Filed on behalf of Junior Party
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,
UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER

Paper No. ___

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER
Junior Party

Applications 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374

v.

TOOLGEN, INC.
Application 14/685,510

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

CVC REPLY 2 (to deny ToolGen P1 benefit)

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I. INTRODUCTION

The PTAB should deny ToolGen benefit to its P1 because P1 does not describe a codon-optimized Cas9 nucleic acid. To get its interfering claims allowed, ToolGen told the Patent Office that codon optimization of Cas9 nucleic acid was required to express a functional Cas9 protein in eukaryotic cells and it was unpredictable. As CVC's motion showed, under the party admission and judicial estoppel doctrines, ToolGen is bound by those statements and can only rely on an embodiment that includes a codon-optimized Cas9 nucleic acid, irrespective of which half of the count it attempts to prove for a CRTP. Further, under the written description case law, P1 must describe a codon-optimized Cas9 nucleic acid with specificity. Yet, as CVC's motion showed, in view of ToolGen's prior statements, ToolGen's P1 does not describe a codon-optimized Cas9 nucleic acid with sufficient detail to allow a POSA to discern any codon-optimized nucleic acid that, according to ToolGen, would express a functional Cas9 protein.

ToolGen does not rebut CVC's showing that ToolGen argued codon optimization was required and unpredictable. For example, ToolGen fails to mention, let alone refute, its prosecution statement that Cas9 codon optimization was "required in the science." MF11. And ToolGen addresses only *one* out of *nine* of its prosecution statements where it stated that codon optimization was required in its claimed invention, leaving the other statements unrebutted. Even for that one statement, ToolGen concedes that it had in fact distinguished its claimed invention from the prior art based on codon optimization. MF91. ToolGen also readily agrees that it told the Office that it was "unpredictable" whether a codon-optimized Cas9 nucleic-acid would work in a eukaryotic cell. *See*, *e.g.*, Opp., 10:12-11:2; MF92. Thus, ToolGen has not rebutted CVC's showing that the PTAB should hold ToolGen to its prior statements and deny it benefit to its P1.

II. ARGUMENT

a. ToolGen unequivocally stated during prosecution that a codon-optimized Cas9 nucleic acid was "required in the science" and by its claimed invention.

On pg. 6, line 9 to pg. 8, line 9 of the opposition, ToolGen argues that it never asserted during prosecution that codon optimization was required for CRISPR/Cas9 functionality in eukaryotic cells. The response is that ToolGen fails to address its unambiguous statement to the Office that codon optimization was "in a broader sense . . . required in the science to get [CRISPR-Cas9] to work" in a eukaryotic cell. Mot., 5:3-10; Ex. 2012, 8606:5-11; MF11. ToolGen does not even attempt to explain away this statement. Remarkably, ToolGen asserts that its statements were "not about CRISPR/Cas9 use in eukaryotes generally" and attempts to sidestep the issue, asserting that an "artisan would not have known what was required for CRISPR/Cas9 functionality in eukaryotic cells." Opp., 6:16-19. But the issue is what ToolGen told the Office, not what a POSA would have known. ToolGen's expert, Dr. Cullen, merely asserts that *he* "never offered the opinion that CRISPR/Cas9 would not function in eukaryotic cells without the use of codon optimization[.]" Ex. 1403, ¶ 206; MF90. But that assertion cannot nullify ToolGen's statement that codon optimization was "required in the science." MF11.

