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

Application No. 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 REPLY 1
(for contingent priority benefit to P3 or PCT)

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CASES

CVC opposes a motion that ToolGen did not bring. ToolGen's Motion 1, which is contingent on the grant of CVC Motion 2, sought to accord ToolGen the benefit of its P3 or its PCT. ToolGen's Motion demonstrated that its applications describe and enable multiple embodiments of ***the CVC half of Count 1***. CVC's Opposition 1 ("Opp.") does not present any competing arguments; in fact, CVC's expert admitted that he did not even analyze the CVC half of Count 1. The analysis should end there.

Instead of opposing the merits, CVC argues, without authorization, that the Board should re-write Count 1 to require an NLS-tagged and codon-optimized Cas9 nucleic acid, where none is recited in the CVC half. In doing so, CVC misrepresents the facts and relies on inapplicable law. CVC points to non-obviousness arguments that ToolGen made during prosecution, but those arguments were made in a different factual context (*e.g.*, the prior art contained no disclosure of successful CRISPR-Cas9 use in eukaryotic cells), and, regardless, were not contrary to any position taken by ToolGen here. Even if CVC's half of Count 1 required NLS tagging and codon optimization as CVC incorrectly posits, both were known in the art, which CVC admits, and both are expressly disclosed in ToolGen's P3 and PCT.

I. TOOLGEN'S P3 AND PCT PROVIDE A CONSTRUCTIVE REDUCTION TO PRACTICE OF CVC'S HALF OF COUNT 1, AND CVC HAS NEITHER SHOWN NOR EVEN ARGUED OTHERWISE

A. CVC Does Not Dispute That ToolGen's P3 And PCT Disclose An Embodiment Of The CVC Half Of Count 1 As Written

CVC argues that ToolGen failed to adequately describe an NLS-tagged and codon-optimized Cas9 nucleic acid. Opp. 1:3–15. The response is that these elements are not contained in the CVC half of Count 1, under which ToolGen moved, a fact which CVC and its expert, Dr. Bailey, admits. Opp. 2:6–8; Ex. 1603 (Bailey Tr.), 23:22–23 (no recitation of nuclear localization signal); Ex. 1550 (Bailey Tr.), 124:18–125:1 (no requirement of codon optimization); F124. Of

course, to be accorded benefit, a party needs only show a constructive reduction to practice of a single embodiment within the count. *See Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (C.C.P.A 1975).

ToolGen's Motion was based on CVC's half of Count 1, which Dr. Bailey admitted he did not analyze. Ex. 1603, 23:8–13; F125. Making matters worse, Dr. Bailey premised his testimony entirely on the lawyer-provided assumption that ToolGen ***must*** show codon optimization and NLS tagging to satisfy Count 1. *Id.* at 36:9–45:19; F126. Accordingly, neither CVC nor Dr. Bailey disputes that ToolGen's P3 and PCT both meet every limitation of the CVC half of Count 1 as written. For that reason alone, ToolGen's contingent motion should be granted.

B. CVC's Estoppel Theories Fail Both As A Matter of Fact And As A Matter of Law

CVC argues that ToolGen should be estopped from relying on any P3 or PCT embodiment that does not include a codon-optimized Cas9 nucleic acid and a nuclear localization signal. Opp. 16:9–19:12. The response is that CVC admits that neither are required to satisfy Count 1. Opp. 2:6–8; F127. CVC's argument lacks factual and legal support.

1. CVC Mischaracterizes ToolGen's Prosecution Arguments As Focused on Codon Optimization Or NLSs Independently, When ToolGen Actually Argued That Its Claims Were Nonobvious Because There Was No Reasonable Expectation of Successfully Using CRISPR-Cas9 In Eukaryotic Cells

In arguing for estoppel, CVC relies on contextual fragments of prosecution arguments, omits critical words from statements, stitches together disparate questions and answers, and misrepresents ToolGen's positions, and its expert Dr. Cullen's opinions, during prosecution, in order to craft a false narrative that ToolGen achieved patentability by focusing on codon optimization and NLSs, not the unpredictability in prokaryote-to-eukaryote translation. Opp. 1:12–21; 13:17–15:23. The Board should reject this effort at revisionist history.

