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THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
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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 OPPOSITION 1

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I. INTRODUCTION

The PTAB should deny ToolGen's motion to be accorded benefit to its third provisional (P3) or PCT application. These applications suffer the same deficiencies that CVC's motion demonstrated for ToolGen's first provisional application (P1). They fail to adequately describe the features that ToolGen insisted during prosecution were critical and unpredictable to render its claimed invention patentable: codon optimization and NLS tagging of Cas9. In view of ToolGen's own admissions, none of the disclosures relied upon in its motion show ToolGen possessed an embodiment of the count comprising such an NLS-tagged and codon-optimized Cas9. Not only does ToolGen's motion fail to identify any particular NLS-tagged and codon-optimized Cas9 used in its relied-upon embodiments, even its expert was unable to point to any such disclosure in P3 or PCT. Accordingly, the PTAB should deny ToolGen's Motion 1.

ToolGen's motion ignores its unambiguous representations to the Patent Office—representations that were central to allowance of its involved claims. ToolGen stated to an earlier PTAB panel during prosecution that Cas9 "has to have a nuclear localization signal, and it has to be codon optimized" in its claimed invention. Ex. 2012, 8604:1-3. And when the panel asked what was the "secret sauce" that distinguished its claims over the prior art, ToolGen averred that the "nucleic acid has been engineered with both the nuclear localization signal and codon optimization." *Id*., 8604:24-8605:25. In addition to insisting that NLS and codon optimization were "required in the science to get it to work," ToolGen argued that one would have "no idea what the outcome may be even if one were to apply codon optimization and NLS addition to CRISPR/Cas9." *Id*., 8606:5-11, 8531. ToolGen's positions during prosecution were clear and unmistakable: its invention required an NLS and codon optimization, and NLS addition and codon optimization were unpredictable. Thus, in view of ToolGen's representations, a mere

general reference to NLS addition or codon optimization is inadequate to describe an embodiment with an NLS-tagged and codon-optimized Cas9 that cleaves, edits, or modulates transcription of DNA. The Federal Circuit has held that "generalized language" is insufficient for written description where "it does not convey the detailed identity of [the] invention." *University of Rochester v. G.D. Searle & Co*., 358 F.3d 916, 923 (Fed. Cir. 2004). This is such a case.

ToolGen tries to abandon its own prosecution history by arguing that its P3 and PCT disclose an embodiment of CVC's half of the count, which does not require NLS addition or codon optimization. The issue is not which half of the count ToolGen seeks to prove. Rather, the issue is what embodiments ToolGen may rely on given that it unambiguously told the Patent Office that NLS addition and codon optimization are required and unpredictable. Indeed, ToolGen is in this interference because it advocated this very position to an earlier PTAB panel. The PTAB should now reject ToolGen's attempt to abandon its prosecution positions by arguing opposite positions. Principles of party admission and judicial estoppel preclude ToolGen from taking positions inconsistent with its prior assertions. *Zedner v. United States*, 547 U.S. 489 (2006); *Louis v. Okada*, 59 U.S.P.Q.2d 1073, 1075 (B.P.A.I. 2001) (precedential).

Because P3 and PCT do not disclose the very things ToolGen deemed critical for its invention to function, these applications cannot serve as a CRTP of the count by ToolGen's own standards. "Proof of a reduction to practice, absent an adequate description in the specification of what is reduced to practice, does not serve to describe or identify the invention for purposes of the written description requirement." *In re Alonso*, 545 F.3d 1015, 1021 (Fed. Cir. 2008). Accordingly, the PTAB should deny ToolGen's motion to be accorded benefit to its P3 or PCT.

II. STATEMENT OF MATERIAL FACTS AND EVIDENCE

Appendix A is a list of exhibits cited. Appendix B is a Statement of Material Facts.

III. ARGUMENT

On page 3, lines 14-23 of ToolGen's motion, it is argued that Example 3 of P3 (Ex. 1003) and Examples 3 and 4 of PCT (Ex. 1004) provide a CRTP of CVC's half of the count. Specifically, it is argued on page 9, lines 13-24 and page 17, line 10 to page 18, line 4, that P3 and PCT describe element [2] of CVC's half of the count (*i.e.*, "a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein"). The response is that ToolGen represented to the Patent Office during prosecution that addition of an NLS and codon optimization are required and unpredictable, and render its involved claims patentable. MF69-83. Yet, its motion fails to show written description of any embodiment with such a codon-optimized Cas9 nucleic acid encoding an NLS-tagged Cas9 protein ("NLS-tagged, codon-optimized Cas9 nucleic acid") or an NLS-tagged Cas9 protein (collectively, "NLS-tagged and codon-optimized Cas9"). A general reference to an NLS or codon optimization is insufficient to describe a functional embodiment in view of ToolGen's prior representations regarding unpredictability. If ToolGen is held to its representations—as *Zedner* and *Louis* require—its P3 and PCT fail to provide any identity, much less a detailed identity, of a specific NLS-tagged and codon-optimized Cas9 that cleaves, edits or modulates transcription of target DNA in ToolGen's relied-upon embodiments. *Zedner*, 547 U.S. at 504; *Louis*, 59 U.S.P.Q.2d at 1075.

CVC's Motion 1 explained how ToolGen's representations apply against it regardless of which half of the count is considered. Notably, ToolGen's motion ignores its prior representations and makes no effort to explain why it is no longer bound by them, or how its P3 or PCT describe an embodiment with an NLS-tagged and codon-optimized Cas9 consistent with its representations. Thus, ToolGen's motion fails to show a CRTP and should be denied.

A. ToolGen's motion fails to show that its P3 and PCT provide a CRTP of CVC's half of the count because neither application describes an

embodiment with an NLS-tagged and codon-optimized Cas9 consistent with its prosecution representations.

For benefit of an earlier-filed application, it must provide a CRTP—i.e., "a described and enabled anticipation" for at least one embodiment within the count. *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006); 37 CFR § 41.201. "[T]he hallmark of written description is disclosure." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). "[T]he description must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Id.*; *see also Alonso*, 545 F.3d at 1019 ("To satisfy [the written description] requirement, the specification must describe the invention in sufficient detail so that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought."). It is "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351.

The specification must contain sufficient disclosure to "convey the detailed identity of an invention." *Rochester*, 358 F.3d at 923. This means that "mere indistinct words" may not necessarily be sufficient to allow "one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Id.* In *Rochester*, the court found that the specification lacked written description for the claimed treatment method because "[n]o compounds that will perform the claimed methods [were] disclosed." *Id.* at 927. The court reasoned that the disclosure of how to obtain the compounds or what can be done with the compounds that may be obtained did not help satisfy the written description requirement because the patent did not disclose the "detailed identity" of the compounds. *Id.* at 923, 927.

1. ToolGen's motion fails to show that P3 describes an embodiment of the count consistent with its prosecution representations.

ToolGen asserts that its P3 describes element [2] of CVC's half of the count (*i.e.*, "a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein"). Mot., 9:13-24. Specifically, it asserts that Example 3 provides two embodiments: (1) Embodiment 3-1 where "Cas9 mRNA" and "single-chain guide RNA (i.e., sgRNA)" were injected into the cytoplasm of mouse embryos; and (2) Embodiment 3-2 where "recombinant Cas9 protein" complexed with sgRNA was injected into the cytoplasm or pronucleus of mouse embryos. Mot., 7:32-8:14; Ex. 2477, ¶40. A skilled artisan would have understood that the same recombinant Cas9 protein was injected into the cytoplasm or pronucleus in Embodiment 3-2. Ex. 2477, ¶40. ToolGen repeatedly represented that NLS addition and codon optimization are required yet unlikely to express a functional Cas9 protein in eukaryotic cells. MF69-83. ToolGen may not abandon its prior representations that led to this interference. As such, its P3 must describe a specific NLS-tagged and codon-optimized Cas9 to show possession. Nothing in ToolGen's motion shows that its relied-upon embodiments comprise an NLS-tagged and codon-optimized Cas9 according to its representations. *Ariad*, 598 F.3d at 1351; Ex. 2477, ¶¶10-11, 18-87.

Embodiment 3-1. Embodiment 3-1 is not a CRTP. First, P3 does not provide the sequence of the alleged NLS-tagged, codon-optimized Cas9 mRNA injected in Embodiment 3-1. Ex. 1003; Ex. 2477, ¶42; MF84. There is no sequence listing in P3. Ex. 1003; MF94. As in *Rochester*, the absence of such a disclosure is fatal to ToolGen's reliance on Example 3-1. *Rochester*, 358 F.3d at 927. This is an undisputed fact as ToolGen's expert Dr. Cullen admitted that no "codon-optimized Cas9 sequence [is] included" in P3. Ex. 2474, 77:16-78:2; *see also id.*, 86:13-87:2 (stating "I do not know the sequence . . ."), 87:13-20, 90:18-91:3; MF85.