CVC also showed that ToolGen relied on codon optimization to distinguish its claimed invention from the prior art—*i.e.*, ToolGen's claimed invention required codon optimization. Mot., 3:13-6:27. ToolGen admits as much, noting "statements cited by CVC were about its pending claims[.]" Opp., 6:17-19; MF89. Still, in an attempt to sow confusion, ToolGen challenges CVC's interpretation of only *one* (at Mot., 4:10-5:2) out of at least *nine* instances that CVC referenced where ToolGen had relied on codon optimization to overcome the prior art; while the other instances remain unrebutted. Mot., 3:16-4:1, 4:5-5:2, 5:14-6:22; Ex. 2012, 6745-49, 6783, 6758, 6761-62, 6767, 6895-96, 6899, 8531, 8604:1-3, 8604:24-8605:25; Opp., 6:21-

8:6; MF2-10. And even for that one instance, ToolGen admits to distinguishing its claims from the art based on codon optimization. Opp., 7:9-12; Mot., 4:10-5:2; MF91. ToolGen wrongly asserts that CVC mischaracterized this one instance as a reply to Judge Flax's question about ToolGen's "secret sauce." Opp., 6:22-7:5. CVC did no such thing—CVC never stated or implied (*e.g.*, evidenced by asterisks between the excerpts at Mot., 4:10-5:2) that the statement was a direct reply to Judge Flax's "secret sauce" question. Mot., 1:17-2:1, 4:10-5:2, 8:11-16.

CVC urges the PTAB to review the full exchange surrounding Judge Flax's "secret sauce" question, available at Ex. 2012, 8604:24-8605:25. The record shows that ToolGen's statement was part of an exchange where Judge Flax asked ToolGen what its "secret sauce" was that rendered its claimed invention "specifically different" from the prior art. Ex. 2012, 8604:24-8605:25. When ToolGen evaded that question and pointed to aspects that were not part of its claimed invention, Judge Schneider returned ToolGen to Judge Flax's unanswered question. *Id*. ToolGen then ultimately stated that the "main distinction" in its claims was "providing a nucleic acid into the mammalian cells, and that the nucleic acid has been engineered with . . . codon optimization." *Id.*; Mot., 4:10-16, 1:17-2:1, 8:13-15. Thus, the full exchange shows that ToolGen's statement highlighting codon optimization was in response to Judge Schneider's restatement of Judge Flax's "secret sauce" question. *Id.* And it is undisputed that during this exchange ToolGen distinguished its claimed invention from the prior art based on codon optimization being required. *Id*. Thus, the record is clear: ToolGen stated during prosecution that a codon-optimized Cas9 nucleic acid was "required in the science" and by its claimed invention.

b. ToolGen unequivocally argued codon optimization had unpredictable effects.

On pg. 8, lines 10-11 of the opposition, ToolGen asserts it "never argued codon optimizing a nucleic acid encoding Cas9 was unpredictable." The response is that, despite this assertion, ToolGen concedes that it argued during prosecution that the effects of codon

optimization on expressing a functional Cas9 protein in a eukaryotic cell were unpredictable. Opp., 10:12-11:2, 11:32-12:1; Ex. 1403, ¶¶ 201, 204; Mot., 5:14-6:22, 12:15-13:6, 13:14-15, 15:4-7, 16:10-13; Ex. 2015, ¶¶ 9, 50-67; MF92. For example, ToolGen admits that it argued during prosecution that the "effect of codon optimization" was a reason why a POSA would not have reasonably expected to achieve a functional CRISPR-Cas9 system in eukaryotic cells. Opp., 8:14-9:4; *see also id*., 10:12-14, 11:32-12:1. Similarly, ToolGen quotes Dr. Cullen's statement that as of P1's filing date "it would have been unpredictable what the possible effects of eukaryotic cell codon optimization might be on the activity Cas9 polypeptide expressed from a codon-optimized sequence in a eukaryotic cell." *Id.*, 10:19-23; *see also id.*, 10:15-19, 10:23-11:2.

