programs known by October 23, 2012 would express a functional Cas9 protein in eukaryotic cells. Ex. 2015, Bailey Decl., ¶¶62, 63-65; Ex. 2008, ToolGen's P1.

Response: Denied.

42. The purported target DNA cleavage reported in ToolGen's examples could be from usinga non-codon-optimized Cas9 nucleic acid expressing a functional Cas9 protein in the cells. Ex. 2015, Bailey Decl., ¶58.

Response: Denied.

43. ToolGen argued during prosecution that codon-optimized Cas9 nucleic acid is requiredfor patentability of its involved claims. Ex. 2012, 510 Appl. Pros. History, 8604:24- 8605:25 (Oral Hr., Mar. 11, 2020).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.

44. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is requiredfor CRISPR-Cas9 to function in its claimed invention. *Id*., 8606:5-11 (Oral Hr., Mar. 11,2020).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.

45. ToolGen argued during prosecution that not all codon-optimized Cas9 nucleic acids would be functional. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531(Reply Br., Jan. 8,

2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017).

Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.

Senior Party ToolGen's Additional Material Facts 46-88

46. Count 1 does not require a codon-optimized nucleic acid encoding Cas9. Paper 1, 5-7.

47. The CVC half of Count 1 does not require a nucleic acid encoding Cas9 or a codon-optimized nucleic acid encoding Cas9. Paper 1, 5-7; Ex. 1550, 124:18-125:1.

48. Count 1 does not include the word "enhanced." Paper 1, 5-7.

49. ToolGen's P1 describes a constructive reduction to practice of Count 1. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196.

50. ToolGen's P1 describes a constructive reduction to practice of the ToolGen half of Count 1. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196.

51. ToolGen's P1 describes a constructive reduction to practice of the CVC half of Count 1. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196.

52. ToolGen's P1 does not need to show a codon-optimized nucleic acid encoding Cas9 that results in "enhanced" expression of the Cas9 protein compared to the wild type to show a constructive reduction to practice of Count 1. Ex. 1403 (Cullen Decl.), ¶¶208-210; Paper 1, 5-7.

53. ToolGen's P1 describes a codon-optimized nucleic acid encoding Cas9 that cleaves DNA in a eukaryotic cell. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196.

54. CVC's half of Count 1 requires a Cas9 protein or a nucleic acid encoding Cas9. Paper 1, 6.

55. ToolGen's P1 describes a CRISPR-Cas system comprising a Cas9 protein. Ex. 1403 (Cullen Decl.), ¶¶187, 194, 207.

56. ToolGen's P1 provides three working examples of the successful use of CRISPR/Cas9 in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶¶183-194.

57. During prosecution, ToolGen stated that its "claimed invention is ***not obvious*** at least because one of ordinary skill in the art would have doubted whether a Type II CRISPR/Cas9 system could

be introduced into a eukaryotic/mammalian cell without toxicity and whether, once introduced, could successfully bring about site-specific double-stranded breaks in a target nucleic acid sequence of the cell." Ex. 2012, 6769 (emphasis in original), 6883, 6896, 8529-8530.

58. During prosecution, ToolGen stated that the Examiner offered "only conclusory statements regarding reasonable expectation of success that incorrectly focus[ed] on whether one of ordinary skill in the art would have expected to successfully codon-optimize Cas9 and/or add an NLS to it[,]" which "fail as a matter of law." Ex. 2012, 6769.

59. A POSA would not need a specific sequence listing to understand that the ToolGen inventors possessed a codon-optimized nucleic acid encoding Cas9. Ex. 1403 (Cullen Decl.), ¶211.

60. Without the benefit of ToolGen's P1, a POSA would not have known what was required for CRISPR/Cas9 functionality in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶206.

61. ToolGen never argued that codon optimization was the "secret sauce" to its invention disclosed in ToolGen's P1. Ex. 2012, 8604:24-8605:13 (Oral Hearing Tr.).

62. In prosecution, Dr. Cullen's statements were about the state of the art without the benefit of ToolGen's P1 Disclosure. Ex. 1403 (Cullen Decl.), ¶¶170, 198-200; Ex. 2012, 5645-5654, ¶¶16-18, 29-40 (2016 Cullen Decl.).

63. P1's working examples used a Cas9-coding sequence reconstituted using the human codon usage table to express a Cas9 protein. Ex.2008, 11; Ex.1403(Cullen Decl.), ¶¶164, 176-196, 207.