Second, P3 lacks the following disclosures that a skilled artisan would otherwise need to understand that ToolGen possessed a Cas9 mRNA of the count: (1) the bacterial Cas9 species from which the Cas9 mRNA was derived, (2) whether the Cas9 mRNA was codon-optimized or encoded an NLS-tagged Cas9 protein, (3) which NLS, if any, was attached; or (4) which Cas9 mRNA sequence was injected into the mouse cells. Ex. 1003; Ex. 2477, ¶42; MF86-87, 89-90.

Example 3 itself does not disclose the Cas9 mRNA used in Embodiment 3-1. Ex. 2477, ¶¶42, 54; MF92. To remedy this deficiency, Dr. Cullen cobbles together disparate statements from other portions of the specification. Ex. 1400, ¶¶43, 66; Ex. 2474, 91:4-10; Ex. 1003, 9-10, 26, 34, 36-37. For example, Dr. Cullen relies on the following statements: "recombinant Cas protein may be generated by reconstituting Cas protein-encoding sequence using the human codon table" and "the Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain Ml GAS (NC_002737.1), was reconstituted using the human codon usage table . . . . [and] a nuclear localization signal (NLS) was added to the C-terminus of Cas9." Ex. 1400, ¶¶43, 66; Ex. 2474, 91:4-10; Ex. 1003, 9-10, 26; MF93. P3 does not indicate that these disclosures apply to Example 3. Regardless, because ToolGen insisted during prosecution that codon optimization and NLS addition were unpredictable, these general statements lack sufficient information to describe the specific Cas9 mRNA of Embodiment 3-1. Ex. 2477, ¶¶10, 42-61, 87.

NC_002737.1 at best identifies the sequence of native *S. pyogenes* Cas9 gene and, by extension, native *S. pyogenes* Cas9 mRNA. Ex. 2477, ¶45; MF95. The statements that the sequence was "reconstituted using the human codon usage table" or "human codon table" are also inadequate to describe the Cas9 mRNA of Embodiment 3-1. Ex. 2477, ¶¶44-60. As Dr. Cullen also conceded, P3 does not contain any codon-usage table, let alone a human codon-usage table. Ex. 2477, ¶46; Ex. 2474, 91:11-92:7; Ex. 1003; MF96. P3 also does not indicate which

table should be used to reconstitute the Cas9 mRNA sequence or provide any information on the process or rules for selecting codons from a table. Ex. 1003; Ex. 2477, ¶46; MF96. Without knowing the process or set of rules for selecting codons, numerous sequences could be reconstituted from even a single codon-usage table. Ex. 2477, ¶46; MF97.

By June 2013, multiple human codon-usage tables were known in the art, and these tables often identified a different codon as the most frequent codon for certain amino acids. Ex. 2477, ¶47; Ex. 2449; Ex. 2077, Table 8; Ex. 2078, Table 1; *see also* Ex. 2477, ¶¶18-25; MF98. The most frequent codons for as many as 12 of the 20 amino acids differed from one table to another. Ex. 2477, ¶47; MF99. Put simply, even if the most frequent codon for each amino acid were picked from the multiple tables, P3 would lead to myriad different Cas9 mRNAs, not all of which would be codon optimized to express a functional Cas9 protein in mouse cells according to ToolGen's arguments to the Patent Office. *Id.*, ¶¶47, 57-59; MF100. Moreover, the process for optimizing nucleotide sequences does not simply involve selecting the most frequent codon. *Id.*, ¶47; MF101. Thus, a skilled artisan would not be able to discern the sequence that allegedly functioned in the mouse cells in Embodiment 3-1. *Id.*, ¶¶47-49, 57-59.

P3 also does not disclose a particular codon-optimization program or indicate which program should be used. Ex. 1003; Ex. 2477, ¶¶26-28, 48; MF102. By June 2013, several codon-optimization programs that relied on data from different codon-usage tables and applied different criteria to select codons were known. Ex. 2477, ¶48; MF103. They would have also provided myriad different nucleic acid sequences, not all of which according to ToolGen would express a functional Cas9 protein in mouse cells, and *none* of which were actually disclosed in P3. *Id.* Dr. Cullen failed to consider these differences between the programs. Ex. 2474, 96:4-16; MF121.

Additionally, several bacterial Cas9 protein species and NLSs were known in the art before P3's filing date. Ex. 2477, ¶¶43, 50-51, 53; Ex. 2474, 60:11-19 (Dr. Cullen testifying "dozens and dozens" of NLSs were known before 2012); Ex. 2182; Ex. 2191; Ex. 2192; Ex. 2193; MF91, 104, 123. Yet, P3 does not disclose which of the many bacterial Cas9 species and NLS allegedly were used in Embodiment 3-1. Ex. 2477, ¶¶42-43, 51-53; Ex. 1003. These alternatives provided additional possibilities for the Cas9 mRNA sequence that P3 does not describe. Ex. 2477, ¶¶50-53, 57, 60.

P3 states that "Cas9 encoding nucleic acid may comprise the nucleotide sequence of SEQ ID NO:2." Ex. 1003, 10. As Dr. Cullen conceded, P3 does not provide the sequence of SEQ ID NO. 2. Ex. 2474, 79:16-22; Ex. 1003, 10; Ex. 2477, ¶54; MF105. Dr. Cullen further conceded that P3 "does not" disclose that SEQ ID NO: 2 is codon optimized for expression in eukaryotic cells. Ex. 2474, 84:2-22 (testifying "don't know whether it's codon optimized or not"); Ex. 1003; Ex. 2477, ¶54; MF106. Thus, this disclosure does not remedy P3's failures. Ex. 2477, ¶54.

Taking as true ToolGen's insistence that NLS addition and codon optimization are unpredictable, the generic disclosures in P3 do not describe an embodiment on which ToolGen can rely to show CRTP. Ex. 2477, ¶¶57-61. If these features were as unpredictable as ToolGen said they were, and given the myriad different possible sequences, a skilled artisan would not have been able to discern from P3 the detailed identity of the NLS-tagged, codon-optimized Cas9 mRNA allegedly used in Embodiment 3-1. Ex. 2477, ¶¶57-61; *Rochester*, 358 F.3d at 923 (requiring disclosure sufficient to "convey the detailed identity of an invention"). Thus, in light of ToolGen's persistent arguments that NLS addition and codon optimization are unpredictable, P3's Embodiment 3-1 fails to adequately describe an NLS-tagged, codon-optimized Cas9 mRNA. Ex. 2477, ¶¶10, 40-61, 87.

Embodiment 3-2. Embodiment 3-2, also is not a CRTP. Like Embodiment 3-1, P3 lacks any sequence of an NLS-tagged Cas9 protein, let alone the sequence of the allegedly injected NLS-tagged Cas9 protein.[1] *Rochester*, 358 F.3d at 927; Ex. 1003; Ex. 2477, ¶65; MF84, 107. P3 also lacks details a skilled artisan would need to identify the NLS-tagged Cas9 protein allegedly used in Embodiment 3-2, including: (1) the bacterial Cas9 species from which the Cas9 protein was derived, (2) whether the Cas9 protein was NLS-tagged, (3) which NLS was attached; or (4) which Cas9 protein sequence was injected into the mouse cells. Ex. 1003; Ex. 2477, ¶62; MF86, 88-90. Even Dr. Cullen was unable to find any disclosure in P3 identifying the sequence of an NLS tag on the Cas9 protein used in Embodiment 3-2 contained an NLS. Ex. 2474, 99:5-20.

For Embodiment 3-2, Example 3 obliquely states that "[r]ecombinant Cas9 protein was obtained from ToolGen, Inc." Ex. 1003, 37; Ex. 2477, ¶63; MF109. All P3 explains is that "recombinant" means that a protein was "modified by the introduction of heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein" and that "a recombinant Cas9 protein *may be* generated by reconstituting Cas protein-encoding sequence using the human codon table." Ex. 1003, 9 (emphasis added); Ex. 2477, ¶63; MF93, 124. But for the reasons discussed for Embodiment 3-1, these disclosures are insufficient to describe an NLS-tagged Cas9 of Embodiment 3-2 in view of ToolGen's unpredictablity arguments. Ex. 2477, ¶¶62-68.

ToolGen purports that Embodiment 3-2 shows successful target DNA cleavage in mouse embryos. Mot., 7:5-14:8. However, "[p]roof of a reduction to practice, absent an adequate description in the specification of what is reduced to practice, does not serve to describe or identify the invention for purposes of the written description requirement." Further, as Dr. Bailey

[1] Codon optimization is not relevant as a protein was injected in the cells. Ex. 2477, ¶62.

explains, an allegation that DNA cleavage occurred does not prove that the Cas9 used was NLS-tagged or codon-optimized, because, as has been demonstrated, neither NLS addition nor codon optimization is actually necessary for achieving Cas9-mediated cleavage in eukaryotic cells. Ex. 2477, ¶18, 51, 55, 56, 64. Thus, all P3 provides is a "generalized language" that is insufficient to satisfy written description as "it does not convey the detailed identity of [the] invention" in view of ToolGen's prosecution representations. *Rochester*, 358 F.3d at 923; Ex. 2477, ¶¶10, 40-68, 87.