To start, CVC alleges that ToolGen argued that the "secret sauce" distinguishing ToolGen's claims over the prior art was that the "nucleic acid has been engineered with both the [NLS] and codon optimization." Opp. 1:15–18, 14:7–9, 16:24–17:2. The response is: this never happened. CVC's excerpted quote takes a question asked by Judge Flax and matches it with ToolGen's answer to a ***different*** question from a ***different*** Judge; ToolGen's answer to Judge Flax's question never mentioned codon optimization or NLS. Ex. 2012 (Oral Hearing Tr.), 8604:24–8605:13; F128 When ToolGen ***did*** reference codon optimization and NLS, the question being answered was Judge Schneider's subsequent inquiry whether one of ToolGen's pending claims contained limitations as to "amounts or levels of different things" that would distinguish ToolGen's claims from prior art done in prokaryotic cells. Ex. 2012, 8605:14–18. Unremarkably, those distinctions were found in the claim limitations, including the "main distinction" of using CRISPR/Cas9 in mammalian cells. Ex. 2012, 8605:14–8606:4 (Oral Hearing Tr.).

Next, CVC alleges that ToolGen argued that an NLS-tagged, codon-optimized nucleic acid was "required" for CRISPR-Cas9 to function in eukaryotes. Opp. 1:13–15, 1:18–22. The response is, CVC plucks these statements out of their proper context, and, by doing so, misrepresents the prosecution record. Without the benefit of ToolGen's P1, the ordinary artisan would not have known what was required for CRISPR-Cas9 functionality in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶206; F129. In addition to the successful experiments in ToolGen's P1, Example 3 in P3 and PCT describes in detail and enables a POSA to make and use at least two additional embodiments of *Foxn1*-targeting Cas9-sgRNA that successfully cleaved the *Foxn1* gene target sequence in mouse embryonic cells. Ex. 1003, 36–45 & Figs. 5–8; Ex. 1004, 37–50 & Figs. 5–8. Similarly, Example 4 in PCT describes and enables another embodiment of the Count: the successful sequence-specific cleavage and editing of two target sequences in the genomic DNA

(an exon of the *BRI1* gene) of protoplast cells of Arabidopsis (*i.e.*, plant cells). Ex. 1004, 50–52 & Figs. 11–12. The ToolGen statements cited by CVC were about ToolGen's pending claims that included, *inter alia*, NLS and codon optimization limitations, not about CRISPR/Cas9 use in eukaryotes generally. Ex. 2012, 8605:14–8607:4.

Finally, CVC contends that ToolGen 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.'" Opp. 15:8–12, 15:13–23. The response is, CVC manufactures this quotation by cherry picking different excerpts out of a lengthy paragraph discussing 6 reasons (including NLSs/codon optimization) that, as of October 23, 2012 and without the benefit of ToolGen's P1, a POSA would not have had a reasonable expectation of successfully using CRISPR-Cas9 in eukaryotic cells. Ex. 2012, 6758. CVC omits five of those reasons. It also contains no assertion contrary to any argument ToolGen makes here. ToolGen consistently argued during prosecution that its claimed invention was not obvious because a POSA would doubt whether CRISPR-Cas9 could successfully function in a eukaryotic cell. Ex. 2012, 6769 (emphasis in original); F130.

In support, Dr. Cullen explained that a POSA "would have had no basis to reasonably believe" Type II CRISPR-Cas9 "could successfully have been used to introduce site-specific double-stranded breaks in a target nucleic acid sequence in eukaryotic cells, for example in mammalian*, e.g.*, human, cells." Ex. 2012, 5644. Dr. Cullen opined that, without the benefit of working examples, ***there were numerous reasons for this lack of expectation of success*** in using CRISPR-Cas9 in eukaryotic cells. Ex. 2012, 5653; F131. Despite this, it was the Examiner—not ToolGen—that mistakenly focused on the general techniques of codon optimization and NLSs,

instead of the argued overall unpredictability of CRISPR-Cas9 in eukaryotic cells. That mistake led her to repeatedly reject ToolGen's pending claims because both NLSs and codon optimization were known in other contexts. Ex. 2012, 6769.

ToolGen appealed, asserting that the Examiner's focus on codon optimization and NLSs was in error, and again arguing that there was no "reasonable expectation of success" because 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, 6883, 8531; F132. This is the same argument ToolGen makes in opposition to CVC's Motion 1 for benefit of its P1/P2. ToolGen Opposition 1, 26:18–27:6; Ex. 1403, ¶¶64–133.