64. ToolGen's P1 discloses the well-known *S. pyogenes* Cas9 sequence as the sequence being codon-optimized for use in its working examples, and POSA would have understood the specific Cas9 sequence based on ToolGen's P1 in view of the references known to a POSA. Ex. 1403 (Cullen Decl.), ¶¶176-182; Ex. 2008, 11; *see also* CVC Substantive Motion 1, Paper 368, 23:24-24:1; Ex. 2013 (Doyon Decl.), ¶150.

65. ToolGen's P1 alleviated the unpredictability of applying CRISPR/Cas9 systems in eukaryotic cells with an actual demonstration of a CRISPR/Cas9 system that successfully introduced site-specific double-stranded breaks in a target nucleic acid sequence within a eukaryotic cell using a codon-optimized nucleic acid encoding Cas9. Ex. 2008, 5-13; Ex. 2012, 5646, ¶18 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶¶164, 176-196.

66. During prosecution, ToolGen stated that it "was the first to engineer a Type II CRISPR/Cas system to successfully introduce site-specific, double-stranded breaks in target sequences of mammalian cells." Ex. 2012, 6868 (Appeal Brief).

67. In prosecution (Ex. 2012, 8531), ToolGen stated that "[p]rior to Appellant's claimed invention, CRISPR/Cas9 had never been shown to introduce site-specific double-stranded breaks in target sequences in mammalian cells, and a POSA would have had no idea what the outcome may have been even if one were to apply codon optimization and NLS addition to CRISPR/Cas9."

68. During prosecution (Ex. 2012, 6893), ToolGen stated:

> The Examiner either summarily dismissed or failed to address the evidence presented by Applicant in the Cullen Declaration, showing that one of ordinary skill in the art would not have had a reasonable expectation of success, based on [CVC's] '797 Pl/P2, Gustafsson and Chiu, for a method of introducing a site-specific, double-stranded break at a target nucleic acid sequence in a mammalian cell using a Type II CRISPR/Cas system."

69. In prosecution (Ex. 2012, 6894), ToolGen stated that the "Cullen Declaration discussed numerous reasons why one of ordinary skill in the art, as of October 23, 2012, would not have had and, in fact, did not have a reasonable expectation of success for the claimed method . . . ."

70. During prosecution (Ex. 2012, 5646, ¶17 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶¶200-201), Dr. Cullen stated:

> [T]he intracellular environment of a eukaryotic cell is wholly incomparable to the controlled, artificial environment afforded by a test tube, and as such, the *in vitro* data in Jinek 2012 and '797 P1/P2 would have provided nothing to one of

> ordinary skill in the art as of October 23, 2012 that would have contributed to a reasonable expectation of success in eukaryotic cells.

71. During prosecution, ToolGen stated that one (among nine) of the reasons for the unpredictability in applying CRISPR/Cas9 systems in eukaryotic cells was "bacterial proteins may not fold properly in mammalian cells" and therefore could lack activity. Ex. 2012, 6895-96.

72. In prosecution, Dr. Cullen stated that his primary concerns were related to the differences between prokaryotic and eukaryotic environments and that codon optimization can affect protein folding: "[T]he importance of native codon organization to proper folding was known by one of ordinary skill in the art by October 23, 2012." Ex. 2012, 5653-5654, ¶39-40 (2016 Cullen Decl.).

73. During prosecution, ToolGen stated:

> Because it was unknown as of October 23, 2012 whether particular codons encoding Cas9 are essential for its proper folding and function in a bacterial background, for example, in *S. pyogenes*, it would have been unpredictable what the possible effects of eukaryotic cell codon optimization might be on the activity Cas9 polypeptide expressed from a codon-optimized sequence in a eukaryotic cell.

Ex. 2012, 5653-5654, ¶39-40 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶201.

74. During prosecution, Dr. Cullen stated that a POSA would have appreciated that "codon optimization of a nucleic acid encoding Cas9 could result in a Cas9 exhibiting inactive or aberrant function, likely due to inappropriate Cas9 folding. So, the failure to successfully use a Type II CRISPR/Cas9 in a eukaryotic cell [and] the expectation of success at the time would have been diminished even further." Ex. 2012, 5654, ¶40 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶201.

75. During prosecution, Dr. Cullen stated that the references used by the Examiner to show codon optimization "serve as verifications that . . . the technique of codon optimization [was] known by October 23, 2012." Ex. 2012, 5646, ¶17 (2016 Cullen Decl.).

76. During prosecution, Dr. Cullen stated:

> [T]he only thing that would have alleviated the unpredictability in the art as of October 23, 2012 and allayed the concerns one of ordinary skill in the art would have been the actual demonstration of a Type II CRISPR/Cas9 system successfully introducing site-specific double-stranded breaks in a target nucleic acid sequence within a eukaryotic cell. [ToolGen's P1], filed on October 23, 2012, does just this, by demonstrating successful site specific cleavage in human cells of the genomic DNA of not only one, but two, endogenous human genes (CCR5 and C4BPB) as well as successful cleavage of a gene (green fluorescent protein) present on a plasmid.