ToolGen must be held to its positions before to the Patent Office regarding the alleged complexity and unpredictability in expressing the Cas9 protein in eukaryotic cells. If so, then P3 cannot meet the written description requirement of an NLS-tagged and codon-optimized Cas9. *See Zedner*, 547 U.S. at 504; *Louis*, 59 U.S.P.Q.2d at 1075; *Springs Window Fashions LP v. Novo Indus., L.P.,* 323 F.3d 989, 995 (Fed. Cir. 2003). ToolGen's motion ignores what its counsel in this interference told the PTAB during prosecution, and fails to explain why its representations no longer bind it or how P3 describes element [2] of CVC's half of the count in light of its representations. Accordingly, ToolGen's motion fails to show that its P3 satisfies written description and, thus, a CRTP *where the Cas9 is NLS-tagged and codon-optimized*. *Ariad*, 598 F.3d at 1351; *Rochester*, 358 F.3d at 923; *Falkner*, 448 F.3d at 1362. The PTAB should deny ToolGen's motion to be accorded benefit to its P3 filing date.

2. ToolGen's motion fails to show that PCT describes an embodiment of the count consistent with its prosecution representations.

ToolGen contends that its PCT describes element [2] of CVC's half of the count (*i.e*., "a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein"). Mot., 17:10-18:4. ToolGen points to three embodiments, of which two embodiments (3-1 and 3-2 in Example 3) are the same as in P3 and are discussed in Section III.A.1 above. Mot., 17:4-17; Ex. 1400, ¶39; Ex. 2474, 118:9-22; Ex. 2477, ¶¶69, 71; Ex. 1004, 37-50; Ex. 1003, 36-45.

ToolGen's expert again concedes that PCT, like P3, does not disclose a single codon-usage table, and he was unable to identify which Cas9 mRNA or Cas9 protein was introduced into the cells in Embodiments 3-1 and 3-2. Ex. 2474, 91:11-92:7; 113:2-9, 119:15-120:2, 126:4-127:22; MF96. Thus, these embodiments in PCT are not a CRTP for the reasons discussed above in section III.A.1 as of the PCT's October 2013 filing date. Ex. 2477, ¶¶69-75, 77, 78-80, 82; MF84-110.

The third embodiment, Embodiment 4 (in Example 4), purports to transfect an NLS-tagged Cas9 protein complexed with a sgRNA into the protoplast cells of the *Arabidopsis* plant.[2] Ex. 1004, 50-52; Ex. 2477, ¶¶69-70, 83; Ex. 1400, ¶116. In view of ToolGen's prosecution representations, PCT must describe the specific protein used in Embodiment 4. However, PCT fails to provide such information, much less the identity of the Cas9 protein purportedly used in Embodiment 4. *Ariad*, 598 F.3d at 1351; *Rochester*, 358 F.3d at 923; Ex. 2477, ¶¶84-86.

PCT does not indicate which Cas9 sequence or which NLS was used in Embodiment 4. Ex. 1004; Ex. 2477, ¶84; MF111. Indeed, Dr. Cullen was unable to identify which Cas9 protein was introduced in the cells in Embodiment 4. Ex. 2474, 149:16-151:16. Example 4 vaguely states that a "Cas9 coding sequence . . . derived from Streptococcus pyogenes strain M1 GAS (NC_002737.1), was cloned [and a] nuclear targeting sequence (NLS) was included . . . ." Ex. 1004, 50; Ex. 2477, ¶85; Ex. 1400, ¶¶135, 145; MF112. But "dozens and dozens" of NLSs were known in the art. Ex. 2477, ¶85; Ex. 2474, 60:11-19; Ex. 2182; Ex. 2191; Ex. 2192; Ex. 2193; MF104, 123. Yet, PCT does not disclose which NLS was used in Embodiment 4. Ex. 1004; Ex. 2477, ¶84; MF111. Thus, under ToolGen's view, a skilled artisan would not have been able to

[2] Codon optimization is not relevant as a protein was injected in the cells. Ex. 2477, ¶84.

discern the NLS-tagged Cas9 protein used in Embodiment 4 from myriad possible—yet unpredictable—NLS-tagged Cas9 protein sequences. Ex. 2477, ¶¶83-85.

Although PCT provides five Cas9 nucleic acid sequences and two Cas9 amino acid sequences in a sequence listing, it also does not disclose which one of these sequences, if any, was used in Embodiments 3-1, 3-2, or 4—a fact that ToolGen's motion fails to address. Ex. 1004, 130-133, 160-183; Ex. 2477, ¶¶76, 81, 85; MF114, 118, 122. But, a skilled artisan would have understood that these sequences were not used in the embodiments. *Id.*, ¶¶76, 81, 85. The disclosed nucleic acid sequences are SEQ ID NOs 1, 106, 107, 108, and 110. Ex. 1004, 130-133, 160-183. These sequences would not have been understood by a skilled artisan to be the sequence of an NLS-tagged, codon-optimized Cas9 mRNA used in Embodiments 3-1, or the sequences encoding the Cas9 proteins introduced into the mouse and plant cells in Embodiments 3-2 and 4. Ex. 2477, ¶¶76, 81, 85. SEQ ID NO 1 does not have an added NLS, and SEQ ID NO 108 is a native (non-codon-optimized) sequence without an added NLS. Ex. 1004, 130-133, 160-183; Ex. 2474, 175:22-176:19; Ex. 1400, ¶107; Ex. 2477, ¶76; MF115. SEQ ID NOs 106 and 107 are labeled as sequences for "human cell experiments," not mouse or plant experiments. Ex. 1004, 160, 163; Ex. 1400, ¶107; Ex. 2477, ¶76; MF116. Finally, SEQ ID NO 110 is a "Cas9-coding sequence in pET-Cas9N3T for production of recombinant Cas9 protein in [a bacteria], E. coli," not for injection into mouse or plant cells. Ex. 1004, 174; Ex. 2477, ¶76; MF117.

The two disclosed amino acid sequences are SEQ ID NOs 109 and 111. Ex. 1004, 130-133, 160-183; Ex. 2477, ¶¶81, 85; MF118. Neither of these would have been understood by a skilled artisan to be the sequence of an NLS-tagged Cas9 protein that could have been used in Embodiments 3-2 and 4. Ex. 2477, ¶¶81, 85. SEQ ID NO 109 is a native sequence without an added NLS. Ex. 1004, 174; Ex. 1400, ¶107; Ex. 2474, 176:20-177:8; Ex. 2477, ¶¶81, 85;

MF119. And SEQ ID NO 111 is an "amino acid sequence of Cas9 (pET-Cas9N3T)" encoded by SEQ ID NO 110 (for protein production in bacteria). Ex. 1004, 177; Ex. 1400, ¶107; Ex. 2474, 177:13-18; Ex. 2477, ¶¶81, 85; MF120. PCT does not disclose whether pET-Cas9N3T was used as a vector in Embodiments 3-2 or 4. Ex. 1004; Ex. 2477, ¶¶81, 85. Thus, despite the disclosure of some sequences, a skilled artisan would not have been able to discern the Cas9 mRNA or protein sequence used in ToolGen's relied-upon embodiments. *Id.*, ¶¶11, 69-87.

Just because PCT purportedly shows target DNA cleavage using CRISPR-Cas9 in mouse or plant cells that does not mean it provides a written description. *Alonso*, 545 F.3d at 1021; Ex. 1004, 37-52; Ex. 2477, ¶¶75, 80, 85. All ToolGen's PCT provides is "generalized language," but that is insufficient for written description as "it does not convey the detailed identity of [the] invention" under ToolGen's representations. *Rochester*, 358 F.3d at 923; Ex. 2477, ¶¶11, 69-87.

B. ToolGen's motion ignores its repeated and unequivocal representations during prosecution that NLS addition and codon optimization are required and unpredictable.