The Board agreed with ToolGen, overruled the Examiner, and held ToolGen's claims nonobvious. In doing so, the Board found that even though NLSs and codon optimization were known techniques, they did not allay a POSA's concerns of the "***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 (Decision on Appeal), 8645 (emphasis added).

2. CVC's Arguments Regarding Prosecution History-Estoppel and Judicial Estoppel Fail As A Matter Of Law

a. Prosecution-History Estoppel Is Inapplicable

CVC misapplies the doctrine of prosecution-history estoppel. Opp. 16:10–17:20. Prosecution-history estoppel exists when a patentee tries to assert infringement beyond the scope of its claims, as construed in light of the prosecution history. *Springs Window Fashions LP v. Novo Indus, L.P.*, 323 F.3d 989, 995 (Fed. Cir. 2003) ("A patentee may not state during prosecution that the claims do not cover a particular device and then change position and later

sue a party who makes that same device for infringement."). The scope of ToolGen's claims is not at issue here—the only question is whether ToolGen's P3 and PCT disclose an embodiment of Count 1. *See Furman v. Cheng*, 59 U.S.P.Q.2d 1668, 2001 WL 583153, at *4 (B.P.A.I. May 11, 2001) ("Benefit is accorded with respect to a count, not claims corresponding to a count.").

b. Judicial Estoppel Is Inapplicable

CVC's arguments regarding judicial estoppel fail as well. Opp. 17:23–19:12. As shown above, ToolGen did not take a position in prosecution inconsistent with ToolGen's P3 or PCT showing a constructive reduction to practice of Count 1, with or without an NLS and codon optimization. *See Egenera, Inc. v. Cisco Sys., Inc.*, 972 F.3d 1367, 1378–79 (Fed. Cir. 2020) (requiring a party to take two mutually exclusive positions). ToolGen's prosecution arguments were about an ordinary artisan's expectation of success in an unpredictable field without the benefit of ToolGen's working examples in P1. They were non-obviousness, not written-description, arguments and were made in a different factual context—that of overcoming prior art that did not disclose successful CRISPR-Cas9 use in eukaryotic cells. *See Akamai Tech., Inc. v. Limelight Networks, Inc.*, 805 F.3d 1368, 1378–79 (Fed. Cir. 2015) (refusing to apply judicial estoppel where distinct issues were involved).

C. Even If Codon Optimization And An NLS Were Required, CVC Has Failed To Show That ToolGen Did Not Meet The Written-Description Requirement

Even if one were to accept CVC's faulty premise—that ToolGen has to prove elements that do not exist in CVC's half of Count 1—the response is that P3 and PCT describe an NLS-tagged and codon-optimized Cas9 nucleic acid. CVC, ToolGen, both experts, and the Board agree that NLS-tagging and codon optimization were well-known techniques known to a POSA at the time of ToolGen's applications. Ex. 1403, ¶171; Ex. 2015 (Bailey Decl.), ¶¶39, 93–97; Ex. 2012 (Decision on Appeal), 8645 ("that NLSs and codon-optimization were known

techniques"); F133. *See Spectra–Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art.").

Significantly, CVC admits that P3 and the PCT disclose an NLS-tagged and codon-optimized Cas9 nucleic acid, just not in the words CVC chooses. CVC relies on *Univ. of Rochester* to characterize P3 and PCT's disclosure as "generalized language" that is insufficient for written description. Opp. 2:3–5, 10:4–6, 13:9–11. The further response is *Univ. of Rochester* is inapposite; P3 and the PCT disclose each in detail. Ex. 1003, 26 ("Specifically, 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 peptide tag (NH2-GGSGPPKKKRKVYPYDVPDYA-COOH) containing the HA epitope and a nuclear localization signal (NLS) was added to the C-terminus of Cas9."); Ex. 1004, ¶292 (same).