Unable to dispute its prosecution statements, ToolGen reframes the issue as a dispute over CVC's *interpretation* of its statements. Opp., 10:13-11:17, 11:20-22, 15:15-17; Ex. 1403, ¶¶ 208 (lines 9-12), 174 (lines 14-16), 201-204. But CVC's written description challenge is premised on the correct interpretation of ToolGen's unambiguous and undisputed assertions that expressing a functional Cas9 protein from a codon-optimized nucleic acid was unpredictable. Mot., 5:14-6:22, 12:15-13:6, 13:14-15, 15:4-7, 16:10-13; Ex. 2015, ¶¶ 9, 50-67. And while CVC cited at least *five* instances where ToolGen asserted that expressing a functional Cas9 protein from a codon-optimized nucleic acid was unpredictable, ToolGen attempts to explain away only *one* instance (at Mot., 1:6-7, 2:3-5, 6:13-15), leaving the rest unrebutted. Opp., 9:10-18; Mot., 5:14-6:22; Ex. 2012, 6758, 6761-62, 6767, 6895-96, 6899, 8531; MF4-8. Thus, the record shows ToolGen argued that codon optimization was unpredictable because it had unpredictable effects.

c. The PTAB should not allow ToolGen to rely on any embodiment lacking a codon-optimized Cas9 nucleic acid or to argue that codon optimization had predictable effects.

CVC showed that under the party admission and judicial estoppel doctrines, (1) ToolGen can only rely on an embodiment that includes a codon-optimized Cas9 nucleic acid that

expresses a functional protein in eukaryotes for a CRTP under either half of the count, and (2) ToolGen's P1 fails to describe such a codon-optimized nucleic acid. Mot., 2:15-20; 7:1-16:18.

On pg. 12, line 8 to pg. 14, line 16 of the opposition, ToolGen argues it is not bound to its statements under the party admission and judicial estoppel doctrines. The response is that ToolGen fails. To escape the consequence of the party admission doctrine, ToolGen argues that the doctrine (calling it prosecution history estoppel) "applies when a patentee tries to assert infringement beyond the scope of its claims" and the "scope of [its] claims is not at issue here." Opp., 14:12-16. ToolGen is wrong because the doctrine is not limited to such determinations. For example, the Board in *Louis v. Okada*—a precedential, expanded panel case—applied the doctrine to deny a movant's request to broaden the count in view of the movant's prosecution statements. Mot., 8:1-8; *Louis v. Okada*, 59 U.S.P.Q.2d 1073 (B.P.A.I. 2001). And, even if the Office did not rely on ToolGen's assertions during prosecution, ToolGen is still bound by them under this doctrine. "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." Mot., 7:14-16 (citing *Springs Window Fashions LP v. Novo Indus., L.P.*, 323 F.3d 989, 995 (Fed. Cir. 2003)). "The fact that an examiner placed no reliance on an applicant's statement . . . does not mean that the statement is inconsequential." *Springs Window*, 323 F.3d at 995. And, here, the statements were consequential resulting in ToolGen's claims being allowed and leading to this interference.

Attempting to avoid the judicial estoppel doctrine, ToolGen argues that (1) its prosecution assertions were "to nonobviousness, not written description" and (2) that it did not prevail in prosecution because of its codon-optimization assertions. Opp., 12:8-14:9. Neither argument has merit. *First*, ToolGen's assertions are unaffected by the context of the rejection. It does not matter whether the issues of nonobviousness and written description are "fundamentally

different." Opp., 13:4-5. Identity of issues is not required for *judicial* estoppel, which seeks "to protect the integrity of the judicial process." *New Hampshire v. Maine*, 532 U.S. 742, 749-50 (2001) (internal quotations omitted). ToolGen cannot now take a "clearly inconsistent" position from its previous position. *Zedner v. United States*, 547 U.S. 489, 504 (2006).

Second, as CVC showed, the Office did rely on ToolGen's codon-optimization assertions in finding its involved claims allowable. Mot., 6:23-27, 10:13-18; Ex. 2012, 8637-39, 8642, 8643, 8645, 8646, 8651; MF12-13. ToolGen's argument that the earlier PTAB panel did not rely on ToolGen's arguments because that panel "does not cite to the [oral] hearing transcript" is irrelevant. Opp., 13:12-14. The panel *repeatedly* discussed codon optimization. *See*, *e.g.*, Ex. 2012, 8633, 8634, 8636, 8637-39, 8640, 8644, 8645. The panel relied on, and even quoted, ToolGen's statements, such as Dr. Cullen's testimony on codon-optimization unpredictability: "uncertainties [were] known to have arisen from modification of proteins like Cas9." Ex. 2012, 8637; *see also id.* 8638-39 ("Dr. Cullen also addressed several uncertainties . . . in modifying proteins like Cas9."). The potential that the panel may have also considered ToolGen's other arguments does not change the fact that the panel *clearly relied* on ToolGen's codon-optimization assertions.