ToolGen's involved claims require a Cas9 nucleic acid that "is codon-optimized for expression in mammalian cells" and a Cas9 polypeptide that "comprises a nuclear localization signal." Paper 6; MF69. ToolGen relied on these limitations to distinguish its claims from the prior art and to overcome the anticipation and obviousness rejections. Ex. 2012, 6745-6749, 6756; MF70-83. ToolGen argued that its invention required an NLS and codon optimization and that CRISPR-Cas9 would not function in eukaryotic cells without these features. MF69-82. It further argued that modifying Cas9 by NLS addition or codon optimization was unpredictable, and not all modified Cas9 nucleic acids or proteins would be functional in eukaryotic cells. MF71-75, 79-82. Its representations applied as much to NLS-tagging as to codon optimization. MF69-82. Relying on these representations, the PTAB reversed the obviousness rejection and,

on remand, the examiner found ToolGen's claims "in condition for allowance." Ex. 2012, 8638, 8642, 8643, 8645, 8646, 8651; MF83. ToolGen's motion fails to address these representations and explain why it is not bound by them or how P3 or PCT describe a specific NLS-tagged and codon-optimized Cas9 consistent with the representations.[3]

During its oral argument before the PTAB, ToolGen emphasized the NLS and codon optimization requirements in its claimed invention. Ex. 2012, 8604:1-3, 8604:24-8605:25, 8606:5-11; MF76-78. For example, when the PTAB asked what the "secret sauce" was in its claimed invention, ToolGen emphasized that the "main distinction[s]" from the prior art are "the nuclear localization signal and codon optimization." Ex. 2012, 8604:24-8605:25; MF77. ToolGen also confirmed to the PTAB that an NLS and codon optimization were "the two things that were required in the science to get [CRISPR-Cas9] to work." Ex. 2012, 8606:5-11; MF78. Yet, ToolGen now is abandoning its explanation of the science it led the PTAB to believe.

[3] Contrary to ToolGen's assertions, CVC's position is that the techniques of NLS addition and codon optimization were known long before the filing dates of ToolGen's P3 and PCT. Ex. 2477, ¶¶18, 51, 55, 56, 64; Ex. 2182; Ex. 2191; Ex. 2192; Ex. 2193; Ex. 2075; Ex. 2083; Ex. 2096. Codon optimization replaces existing codons with a set of more suitable codons for enhancing the "expression of the foreign gene in the host cell." Ex. 2477, ¶18; Ex. 2075, 187. And NLSs in general enhance nuclear localization of proteins. Ex. 2477, ¶56. Although both NLS addition and codon optimization were routine, predictable, and known to be not required for CRISPR-Cas9 to function before the filing dates of P3 and PCT, ToolGen argued otherwise during prosecution. Ex. 2477, ¶¶18, 51, 55, 56, 64; Ex. 2182; Ex. 2191; Ex. 2192; Ex. 2193; Ex. 2156; Ex. 2075; Ex. 2083; Ex. 2096; Ex. 2028; Ex. 2076.

In its appeal brief, ToolGen similarly argued that it was not "predictable" whether the Cas9 protein would "preserve its functionality" when expressed from a codon-optimized nucleic acid. Ex. 2012, 6895-6896; *see also id.*, 6899; MF73-74. And, in its reply brief, ToolGen argued that a skilled artisan "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); MF75. ToolGen never retracted these assertions, and it may not do so now.

ToolGen took similar positions throughout prosecution. *See* Ex. 2012, 6758, 6761-6762, 6767; MF71-72. For example, it stated 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" because of the "challenges presented by modification (e.g., tagging and codon-optimization) of nucleic acids to be expressed in eukaryotic/mammalian cells." Ex. 2012, 6758 (emphasis in original) (internal citations omitted); MF71.

Dr. Cullen, ToolGen's expert here, also supported ToolGen during prosecution, arguing that both NLS addition and codon optimization are unpredictable—a position that he still maintains but failed to reconcile when supporting ToolGen's motion. Ex. 2012, 5653-5654; Ex. 2474, 57:16-58-21, 65:19-66:1; MF79-82. For example, Cullen stated, "modification of Cas9 . . . for example by tagging it with a NLS and/or optimizing its codon sequence, could have rendered it inactive upon expression in a eukaryotic cell." Ex. 2012, 5653; MF79. And he stated, "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, 5654; MF81. According to Cullen, "addition of a NLS to Cas9 or codon optimization of a nucleic acid encoding Cas9 could result in . . . failure to successfully use a Type II CRISPR/Cas9 in a eukaryotic cell." Ex. 2012, 5654; MF82.

C. ToolGen is bound by its prosecution representations and may not rely on embodiments that lack an NLS-tagged and codon-optimized Cas9.

Under party admission and judicial estoppel doctrines, ToolGen should be held to its prior positions and representations. ToolGen's motion is silent on its past positions and fails to explain why it should not be held to them or how its P3 and PCT identify a specific NLS-tagged and codon-optimized Cas9 consistent with its representations.

1. ToolGen's representations are binding admissions that its motion fails to address.

ToolGen may not abandon its prosecution statements that led directly to this interference. *Springs Window*, 323 F.3d at 995; *Louis*, 59 U.S.P.Q.2d at 1075. "The public notice function of a patent and its prosecution history requires that a *patentee be held to what he declares during the prosecution* of his patent." *Springs Window*, 323 F.3d at 995 (emphasis added). The *Springs Window* court found the party's prosecution statements were "detailed, consistent, and repeated" and not "simply an inadvertent misstatement by the prosecuting attorney." *Id.* at 996. Therefore, it rejected the party's infringement argument that "would undercut the public's reliance on a statement that was in the public record and upon which reasonable competitors formed their business strategies." *Id.* at 995. Just like the *Springs Window* court held the patentee to its prosecution statements that led to the asserted patent, ToolGen should be held to its prosecution positions that led to this interference.

ToolGen's efforts to distinguish prior art based on NLS addition and codon optimization were "effected with reasonable clarity and deliberateness," were "detailed, consistent, and repeated," and were not "simply an inadvertent misstatement by the prosecuting attorney." *Springs Window*, 323 F.3d at 994, 996; Ex. 2012, 8604:1-3, 8604:24-8605:25, 8606:5-11; MF69-83. For example, ToolGen argued that the "secret sauce" that distinguished its claims over the

prior art was that the "nucleic acid has been engineered with both the nuclear localization signal and codon optimization." Ex. 2012, 8604:24-8605:25; MF77. ToolGen also unequivocally represented to the PTAB that NLS addition and codon optimization were required "in the science" for CRISPR-Cas9 to function in eukaryotic cells and that a skilled artisan "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, 8606:5-11, 8531; MF75, 78. Thus, ToolGen argued "with reasonable clarity and deliberateness." *Springs Window*, 323 F.3d at 994.

The PTAB's predecessor has held a party to its prosecution statements in an interference. *See, e.g., Louis*, 59 U.S.P.Q.2d at 1075. In *Louis*, a party moved to change the count to remove a recited claim feature to better align with its best proofs. The Board denied the motion because that was the feature on which the party had relied during prosecution to overcome the prior art and get the claims allowed. *Id.* The Board further faulted the movant for not even addressing the examiner's rejection after making "an apparent about-face with respect to arguments previously made to the examiner to overcome [the] rejection." *Id.*

As in *Louis*, ToolGen's motion does not address its prior admissions and is doing "an apparent about-face with respect to [the] arguments previously made to the examiner to overcome a rejection" by arguing a CRTP based on the embodiments that do not include an NLS-tagged and codon-optimized Cas9 consistent with its admissions. *Id*. ToolGen's binding admissions regarding the necessity and unpredictability of NLS addition and codon optimization preclude its reliance on these examples. Thus, the PTAB should deny the motion.

2. Judicial estoppel precludes ToolGen from now taking a contrary position in its motion.

Judicial estoppel also precludes ToolGen from relying on the embodiments in Example 3 of P3 and Examples 3 and 4 of PCT to show a CRTP because they do not describe an NLS-

tagged and codon-optimized Cas9 in light of ToolGen's prosecution arguments. *Zedner*, 547 U.S. at 504; *New Hampshire v. Maine*, 532 U.S. 742, 742 (2001); *Wilson v. Martin,* 789 Fed. Appx. 861, 872 (Fed. Cir. 2019). "Where a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position . . . ." *Zedner*, 547 U.S. at 504; *New Hampshire*, 532 U.S. at 742; *see also Wilson,* 789 Fed. Appx. at 872. "[J]udicial estoppel, generally prevents a party from prevailing in one phase of a case on an argument and then relying on a contradictory argument to prevail in another phase." *Zedner*, 547 U.S. at 504; *New Hampshire*, 532 U.S. at 749. "The Board has authority and discretion to apply the doctrine of judicial estoppel." *Wilson,* 789 Fed. Appx. at 872. It "applies just as much when one of the tribunals is an administrative agency as it does when both tribunals are courts." *Trustees in Bankr. of N. Am. Rubber Thread Co. v. United States,* 593 F.3d 1346, 1354 (Fed. Cir. 2010).