First, ToolGen's P3 and PCT explicitly reference the well-known *S. pyogenes* Cas9 sequence as the sequence being codon-optimized and refers to the accession number (NC_002737.1). As Dr. Cullen and CVC agree, the *S. pyogenes* Cas9 sequence was well-known in the art. Ex. 1403, ¶¶176–181; *see also* CVC Motion 1, Paper 368, 23:24–24:1 ("The sequence of the *S. pyogenes* Cas9 gene, and methods for obtaining it, were in the art by May 25, 2012."). Further, ToolGen's P3 and PCT's inclusion of the accession number conveys to a POSA the exact Cas9 sequence to be codon-optimized. Ex. 1403, ¶¶177–181; Ex. 1003, 26; Ex. 1004, ¶292 (same); F134; MF19. *See Enzo Biochem Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 965–66 (Fed. Cir. 2002) (finding written description satisfied where "a [POSA], reading the accession numbers in the patent specification, can obtain the claimed sequences from the ATCC depository").

Second, it was well-known to a POSA that nucleic acids could be 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, ¶¶171–174; Ex. 2096, 3–5; Ex. 2449; Ex. 2075; Ex. 2015, ¶39; F135. As Dr. Cullen and Dr. Bailey agree, both P3 and the PCT reference the use of codon-optimization tables, which "were known and readily available to a POSA in 2012." Ex. 1403, ¶173; Ex. 2015, ¶41; F136. Additionally, "[a] POSA would have been aware of various methods and algorithms for codon optimization using a codon-usage table." Ex. 1403, ¶173. A POSA having access to the Cas9-coding sequence for *S. pyogenes* would know how to create a codon-optimized Cas9 sequence. *Id.* at ¶177.

Third, ToolGen's P3 and PCT explicitly reference the protein sequence of the NLS used, "NH2-GGSGPPKKKRKVYPYDVPDYA-COOH." Ex. 1003, 26; Ex. 1004, ¶292 (same); F137. In fact, this specific NLS was the first NLS discovered in 1984. Ex. 1608, 499 (Kalderon 1984) ("[W]e conclude that Pro-Lys-Lys-Lys-Arg-Lys-Val [*i.e.*, PKKKRKV] can act as a nuclear location signal."). As Dr. Bailey and the Board agreed, using nuclear localization signals for targeting proteins to the nucleus was a well-known technique in the art. Ex. 2015, ¶95–98; Ex. 2012, 6769; F138.

Fourth, the specification at issue in *Univ. of Rochester* did not reference or direct a POSA to the chemical compound that was the subject of the method claims at issue. *See Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 929 (Fed Cir. 2004). Here, both P3 and the PCT expressly reference codon optimization and NLS and direct a POSA how to implement both. Ex. 1003, 26; Ex. 1004, ¶292 (same).

II. CONCLUSION

If the Board were to find that ToolGen is not entitled to the benefit of its P1, it should then grant ToolGen the benefit of its P3 and PCT applications.

Respectfully submitted,

Dated: August 27, 2021

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APPENDIX 1: LIST OF EXHIBITS CITED

Ex. No.	Description
1003	U.S. Provisional Application No. 61/837,481, filed June 20, 2013.
1004	International PCT Application PCT/KR2013/009488, filed on October 23, 2013.
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.
1603	Second Deposition Transcript of Dr. Scott Bailey, The Regents of the University of California v. ToolGen, Inc., Interference No. 106,127, August 10, 2021
1608	*Kalderon et al*., A Short Amino Acid Sequence Able to Specify Nuclear Location, *Cell*, 39, 499-509 (1984).
2012	File History for U.S. Appl. No. 14/685,510
2015	Declaration of Scott Bailey, Ph.D.
2075	*Sandhu 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 Biotechnol*. 22(7):346-353 (2004)
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).

APPENDIX 2: STATEMENT OF MATERIAL FACTS

Senior Party ToolGen's Material Facts 1-68 and Junior Party's Answers

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 2 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.

Junior Party's Alleged Facts 69-123 and Senior Party ToolGen's Answers

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.

Response: Admitted only to the extent ToolGen's involved claims included limitations of a Cas9 nucleic acid that "is codon-optimized for expression in mammalian cells" and a Cas9 protein that "comprises a nuclear localization signal."

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.

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

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).

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

Response: Admitted only to the extent those words appear in the Oral Hearing transcript; otherwise, denied.

77. During oral hearing, ToolGen told the PTAB that the "main distinction" from the prior art 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.

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

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.

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

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.

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

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.

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

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.

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

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.

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

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.

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

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Denied.

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.

Response: Admitted.

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.

Response: Denied.

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.

Response: Admitted 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; otherwise, denied.

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

Response: Denied.

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.

Response: Admitted.

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.

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

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.

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

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.

Response: Admitted.

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.

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

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.