Thus, ToolGen cannot escape its prosecution assertions. As such, ToolGen can only rely on an embodiment that includes a codon-optimized Cas9 nucleic acid, and its P1 must describe such an embodiment consistent with its codon-optimization unpredictability assertions.

d. Based on ToolGen's assertion that codon optimization had unpredictable effects, its P1 does not describe a codon-optimized Cas9 nucleic acid.

On pg. 14, line 17 to pg. 19, line 17 of the opposition, ToolGen argues that P1 describes a codon-optimized Cas9 nucleic acid. The response is that under *Ariad*, *Rochester*, and *Alonso*, P1 does not adequately describe a codon-optimized Cas9 nucleic acid given (1) ToolGen's

assertions that a codon-optimized nucleic acid would not have predictably expressed a functional Cas9 protein in eukaryotes and (2) the myriad different codon-optimized Cas9 nucleic acid sequences that a POSA could have "reconstituted using the human codon usage table" based on P1's disclosure. Mot., 11:10-16:18; Ex. 2008, 11; *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*); *In re Alonso*, 545 F.3d 1015, 1019 (Fed. Cir. 2008); *University of Rochester v. G.D. Searle & Co*., 358 F.3d 916, 923-924, 927 (Fed. Cir. 2004).

Even if a POSA understood, as ToolGen argues, "reconstituting a nucleic acid sequence using a codon usage table to be codon optimization" or that codon optimization was a routine technique, P1 would at most teach that a Cas9 nucleic acid could be codon optimized. Opp., 16:7-9, 13-15. But, in view of ToolGen's unpredictability assertions, a POSA would still be in the dark as to the identity of *which* codon-optimized nucleic acid sequence of the myriad different sequences would express a functional Cas9. Mot., 13:14-16:7. Thus, to be accorded benefit, P1 must describe the specific codon-optimized nucleic acid sequence(s) that would express a functional Cas9. Mot., 11:10-16:18. P1 fails to do that. *Id*.

ToolGen also mischaracterizes CVC's written description challenge. *First*, ToolGen suggests that CVC did not treat its prosecution statements as statements about the art *before* P1's filing date, or that CVC did not consider its statements *together with* P1's disclosure. Opp., 10:15-11:2; Ex. 1403, ¶¶ 170, 198-203. This is incorrect and illogical. CVC and Dr. Bailey treated ToolGen's statements as statements about the art before P1's filing date and assessed written description support in P1 based on its disclosure (including the working examples). *See*, *e.g.*, Mot., 3:11-12; 13:3-6, 13:14-15, 15:4-6, 16:10-13; Ex. 2015, ¶¶ 9, 38-67. For example, CVC argued that "[a]ccording to ToolGen's prosecution argument, codon optimization was unpredictable; thus, a skilled artisan *reading its P1* would not have been able to discern a codon-

optimized Cas9 nucleic acid that ToolGen alleged its invention requires." Mot., 15:4-6 (emphasis added); *see also id.* 3:11-12; 13:3-6, 13:14-15, 16:10-13. Dr. Bailey also opined that "[b]ased on the limited disclosure in ToolGen's P1 and ToolGen's representations made to the [] Office, a POSA would have concluded that *ToolGen's P1* lacks adequate description of a codon-optimized Cas9 nucleic acid." Ex. 2015, ¶ 55 (emphasis added); *see also id.*, ¶¶ 64, 65. To suggest otherwise is illogical for one cannot assess a document without considering what it discloses.