There are several factors considered when applying judicial estoppel. Foremost is whether a party has taken a position that is "clearly inconsistent" with a prior position. *See Zedner*, 547 U.S. at 504. The new "position[] must be mutually exclusive and directly inconsistent" with the earlier one. *Egenera, Inc. v. Cisco Sys., Inc.,* 972 F.3d 1367, 1379 (Fed. Cir. 2020) (cleaned up). Whether the party had successfully persuaded a tribunal to accept its earlier position is another relevant factor. *See Zedner,* 547 U.S. at 504. Also relevant is whether the party "would derive an unfair advantage or impose an unfair detriment on the opposing part if not estopped." *Id*. Here, these factors weigh strongly in favor of estopping ToolGen from now taking the directly inconsistent position that its P3 and PCT disclose a CRTP of CVC's half of the count without a description of an embodiment with NLS and codon optimization.

ToolGen's motion, by relying on generic disclosures of Cas9 mRNA and protein in P3

and PCT, directly contradicts ToolGen's prosecution position that NLS addition and codon optimization are required, yet unpredictable, to get CRISPR-Cas9 to function in eukaryotic cells. In fact, the motion does not even address the prior representations. It is beyond reasonable dispute that ToolGen's NLS addition and codon optimization arguments were necessary to the PTAB's decision reversing the obviousness rejection and the examiner's indication of allowance that led to this interference (and the parallel Interference No. 106,126 with Broad). Ex. 2012, 8638, 8642, 8643, 8645, 8646, 8651; MF83. Thus, ToolGen would derive an unfair advantage by being accorded benefit of its P3 or PCT filing date notwithstanding the absence of a description of an NLS-tagged and codon-optimized Cas9. If the PTAB were to grant ToolGen's motion, it would encourage other parties to advocate one position during prosecution to initiate an interference and then advocate the opposite position to survive the interference. Accordingly, judicial estoppel should apply and ToolGen's motion should be denied.

IV. CONCLUSION

For the reasons above, ToolGen's motion fails to show that it is entitled to be accorded benefit to P3 or PCT. The motion should be denied.

Respectfully submitted,

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1 **APPENDIX A – LIST OF EXHIBITS**

Exhibit No.	Description
1001	U.S. Provisional Application No. 61/717,324, filed October 23, 2012
1002	U.S. Provisional Application No. 61/803,599, filed March 20, 2013
1003	Prov. Appl. No. 61/837,481, filed June 20, 2013
1004	Int'l PCT Appl. PCT/KR2013/009488, filed on October 23, 2013
1005	International Publication WO 2014/065596 A1, published May 1, 2014
1006	U.S. Application No. 14/685,510, as filed April 13, 2015, and Current Claims as of June 12, 2018
1008	Prosecution History of U.S. Provisional Application No. 61/717,324, filed October 23, 2012
1009	Prosecution History of U.S. Provisional Application No. 61/803,599, filed March 20, 2013
1010	Prosecution History of U.S. Provisional Application No. 61/837,481, filed June 20, 2013
1203	Deltcheva *et al.*, "CRISPR RNA Maturation by *Trans*-Encoded Small RNA and Host Factor RNase III," *Nature*, 471, 602–07 (2011), with Supplementary Information.
1204	Ferretti *et al.*, "Complete Genome Sequence of an M1 Strain of *Streptococcus pyogenes*," *Proc. Natl. Acad. Sci.*, 98(8), 4658-4663 (2001)
1400	May 20, 2021 Declaration of Bryan R. Cullen, Ph.D.
2012	File History for U.S. Appl. No. 14/685,510
2028	Hwang, W.Y., *et al*., "Efficient genome editing in zebrafish using a CRISPR-Cas system," *Nature Biotechnology*, 31(3):227-229, Supplementary Information (2013)
2029	Deltcheva, E., *et al.*, "CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III," *Nature*, 471:602-609, Supplementary Information (2011)
2031	Jinek, M., *et al.*, "A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity," *Science* 337(6096):816-821 (2012) with Supplementary Information
2075	Sandhu, K., *et al*., "GASCO: Genetic Algorithm Simulation for Codon Optimization," *In Silico Biology* 8: 187–192 (2008)

Exhibit No.	Description
2076	Nakayama, T., *et al*., "Simple and efficient CRISPR/Cas9-mediated targeted mutagenesis in *Xenopus tropicalis*," *Genesis* 51(12): 835–843 (2013)
2077	Jorgensen, F.G., *et al*., "Comparative analysis of protein coding sequences from human, mouse and the domesticated pig," *BMC Biology* 3(2): 1-15 (2005)
2078	Alff-Steinberger, C., "Codon Usage in Homo sapiens: Evidence for a Coding Pattern on the Non-Coding Strand and Evolutionary Implications of Dinucleotide Discrimination," *J. Theor. Biol.* 124: 89-95 (1987)
2083	Villalobos, A., *et al*., "Gene Designer: a synthetic biology tool for constructing artificial DNA segments," *BMC Bioinformatics* 7:285 (2006)
2096	Gustafsson, C., *et al*., "Codon bias and heterologous protein expression," *Trends Biotechnol*., 22(7):346-353 (2004)
2126	Horvath, P*., et al.*, "Diversity, Activity, and Evolution of CRISPR Loci in Streptococcus thermophilus," *J. Bacteriol.*, 190(4):1401-1412 (2008)
2132	Sapranauskas, R., *et al.*, "The Streptococcus thermophilus CRISPR/Cas system provides immunity in Escherichia coli," *Nucl. Acids Res.*, 39(21):9275-9282, Supplementary Figures (2011)
2156	Shen, B., *et al*., "Generation of gene-modified mice via Cas9/RNA-mediated gene targeting," *Cell Research,* 23:720-723, Supplementary Information (2013)
2182	Chugh, A., *et al.*, "Cell-Penetrating Peptides: Nanocarrier for Macromolecule Delivery in Living Cells," *IUBMB Life*, 62(3):183-193 (2010)
2191	Derossi, D., *et al.*, "The Third Helix of the Antennapedia Homeodomain Translocates through Biological Membranes," *J. Biol. Chem*., 269(14):10444-10450 (1994)
2192	Noguchi, H., *et al.*, "PDX-1 Protein Containing Its Own Antennapedia-Like Protein Transduction Domain Can Transduce Pancreatic Duct and Islet Cells," *Diabetes*, 52:1732-1737 (2003)
2193	Moede, T., *et al.*, "Identification of a nuclear localization signal, RRMKWKK, in the homeodomain transcription factor PDX-1," *FEBS Letters*, 461:229-234 (1999)
2449	Codon Usage Table Homo sapiens [gbpri]: 93487 CDS's (40662582 codons), *available at* https://www.kazusa.or.jp/codon/cgibin/showcodon.cgi?species=9606 (last visited May 19, 2021)

Exhibit No.	Description
2474	Deposition Transcript of Bryan Cullen, Ph.D., Patent Interference No. 106,127 (June 22, 2021)
2477	Second Declaration of Scott Bailey, Ph.D.
2511	Chylinski, K. *et al.*, "The tracrRNA and Cas9 families of type II CRISPR-Cas immunity systems," *RNA Biology* 10(5):726-737 (2013)

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APPENDIX B – STATEMENT OF MATERIAL FACTS

Senior Party's Alleged Facts 1-68

1. U.S. Provisional Patent App. No. 61/717,324 ("P1") was filed Oct. 23, 2012 and lists Seung Woo Kim, Sojung Kim, and Jin-Soo Kim as co-inventors. Ex. 1001, 15-16; Ex. 1008, 15-16. **Response: Admitted.**

2. U.S. Provisional Patent App. No. 61/803,599 ("P2") was filed Mar. 20, 2013 and lists Jin-Soo Kim, Jong Min Kim, and Seokjoong Kim as co-inventors. Ex. 1002, 7-8; Ex. 1009, 7-8. **Response: Admitted.**

3. U.S. Provisional Patent App. No. 61/837,481 ("P3") was filed Jun. 20, 2013 and lists Seung Woo Cho, Sojung Kim, and Jin-Soo Kim as co-inventors. Ex. 1003, 68-69; Ex. 1010, 68-69. **Response: Admitted.**

4. International Patent App. No. PCT/KR2013/009488 ("PCT") was filed Oct. 23, 2013 and lists Jin-Soo Kim, Seung Woo Cho, Sojung Kim, Jong Min Kim, and Seokjoong Kim as co-inventors. Ex. 1004, 1, 3-4; Ex. 1005, 1. **Response: Admitted.**

5. PCT was filed within 12 months of the filing dates of P1, P2, and P3, claims priority to P1, P2, and P3, and makes specific reference to P1, P2, and P3. Ex. 1004, 1-6; Ex. 1005, 1. **Response: Admitted.**

6. U.S. Patent App. No. 14/685,510 ("'510 Application") was filed Apr. 13, 2015 and lists Jin-Soo Kim, Seung Woo Cho, and Sojung Kim as co-inventors. Ex. 1006, 2-12. **Response: Admitted.**