Ex. 2012, 5646, ¶18. (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶199.

77. Before ToolGen's P1, the outcome of using CRISPR/Cas9 in mammalian cells was not known, but the technique of codon optimization was. Ex. 1403 (Cullen Decl.), ¶¶202-205.

78. In prosecution, the Board stated that "Dr. Cullen opined that even though the technique of codon optimization … [was] known in the prior art, a skilled artisan would not have reasonably expected the Type II CRISPR/Cas system to function in eukaryotic cells." Ex. 2012, 8638.

79. At the time ToolGen's P1 was filed, a POSA would understand that reconstitution of a sequence using a human codon usage table is codon optimization. Ex. 1403 (Cullen Decl.), ¶¶173, 176; Ex. 1550 (Bailey Tr.), 108:7-10; Ex. 2015 (Bailey Decl.) ¶¶38-49.

80. During prosecution (Ex. 2012, 8645), the Board stated:

> [ToolGen] argues that, like the evidence discussed above, Chen, Close, Gustafsson, and Chiu may verify that NLSs and codon-optimization were known techniques, but they do not allay the concerns of those of skill in the art concerning transitioning the use of CRISPR/Cas9 from prokaryotic cells to eukaryotic cells. *Id*. We are again persuaded by [ToolGen's] arguments and evidence. As discussed above, the evidence of record supports that there was a high level of uncertainty and unpredictability in the art and that the skilled artisan would not have had a reasonable expectation of successfully transitioning the CRISPR/Cas9 technology to eukaryotic cells, e.g., mammalian cells as claimed. This evidence, on the whole, supports [ToolGen's] contentions that the claims would not have been obvious.

81. Dr. Bailey did not analyze P1 from the perspective of a POSA at the time ToolGen's P1 was filed. Mot. 11:19-20; Ex. 2015 (Bailey Decl.), ¶38; Ex. 1550 (Bailey Tr.), 102:11-105:7.

82. Dr. Bailey was provided assumptions that a POSA would believe to be true by CVC's lawyers

and was instructed not to answer questions about the basis for any of these assumptions. Mot. 11:19-20; Ex. 2015 (Bailey Decl.), ¶38; Ex. 1550 (Bailey Tr.), 102:11-105:7.

83. Dr. Bailey assumed that a POSA would believe codon optimization to be (i) required for CRISPR/Cas9 functionality, (ii) unpredictable, and (iii) unlikely to lead to a functional Cas9 protein. Ex. 2015 (Bailey Decl.), ¶¶ 50-54.

84. At the time ToolGen's P1 was filed, a POSA would know "codon-optimization was a well-known, routine technique that was used frequently and successfully in the field to achieve enhanced protein expression of a foreign gene." Ex. 2015 (Bailey Decl.), ¶63, n.1.

85. A POSA reading ToolGen's P1 would have understood the ToolGen inventors possessed a codon-optimized nucleic acid encoding Cas9 as described in the specification and would have had no reason to doubt possession. Ex. 1403 (Cullen Decl.), ¶¶175, 183-196, 208-211.

86. On cross-examination, Dr. Bailey agreed that ToolGen's P1 section on "Construction of Cas9-encoding plasmids . . . is the section where P1, Exhibit 2008, discloses the codon optimization of the Cas9-encoding plasmids." Ex. 1550 (Bailey Tr.), 108:7-10; Ex. 2008, 11.

87. At the time ToolGen's P1 was filed, a POSA would know that nucleic acids were routinely codon-optimized through the use of codon usage tables (such as the Kazusa human codon usage table) to replacing codons in the wild type gene sequence with codons that code for the same amino acids but more closely reflect the codon usage of the host cell. Ex.1403 (Cullen Decl.), ¶¶171-75; Ex. 2096, 3-4; Ex. 2449; Ex. 2075; Ex. 2015 (Bailey Decl.), ¶39; Ex. 1550 (Bailey Tr.), 120:6-16.

88. ToolGen's P1 discloses that the nucleic acid encoding Cas9 used in its working examples was codon-optimized using a human codon usage table: "The Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain M1 GAS (NC_002737.1), was reconstituted using the human codon usage table and synthesized using oligonucleotides." Ex. 2008, 11.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **TOOLGEN OPPOSITION 2** was filed via the Interference Web Portal on July 15, 2021 by 5:00 PM ET, and thereby served on the attorneys of record for the Junior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to agreement of the parties, service copies are being sent by email by 11:00 pm ET to counsel for Junior Party as follows:

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