Second, ToolGen argues that CVC misrepresented or misinterpreted its statements about codon-optimization unpredictability. Opp., 10:12-11:17, 11:20-22, 15:15-17; Ex. 1403, ¶¶ 208 (lines 9-12), 174, 201-204, 208-210. This is also untrue. CVC correctly applied ToolGen's statements as asserting unpredictability in *expressing a functional Cas9 protein* in a eukaryotic cell from a codon-optimized nucleic acid (and not, as ToolGen suggests, as stating that the *act of replacing codons* was unpredictable or that the technique was not routine). Mot., 5:14-6:22, 12:15-13:6, 13:14-15, 15:4-7, 16:10-13; Ex. 2015, ¶¶ 9, 50-67.

Third, ToolGen argues that CVC and Dr. Bailey applied an incorrect definition for codon optimization by requiring *enhanced* protein expression. Opp., 18:6-8, 19:5-17; Ex. 1403, ¶¶ 174, 208-210. Dr. Bailey's opinion did not turn on this understanding of codon optimization. Instead, Dr. Bailey's central point was that ToolGen's P1 does not contain *any sequence* of a codon-optimized Cas9 nucleic acid and, in view of ToolGen's prior unpredictability statements, it does not identify a nucleic acid sequence that expresses a functional Cas9 protein. Ex. 2015, ¶¶ 9, 50-67; Mot., 11:10-16:18. In any case, ToolGen's expert Dr. Cullen agrees that enhanced protein expression is a goal for codon optimization, which he asserted was unpredictable to achieve. Ex. 1403, ¶¶ 171, 172; Ex. 2538, 51:6-22; MF93-94. And Dr. Cullen applied this same understanding in making *his* prosecution opinions. Ex. 2538, 52:1-5; MF94.

Finally, ToolGen argues that Dr. Bailey admitted that P1 describes codon optimization. Opp., 16:18-21, 17:9-12. This is false. Mot., 13:3-16:18; Ex. 2015, ¶¶ 56, 63-64; Ex. 1550, 107:22-111:5. As in his declaration, Dr. Bailey testified: "I don't think a POSA would have understood what's written there [in P1] to be codon-optimized either." Ex. 1550, 107:22-111:5. ToolGen ignores this relevant testimony and informs the PTAB of only partial testimony, disregarding the fact that Bailey asked ToolGen's counsel to clarify the question. *Id.* And even if the PTAB were to agree with ToolGen, this at best means P1 suggests that a Cas9 nucleic acid could be codon optimized—not that P1 *describes* a codon-optimized Cas9 nucleic acid.

ToolGen also (1) attacks Dr. Bailey's analysis of the codon-usage tables known before P1's filing date and (2) argues that its P1 describes a codon-optimized Cas9 nucleic acid because it includes working examples. Ex. 1403, ¶ 175; Opp., 1:2-5, 12:1-7. On the first point, Dr. Cullen argues that Dr. Bailey gave "improper significance to differences between codon usage tables" as both the Kazusa and Jorgenson tables avoid "bad codons" containing CG and UA. Ex. 1403, ¶ 175. The argument fails. Both tables use the alleged bad codons as the most frequent codons for Tyrosine (UAC, UAU). *See* Ex. 2015, ¶ 43. And, even if the codons for Tyrosine were avoided, the tables still use different codons as the most frequent codon for 11 amino acids (such as, Phenylalanine, Serine, Histidine, Glycine) out of 20 possible amino acids. *Id*. Thus, the different tables would still have led to myriad different Cas9 nucleic acid sequences, and based on the P1 disclosure and ToolGen's prosecution statements, a POSA would not have been able to discern the nucleic acid that would express a functional Cas9 protein. Mot., 12:15-15:12.