7. The '510 Application is a continuation application of the PCT, was filed during the pendency of the PCT, and makes specific reference to P1, P2, P3, and PCT and claims priority to P1, P2, P3, and PCT. Ex. 1006, 2-12, 15. **Response: Admitted.**

8. Each of PCT and the '510 Application was timely filed in accordance with 35 U.S.C. §§ 119-120. F5-7. **Response: Admitted.**

9. The specification of the '510 Application states that "the entire contents of each" of P1, P2, P3, and PCT "are incorporated herein by reference." Ex. 1006, 15. **Response: Admitted.**

10. All of the disclosures in P3, including Example 3 and Figures 5-8, are disclosed in the PCT and the '510 Application. Ex. 1003; Ex. 1004; Ex. 1006; see also Ex. 1006, 15. **Response: Unable to admit or deny.**

11. All of the disclosures of the PCT, including Examples 3-4, and Figures 5-8 and 11-12, are disclosed in the '510 Application. Ex. 1004; Ex. 1006; see also Ex. 1006, 15. **Response: Unable to admit or deny.**

12. Example 3 of P3 describes a eukaryotic cell comprising a target DNA molecule and a Type II CRISPR-Cas or CRISPR/Cas9 system comprising (a) a Cas9 protein and (b) a single molecule DNA-targeting RNA. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 53-72. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

13. Example 3 of P3 describes a eukaryotic cell comprising a target DNA molecule and a Type II CRISPR-Cas or CRISPR/Cas9 system comprising (a) a nucleic acid comprising a nucleotide sequence encoding Cas9 protein and (b) a single molecule DNA-targeting RNA. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 53-72. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

14. Example 3 of P3 describes a single molecule DNA-targeting RNA or sgRNA comprising (i) a targeter-RNA capable of hybridizing with a target sequence in a target DNA molecule and (ii) an activator-RNA capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex, wherein the activator-RNA and the targeter-RNA are covalently linked to one another

with intervening nucleotides. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 68-87. **Response: Admitted.**

15. Example 3 of P3 describes a single molecule DNA-targeting RNA or sgRNA capable of forming a complex with a Cas9 protein, thereby targeting the Cas9 protein to a target DNA molecule in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 88-92. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

16. Example 3 of P3 describes a Type II CRISPR-Cas or CRISPR/Cas9 system capable of cleaving or editing a target DNA molecule in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 93-102. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

17. Example 3 of P3 describes how to make a single molecule DNA-targeting RNA. Ex. 1003, 36-37, 63 (Fig. 5(a)); see also id. at 10-13, 28; Ex. 1400, ¶ 71. **Response: Admitted.**

18. Example 3 of P3 describes how to use a single molecule DNA-targeting RNA in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶ 71. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

19. Before June 20, 2013, the Cas9-encoding sequence derived from *Streptococcus pyogenes* strain M1 GAS (NC_002737.1) was known. Ex. 1203; Ex. 1204; Ex. 1400, ¶¶ 27, 43. **Response: Admitted.**

20. Before June 20, 2013, Deltcheva et al. disclosed methods of obtaining the gene sequence of Cas9 derived from *S. pyogenes* strain M1 GAS. Ex. 1203, Supplementary Methods, Supplementary Tables 1, 5, 10. **Response: Admitted.**

21. P3 describes that the Cas9 protein in the Type II CRISPR-Cas9 system can be Cas9 from *S. pyogenes*. Ex. 1003, 36-37; see also id. at 9-10, 26; Ex. 1400, ¶¶ 27, 43, 63-67. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

22. P3 describes how to make a recombinant Cas9 protein, with a nuclear localization signal ("NLS") attached. Ex. 1003, 36-37; see also id. at 9-10, 26; Ex. 1400, ¶¶ 27, 43, 63-67. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

23. P3 describes how to make an mRNA encoding Cas9 protein with an NLS, including codon optimization. Ex. 1003, 36-37; see also id. at 9-10, 26; Ex. 1400, ¶¶ 27, 43, 63-67. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

24. P3 describes how to use a recombinant Cas9 protein or mRNA encoding the Cas9 protein with a single molecule DNA-targeting RNA in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 63-67. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

25. Example 3 of P3 describes that Cas9 mRNA and sgRNA can be delivered into a mouse embryo cell by microinjection. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1400, ¶¶ 63-72. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

26. Example 3 of P3 describes the cleavage or editing of a target DNA molecule in mouse embryo cells after the injection of Cas9 mRNA and sgRNA. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1400, ¶¶ 88-102. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

27. Example 3 of P3 describes that a recombinant Cas9 protein and sgRNA can be delivered into a mouse embryo cell by microinjection. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1400, ¶¶ 63-72. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

28. Example 3 of P3 describes the cleavage or editing of a target DNA molecule in mouse embryo cells after the injection of a recombinant Cas9 protein and sgRNA. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1400, ¶¶ 88-102. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

29. Example 3 of P3, including Figure 5(a), discloses that an sgRNA complexed with a Cas9 protein cleaved a target DNA molecule in Exon 2 of the Foxn1 gene. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1400, ¶¶ 88-102. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

30. Examples 3 and 4 of PCT each describe a eukaryotic cell comprising a target DNA molecule and a Type II CRISPR-Cas or CRISPR/Cas9 system comprising (a) a Cas9 protein and (b) a single molecule DNA-targeting RNA. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 120-56. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

31. Examples 3 and 4 of PCT each describe a eukaryotic cell comprising a target DNA molecule and a Type II CRISPR-Cas or CRISPR/Cas9 system comprising (a) a nucleic acid comprising a nucleotide sequence encoding Cas9 protein and (b) a single molecule DNA-targeting RNA. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 120-56. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

32. Examples 3 and 4 of PCT each describe a single molecule DNA-targeting RNA or sgRNA comprising (i) a targeter-RNA capable of hybridizing with a target sequence in a target DNA molecule and (ii) an activator-RNA capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex, wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 147-81. **Response: Admitted.**

33. Examples 3 and 4 of PCT each describe a single molecule DNA-targeting RNA or sgRNA capable of forming a complex with a Cas9 protein, thereby targeting the Cas9 protein to a target DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex.

1400, ¶¶ 182-89. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

34. Examples 3 and 4 of PCT each describe a Type II CRISPR-Cas or CRISPR/Cas9 system capable of cleaving or editing a target DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 190-204. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

35. PCT describes how to make a single molecule DNA-targeting RNA. Ex. 1004, 37-39, 81 (e.g., Fig. 5(a)); see also id. at 22-23, 32; Ex. 1400, ¶¶ 150, 155. **Response: Admitted.**

36. Examples 3 and 4 of PCT each describe how to use a single molecule DNA-targeting RNA in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 150, 155. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

37. PCT describes that the Cas9 protein in the Type II CRISPR-Cas9 system can be Cas9 from *S. pyogenes*. Ex. 1004, 22, 31, 38, 130-33, 160-83; Ex. 1400, ¶¶ 27, 106-07, 140-45. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

38. PCT describes how to make a recombinant Cas9 protein, with an NLS attached. Ex. 1004, 37-38; see also id. at 22, 31, 130-33, 160-83; Ex. 1400, ¶¶ 27, 106-07, 140-45. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

39. PCT describes how to make an mRNA encoding Cas9 protein with an NLS, including codon optimization. Ex. 1004, 22, 31, 37-38, 130-33, 160-83; Ex. 1400, ¶¶ 27, 106-07, 140-45. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

40. Examples 3 and 4 of PCT each describe how to use a recombinant Cas9 protein or mRNA encoding the Cas9 protein with a single molecule DNA-targeting RNA in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1400, ¶¶ 140-45. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

41. Example 3 of PCT describes that Cas9 mRNA and sgRNA can be delivered into a mouse embryo cell by microinjection. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1400, ¶¶ 139-56. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

42. Example 3 of PCT describes the cleavage or editing of a target DNA molecule in mouse embryo cells after the injection of Cas9 mRNA and sgRNA. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1400, ¶¶ 182-204. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

43. Example 3 of PCT describes that a recombinant Cas9 protein and sgRNA can be delivered into a mouse embryo cell by microinjection. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1400, ¶¶ 139-56. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

44. Example 3 of PCT describes the cleavage or editing of a target DNA molecule in mouse embryo cells after the injection of a recombinant Cas9 protein and sgRNA. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1400, ¶¶ 182-204. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

45. Example 3 of PCT, including Figure 5(a), discloses that an sgRNA complexed with a Cas9 protein cleaved a target DNA molecule in Exon 2 of the Foxn1 gene. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1400, ¶¶ 182-204. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

46. The mouse embryo cells described in Example 3 of P3 and PCT are eukaryotic cells that contain the Foxn1 gene. Ex. 1003, 36-45; Ex. 1004, 37-50; Ex. 1400, ¶¶ 54-55, 121-22. **Response: Admitted.**