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

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

Response: Denied.

102. Neither P3 nor PCT discloses a particular codon-optimization program or indicate which should be used. Ex. 1003; Ex. 1004; Ex. 2477, ¶¶48, 73.

Response: Denied.

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.

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

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

Response: Admitted.

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

Response: Admitted to the extent that SEQ ID NO. 2 is not included in P3.

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.

Response: Admitted to the extent that those words appear in the deposition transcript; otherwise, denied.

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

Response: Denied.

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.

Response: Denied.

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.

Response: Admitted to the extent the quoted language appears in Exhibit 1003 and 1004; otherwise, denied.

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

Response: Denied.

111. 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.

Response: Admitted 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.

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

Response: Denied.

113. 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.

Response: Admitted.

114. 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.

Response: Admitted that SEQ ID NO 1 does not have an added NLS; otherwise, denied.

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

Response: Admitted.

116. 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.

Response: Admitted.

117. 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.

Response: Admitted.

118. 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.

Response: Admitted.

119. 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.

Response: Admitted.

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

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

121. 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.

Response: Denied.

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

Response: Admitted to the extent the quoted language appears in Exhibit 2474; otherwise, denied.

123. 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.

Response: Denied as incomplete.

Senior Party ToolGen's Additional Material Facts 124-138

124. Dr. Bailey admitted that CVC's half of Count 1 does not require a nuclear localization signal or codon optimization. Ex. 1603 23:22-23; Ex. 1550, 124:18–125.

125. Dr. Bailey did not analyze the CVC half of Count 1. Ex. 1603, 23:8–13.

126. Dr. Bailey premised his testimony on the lawyer-provided assumption that ToolGen must show codon optimization and NLS tagging to satisfy Count 1. Ex. 1603 at 36:9–45:29

127. Codon-optimization and NLS-tagging are not required to satisfy Count 1. Opp. 2:6–8.

128. CVC's quote regarding "secret sauce" matches a question by Judge Flax and with an answer to a different question from a different Judge; ToolGen's answer to Judge Flax's question never mentioned codon optimization or NLS. Ex. 2012 (Oral Hearing Tr.), 8604:24–8605:13.

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

130. ToolGen consistently argued during prosecution that its claimed invention was not obvious because a POSA would doubt whether CRISPR-Cas9 could successfully function in a eukaryotic cell. Ex. 2012, 6769 (emphasis in original).

131. Dr. Cullen opined that, without working examples, there were numerous reasons for this lack of expectation of success in using CRISPR-Cas9 in eukaryotic cells. Ex. 2012, 5653.

132. ToolGen argued in prosecution on appeal that the Examiner's focus on codon optimization and NLSs was error and there was no "reasonable expectation of success" because 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, 6883, 8531.

133. ToolGen, both experts, and the Board agree that NLS-tagging and codon optimization were well-known techniques known to a POSA at the time of ToolGen's applications. Ex. 1403, ¶171; Ex. 2015 (Bailey Decl.), ¶39, 93–97; Ex. 2012 (Decision on Appeal), 8645.

134. ToolGen's P3 and PCT's inclusion of the accession number conveys to a POSA the exact Cas9 sequence to be codon-optimized. Ex. 1403, ¶¶177–181; Ex. 1003, 26; Ex. 1004, ¶292 (same).

135. It was well-known to a POSA that nucleic acids could be codon-optimized through the use of codon usage tables by replacing wild-type codons with codons that more closely reflect the codon usage of the host cell. Ex. 1403, ¶¶171–174; Ex. 2015 (Bailey Decl.), ¶39.

136. Drs. Cullen and Bailey agree both P3 and PCT refer to the use of codon-optimization tables, which "were known and readily available to a POSA in 2012." Ex. 1403, ¶173; Ex. 2015, ¶41.

137. ToolGen's P3 and PCT explicitly reference the protein sequence of the NLS used, "NH2-GGSGPPKKKRKVYPYDVPDYA-COOH." Ex. 1003, 26; Ex. 1004, ¶292 (same).

138. As Dr. Bailey and the Board agreed, using nuclear localization signals for targeting proteins to the nucleus was a well-known technique in the art. Ex. 2015, ¶95–98; Ex. 2012, 6769.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **TOOLGEN REPLY 1** was filed via the Interference Web Portal on August 27, 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 to counsel for Junior Party as follows:

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