ToolGen's second argument that its P1 describes a codon-optimized Cas9 because it includes working examples is wrong as a matter of law. Opp., 1:2-5, 12:1-7. "Proof of a reduction to practice" does not salvage an application that does not otherwise "describe or

identify the invention." *Alonso*, 545 F.3d at 1021. ToolGen does not even attempt to counter *Alonso*, discussed in the motion. Mot., 15:13-17. Further, the working examples do not necessarily use a codon-optimized Cas9 nucleic acid. *Id*., 15:17-16:7.

III. CONCLUSION

Because ToolGen's P1 fails to describe a codon-optimized Cas9 nucleic acid in view of ToolGen's prosecution arguments, it lacks a CRTP under either half of the count. The PTAB should therefore grant CVC's motion and deny ToolGen benefit to its P1.

Respectfully submitted,

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APPENDIX 1: LIST OF EXHIBITS

Exhibit No.	Description
1403	July 15, 2021 Declaration of Bryan R. Cullen, Ph.D.
1550	Deposition Transcript of Scott Bailey, Ph.D., The Regents of the University of California v. ToolGen, Inc., Interference No. 106, 127, June 25, 2021.
2008	Prov. Appl. No. 61/717,324
2012	File History for U.S. Appl. No. 14/685,510
2013	May 20, 2021 Declaration of Yannick Doyon, Ph.D.
2015	May 19, 2021 Declaration of Scott Bailey, Ph.D.
2073	Cai, Y., *et al*., "Optimizing the codon usage of synthetic gene with QPSO algorithm," *Journal of Theoretical Biology* 254:123–127 (2008)
2074	Puigbo, P., *et al*., "OPTIMIZER: a web server for optimizing the codon usage of DNA sequences," *Nucleic Acids Research* 35: W126–W131 (2007)
2075	Sandhu, K., *et al*., "GASCO: Genetic Algorithm Simulation for Codon Optimization," *In Silico Biology* 8: 187–192 (2008)
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)
2084	Hoover, D.M. and Lubkowski, J., "DNAWorks: an automated method for designing oligonucleotides for PCR-based gene synthesis," *Nucleic Acids Research* 30: 10e43:1-7 (2002)
2085	Wu, G., *et al*., "The Synthetic Gene Designer: A flexible web platform to explore sequence manipulation for heterologous expression," *Protein Expression and Purification* 47: 441–445 (2006)
2086	Richardson, S., *et al*., "GeneDesign: Rapid, automated design of multikilobase synthetic genes," *Genome Research* 16:550–556 (2006)
2087	Fuglsang, A., "Codon optimizer: a freeware tool for codon optimization," *Protein Expression and Purification* 31: 247–249 (2003)
2088	Gao, W., *et al*., "UpGene: Application of a Web-Based DNA Codon Optimization Algorithm," *Biotechnol. Prog.* 20:443−448 (2004)

Exhibit No.	Description
2089	Grote, A., *et al*., "JCat: a novel tool to adapt codon usage of a target gene to its potential expression host," *Nucleic Acids Research* 33: W526–W531 (2005)
2091	Harish, N., *et al*., "DyNAVacS: an integrative tool for optimized DNA vaccine design," *Nucleic Acids Research* 34: W264–W266 (2006)
2094	Jayaraj, S., *et al*., "GeMS: an advanced software package for designing synthetic genes," *Nucleic Acids Research* 33(9): 3011–3016 (2005)
2096	Gustafsson, C., *et al*., "Codon bias and heterologous protein expression," *Trends Biotechnol*. 22(7):346-353 (2004)
2447	*Streptococcus pyogenes* SF370 chromosome, complete genome , available at https://www.ncbi.nlm.nih.gov/nuccore/NC_002737.1 (last visited May 19, 2021)
2448	*Streptococcus pyogenes* M1 GAS, complete sequence, available at https://www.ncbi.nlm.nih.gov/nuccore/NC_002737.2 (last visited May 18, 2021)
2449	Codon Usage Table Homo sapiens [gbpri]: 93487 CDS's (40662582 codons), available at https://www.kazusa.or.jp/codon/cgi-bin/showcodon.cgi?species=9606 (last visited May 19, 2021)
2538	Deposition Transcript of Bryan Cullen, Ph.D., with errata, Patent Interference No. 106,127 (August 12, 2021)