47. Exon 2 of the Foxn1 gene described in Example 3 of P3 and PCT is a DNA molecule in mouse embryo cells. Ex. 1003, 36-45; Ex. 1004, 37-50; Ex. 1400, ¶¶ 54-55, 121-22. **Response: Admitted.**

48. Figure 5(a) of P3 and PCT depicts Exon 2 of the Foxn1 gene as containing a target sequence. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1400, ¶¶ 54-55, 121-22. **Response: Admitted.**

49. The sgRNAs described in Example 3 of P3 and PCT are engineered and non-naturally occurring. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1400, ¶¶ 56-59, 123-26. **Response: Admitted.**

50. Figure 5(a) of P3 and PCT depicts an sgRNA that is a single molecule DNA-targeting RNA. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1400, ¶¶ 69, 148. **Response: Admitted.**

51. Figure 5(a) of P3 and PCT depicts an sgRNA containing a sequence complementary to and capable of hybridizing with a sequence in Foxn1. Ex. 1003, 36-45, Fig. 5(a); see also Ex. 1004. **Response: Admitted.**

52. Figure 5(a) of P3 and PCT depicts an sgRNA containing a -GAAA- segment linking two portions of the sgRNA to each other. Ex. 1003, Fig. 5(a); see also Ex. 1004; Ex. 1400, ¶¶ 84, 175. **Response: Admitted.**

53. Figure 5(a) of P3 and PCT depicts an sgRNA capable of forming a double-stranded RNA duplex. Ex. 1003, Fig. 5(a); Ex. 1004, Fig. 5(a); Ex. 1400, ¶¶ 79, 166. **Response: Admitted.**

54. Figure 5(a) of P3 and PCT depicts an sgRNA capable of forming a complex with a Cas9 protein. Ex. 1003, Fig. 5(a); Ex. 1004, Fig. 5(a); Ex. 1400, ¶¶ 89, 183. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

55. Figure 5(a) of P3 and PCT depicts an sgRNA capable of targeting a Cas9 protein to a target DNA. Ex. 1003, Fig. 5(a); Ex. 1004, Fig. 5(a); Ex. 1400, ¶¶ 89, 183. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

56. Figures 5(c), 6(c) and 7(c), and Table 7 of P3 and PCT depicts cleavage or editing of a sequence in Exon 2 of the Foxn1 gene. Ex. 1003, 36-45; Ex. 1004; Ex. 1400, ¶¶ 94-99, 191-96. **Response: Admitted to the extent that Figures 5(c), 6(c) and 7(c), and Table 7 of P3 and PCT depict an experiment testing cleavage or editing of a sequence in Exon 2 of the Foxn1 gene.**

57. Example 4 of PCT describes that a recombinant Cas9 protein and sgRNA can be delivered into a protoplast cell of Arabidopsis by transfection. Ex. 1004, 50-52; Ex. 1400, ¶¶ 145, 155. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

58. Example 4 of PCT describes the cleavage or editing of a target DNA molecule in plant protoplast cells after the transfection of a recombinant Cas9 protein and sgRNA. Ex. 1004, 50-52, 90-91; Ex. 1400, ¶¶ 199-201. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

59. The Arabidopsis protoplast cells described in Example 4 of PCT are eukaryotic cells that contain the BRI1 gene. Ex. 1004, 50-52, 90-91; Ex. 1400, ¶¶ 129-130. **Response: Admitted.**

60. The BRI1 gene described in Example 4 of PCT is a DNA molecule in Arabidopsis protoplast cells. Ex. 1004, 50-52, 90-91; Ex. 1400, ¶¶ 129-130. **Response: Admitted.**

61. The sgRNAs described in Example 4 of PCT are engineered and non-naturally occurring. Ex. 1004, 50-52; Ex. 1400, ¶¶ 132-35. **Response: Admitted.**

62. The sgRNAs described in Example 4 of PCT contain a sequence complementary to and capable of hybridizing with a sequence in the BRI1 gene. Ex. 1004, 50-52; Ex. 1400, ¶ 161. **Response: Admitted.**

63. The sgRNAs described in Example 4 of PCT contain a -GAAA- segment linking two portions of the sgRNA to each other. Ex. 1004, 50-52; Ex. 1400, ¶ 178. **Response: Admitted.**

64. The sgRNAs described in Example 4 of PCT are capable of forming a double-stranded RNA duplex. Ex. 1004, 50-52; Ex. 1400, ¶¶ 169-70. **Response: Admitted.**

65. The sgRNAs described in Example 4 of PCT are capable of forming a complex with a Cas9 protein. Ex. 1004, 50-52; Ex. 1400, ¶ 186. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

66. The sgRNAs described in Example 4 of PCT are capable of targeting a Cas9 protein to a target DNA. Ex. 1004, 50-52; Ex. 1400, ¶ 186. **Response: Denied on the basis of judicial estoppel and party admission doctrines.**

67. Figure 12 of PCT depicts cleavage or editing of one or more sequences in the BRI1 gene of Arabidopsis. Ex. 1004, 50-52, 90-91; Ex. 1400, ¶¶ 199-203. **Response: Admitted to the extent that Figure 12 of PCT depicts an experiment testing cleavage or editing of a sequence in Exon 2 of the Foxn1 gene.**

68. Each sgRNA described in Example 3 of P3 and PCT and in Example 4 of PCT is a single molecule DNA-targeting RNA. Ex. 1003, Fig. 5(a); Ex. 1004; Ex. 1400, ¶¶ 69, 148, 151-53. **Response: Admitted.**

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69. ToolGen's claims require the following limitations on which ToolGen relied on to distinguish its claims from the prior art: a Cas9 nucleic acid that "is codon-optimized for expression in mammalian cells" and a Cas9 protein that "comprises a nuclear localization signal." Paper 6; Ex. 2012, 6745-6749.

70. The examiner of ToolGen's App. No. 14/685,510 withdrew an anticipation rejection in view of ToolGen's claim amendment requiring that a Cas9 "nucleic acid is codon-optimized for expression in mammalian cells." Ex. 2012, 6783.

71. ToolGen stated 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" due to the "challenges presented by modification (*e.g.*, tagging and codon-optimization) of nucleic acids to be expressed in eukaryotic/mammalian cells." Ex. 2012, 6758 (emphasis in original).

72. ToolGen stated during prosecution that skilled artisans "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 its codon sequence, could have rendered [Cas9] inactive upon expression in a eukaryotic cell . . . ; and (iii) understood the importance of native codon optimization to proper protein folding . . . ." Ex. 2012, 6761-62.

73. On appeal during prosecution, ToolGen stated that "alteration of codons (which occurs as a result of codon optimization) can result in . . . misfolding. Since improperly folded proteins can lack activity . . . it would not have been predictable, whether a . . . codon-optimized Cas9 would fold in a mammalian cell in a way that would preserve its functionality." Ex. 2012, 6895-96.

74. On appeal during prosecution, ToolGen stated that "it was not known or reasonably expected in the art that a prokaryotic Type II CRISPR/Cas system with codon-optimized Cas9

would successfully function in mammalian cells." Ex. 2012, 6899.

75. On appeal, ToolGen stated: "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.

76. During oral hearing, ToolGen stated: "we're explicitly claiming [that the Cas9 nucleic acid] has to have a nuclear localization signal, and it has to be codon optimized." Ex. 2012, 8604:1-3.

77. During oral hearing, ToolGen told the PTAB that the "main distinction" from the prior art is that the "nucleic acid [in its claimed invention] has been engineered with both the nuclear localization signal and codon optimization." Ex. 2012, 8604:24-8605:25.

78. ToolGen stated that use of an NLS and codon optimization "were . . . the two things that were required in the science to get [CRISPR-Cas9] to work." Ex. 2012, 8606:5-11.

79. During prosecution, Dr. Cullen stated that "modification of Cas9 . . . by tagging it with a NLS and/or optimizing its codon sequence, could have rendered it inactive upon expression in a eukaryotic cell." Ex. 2012, 5653.

80. During prosecution, Dr. Cullen stated that "tagging of proteins with heterologous sequences can result in improper localization and loss of function," including by "addition of even a single amino acid." Ex. 2012, 5653.

81. During prosecution, Dr. Cullen stated that "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, 5654.

82. During prosecution, Dr. Cullen stated that skilled artisans "would not have been able to predict proper folding and retention of function of NLS-tagged, codon-optimized Cas9 upon expression of the protein in eukaryotic cell" and that they "would have appreciated that either addition of a NLS to Cas9 or codon optimization of a nucleic acid encoding Cas9 could result in

. . . failure to successfully use a Type II CRISPR/Cas9 in a eukaryotic cell." Ex. 2012, 5654.

83. Relying on ToolGen's representations, the PTAB reversed the examiner's rejection of ToolGen's involved claims, and the examiner found ToolGen's claims to be in condition for allowance. Ex. 2012, 8638, 8642, 8643, 8645, 8646, 8651.

84. Neither P3 nor PCT provides the sequence of the alleged NLS-tagged, codon-optimized Cas9 nucleic acid sequence of Embodiment 3-1 nor the NLS-tagged Cas9 proteins of Embodiments 3-2 or 4. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶42, 62, 72, 78, 84, 85.

85. Dr. Cullen admitted that no "codon-optimized Cas9 sequence [is] included" in P3. Ex. 2474, 77:16-78:2; *see also id.*, 86:13-87:2, 87:13-20; 90:18-91:3.

86. Neither P3 nor PCT indicates from which bacterial Cas9 species the Cas9 mRNA or Cas9 protein injected into the mouse cells in Embodiments 3-1 and 3-2, respectively, was derived. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶42, 62, 72, 78.

87. Neither P3 nor PCT indicates whether the Cas9 mRNA used in Embodiment 3-1 was codon-optimized or encoded an NLS-tagged Cas9 protein. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶42, 72.

88. Neither P3 nor PCT indicates whether the Cas9 protein used in Embodiment 3-2 was NLS-tagged. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶62, 78.

89. Neither P3 nor PCT indicates which NLS, if any, was attached in Embodiments 3-1 and 3-2. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶42, 62, 72, 78.

90. Neither P3 nor PCT identifies the Cas9 mRNA of Embodiment 3-1 or Cas9 protein of Embodiments 3-2 or 4. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶42, 62, 72, 78, 84, 85.

91. Several Cas9 proteins were known in the art before June 2013. Ex. 2126, Suppl. Fig. 1; Ex. 2132, 9277, Fig. S1; Ex. 2029, Fig. 6, Methods, Suppl. Figs. 12-16, Suppl. Tables 5, 9, 10; Ex. 2031, 818; Ex. 2511, 726-727, Fig. S1; Ex. 2477, ¶¶43, 53.

92. Example 3 of P3 or PCT does not disclose the Cas9 mRNA used in Embodiment 3-1. Ex.

1003; Ex. 1004; Ex. 2477, ¶¶54, 75.

93. P3 and PCT each states the following outside of Example 3 without indicating that these disclosures apply to Example 3: "recombinant Cas protein may be generated by reconstituting Cas protein-encoding sequence using the human codon table" and "the Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain Ml GAS (NC_002737.1), was reconstituted using the human codon usage table . . . . [and] a nuclear localization signal (NLS) was added to the C-terminus of Cas9." Ex. 1003, 9, 26; Ex. 1004, 22, 31; Ex. 2477, ¶¶44, 52, 73.

94. P3 does not contain a sequence listing. Ex. 1003. Ex. 1003; Ex. 2477, ¶54

95. NC_002737.1 is the accession number for the nucleic acid sequence record of the native genome of M1 GAS strain of *S. pyogenes* as it exists in nature. Ex. 2477, ¶45.

96. Neither P3 nor PCT provides a codon-usage table, indicates which table should be used to reconstitute the Cas9 mRNA sequence, or specifies the process or rules for selecting codons from a table. Ex. 1003; Ex. 1004; Ex. 2474, 91:11-92:7, 126:4-127:22; Ex. 2477, ¶¶46, 73.

97. Without knowing the process or set of rules for selecting codons, numerous sequences could be reconstituted from even a single codon-usage table. Ex. 2477, ¶¶46, 73.

98. By June 2013, multiple human codon-usage tables were known, identifying a different most frequent codon for certain amino acids. Ex. 2449; Ex. 2077; Ex. 2078; Ex. 2477, ¶47.

99. The most frequent codon for 12 out of 20 possible amino acids differed from one human codon-usage table to another. Ex. 2449; Ex. 2077, Table 8; Ex. 2078, Table 1; Ex. 2477, ¶47.

100. Even if the most frequent codon for each amino acid were picked from the multiple codon-usage tables, P3 would lead to myriad different Cas9 mRNA sequences. Ex. 2477, ¶¶47, 73.

101. Codon optimization does not simply involve selecting the most frequent codon for an amino acid. Ex. 2477, ¶47.

102. Neither P3 nor PCT discloses a particular codon-optimization program or indicate which

program should be used. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶48, 73.

103. By June 2013, several codon-optimization programs were known, which relied on codon-usage data from different tables and applied different criteria to select codons, and would have generated myriad different codon-optimized mRNA sequences. Ex. 2477, ¶¶47, 73.

104. Multiple NLSs were known before June 2013. Ex. 2477, ¶51; Ex. 2182; Ex. 2191; Ex. 2192.

105. P3 does not provide the sequence of SEQ ID NO. 2. Ex. 1003; Ex. 2477, ¶54.

106. Dr. Cullen stated: "I'm not aware that SEQ ID NO. 2 is included in [] P3" and that "I don't know whether it's codon optimized or not." Ex. 2474, 79:16-22, 84:2-22.

107. P3 does not provide an NLS-tagged Cas9 protein sequence. Ex. 1003; Ex. 2477, ¶¶65-67.

108. Dr. Cullen stated: "I have not been able to identify a statement to the effect that Cas9 contains an NLS" in Embodiment 3-2 of P3. Ex. 2474, 99:5-20.

109. For Embodiment 3-2, Example 3 of P3 or PCT states, "Recombinant Cas9 protein was obtained from ToolGen, Inc," but does not provide the sequence or any other detail about the Cas9 protein. Ex. 1003, 37; Ex. 1004, 38; Ex. 2477, ¶¶63, 80.

110. Without knowing the specific Cas9 protein and NLS, P3 or PCT would generate numerous Cas9 protein sequences, from which a skilled artisan reading the application wouldn't have been able to discern the Cas9 protein that would be functional in Embodiment 3-2. Ex. 2477, ¶¶64, 79.

111. PCT does not indicate which NLS was attached to the Cas9 protein used in Embodiment 4. Ex. 1004; Ex. 2477, ¶84.

112. Example 4 of PCT states that "Cas9 coding sequence . . . derived from Streptococcus pyogenes strain M1 GAS (NC_002737.1), was cloned . . . . nuclear targeting sequence (NLS) was included . . . ." Ex. 1004, 50; Ex. 2477, ¶85.

113. PCT would have generated multiple NLS-tagged Cas9 protein sequences purportedly used in Embodiment 4. Ex. 1004; Ex. 2477, ¶¶85-86.

114. PCT discloses the following five nucleic acid sequences in the sequence listing: SEQ ID NOs 1, 106, 107, 108, and 110. Ex. 1004, 130-133, 160-183; Ex. 2477, ¶¶75-76.

115. SEQ ID NO 1 does not have an added NLS, and SEQ ID NO 108 is a native (non-codon-optimized) sequence and does not have an added NLS. Ex. 1004, 130-133; Ex. 2474, 175:22-176:19; Ex. 1400, ¶107; Ex. 2477, ¶76.

116. SEQ ID NOs 106 and 107 are labeled as sequences for "human cell experiments." Ex. 1004, 160, 163; Ex. 2477, ¶76.

117. SEQ ID NO 110 is labeled as a "Cas9-coding sequence in pET-Cas9N3T for production of recombinant Cas9 protein in [a bacteria], E. coli." Ex. 1004, 174; Ex. 2477, ¶76.

118. PCT discloses the following two amino acid sequence in the sequence listing: SEQ ID NOs 109 and 111. Ex. 1004, 130-133, 160-183; Ex. 2477, ¶¶81, 85.

119. SEQ ID NO 109 is a native Cas9 amino acid sequence and does not have an added NLS. Ex. 1004, 174; Ex. 1400, ¶107; Ex. 2474, 176:20-177:8; Ex. 2477, ¶¶81, 85.

120. SEQ ID NO 111 is an "amino acid sequence of Cas9 (pET-Cas9N3T)" encoded by SEQ ID NO 110 (for making Cas9 in bacteria). Ex. 1004, 174, 177; Ex. 1400, ¶107; Ex. 2477, ¶¶81, 85.

121. Dr. Cullen didn't consider differences in codon-optimization programs. Ex. 2474, 96:4-16.

122. PCT does not disclose which one of SEQ ID NOs. 1, 106, 107, 108, 109, 110, and 111 were used in Embodiments 3-1, 3-2, and 4. Ex. 2477, ¶¶76, 81, 85.

123. Dr. Cullen stated that "dozens and dozens" of NLSs were known before 2012. Ex. 2474, 60:11-19.

124.P3 and PCT each defines the term "recombinant" as a "nucleic acid, protein . . . modified by the introduction of heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein." Ex. 1003, 9; Ex. 1004, 22; Ex. 2477, ¶¶49, 63, 73.

CERTIFICATE OF FILING AND SERVICE

I hereby certify that the foregoing **CVC'S OPPOSITION 1** and the related exhibits were filed via the Interference Web Portal by 8:00 PM Eastern Time on July 15, 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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