APPENDIX 2: STATEMENT OF MATERIAL FACTS

CVC's Material Facts 1-45 (with ToolGen's Responses)

1. ToolGen's involved claims all require a Cas9 nucleic acid that "is codon-optimized for expression in mammalian cells." Paper 6. **ToolGen's Response: Admitted only to the extent that ToolGen's involved claims require "a nucleic acid encoding a Cas9 polypeptide, . . . wherein said nucleic acid is codon-optimized for expression in mammalian cells."**

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

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

4. ToolGen argued during prosecution that a skilled artisan "would not have reasonably expected that a Type II CRISPR/Cas9 system could successfully have been used . . . in eukaryotic (e.g., mammalian) cells. The reasons . . . include . . . challenges presented bymodification (e.g., tagging and codon-optimization) of nucleic acids to be expressed in eukaryotic/mammalian cells." Id., 6758 (Resp., Mar. 3, 2017) (emphasis in original) (internal citations omitted). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page response to an office action supported by a multi-page declaration.**

5. ToolGen argued during prosecution that a skilled artisan would not have reasonably expected the Cas9 protein expressed from a codon-optimized nucleic acid to be functional in "eukaryotic/mammalian cells" because a skilled artisan would have "(i) questioned whether Cas9 could properly fold when expressed in eukaryotic cells . . . ; (ii) recognized that modification of Cas9, e.g., by tagging it with a NLS and/or optimizing itscodon sequence, could have rendered [Cas9] inactive upon expression in a eukaryotic cell. . . ; and (iii) understood the importance of native codon optimization to proper proteinfolding " Id., 6761-6762 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page response to an office action supported by a multi-page declaration.**

6. On appeal, ToolGen argued as follows: "Bacterial proteins may not fold properly in mammalian cells, and alteration of codons (which occurs as a result of codon optimization) can result in altered translation kinetics leading to misfolding. Since improperly folded proteins can lack activity, exhibit aberrant function or be degraded in cells, it would not have been predictable, whether a bacterial protein such as Cas9 and, inparticular, codon-optimized Cas9 would fold in a mammalian cell in a way that would preserve its functionality." Id., 6895-6896 (Appeal Br., June 13, 2018) (internal citations omitted). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page appeal brief supported by a multi-page declaration submitted during prosecution.**

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

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

8. On appeal, ToolGen argued that "a POSA would have had no idea what the outcome may have been even if one were to apply codon optimization and NLS addition to CRISPR/Cas9." Id., 8531 (Reply Br., Jan. 8, 2019). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page appeal brief supported by a multi-page declaration submitted during prosecution.**

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

10. During oral argument, ToolGen told the PTAB that in its claimed invention the "nucleic acid [that] has been engineered with codon optimization" is the "main distinction" from the prior art. Id., 8604:24-8605:25 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page Oral Hearing transcript.**

11. During oral argument, ToolGen argued that codon optimization of Cas9 nucleic acid is "required in the science to get [CRISPR-Cas9] to work." Id., 8606:5-11 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The quoted language is incomplete, taken out of context, and inaccurately excerpted from a multi-page Oral Hearing transcript.**

12. Relying on ToolGen's representations and accepting its arguments, the PTAB reversed the examiner's obviousness rejection of ToolGen's involved claims. Id., 8638, 8642, 8643, 8645, 8646 (PTAB Decision, Jun. 22, 2020). **ToolGen's Response: Denied. The PTAB's basis for its Decision is set forth in that decision.**

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

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

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

16. ToolGen's P1 states that "[t]he Cas9-coding sequence (4,104 bp), derived from Streptococcus pyogenes strain M1 GAS (NC_002737.1), was reconstituted using the human codon usage table and synthesized using oligonucleotides." Ex. 2008, ToolGen'sP1, 11; Ex. 2015, Bailey Decl., ¶56. **ToolGen's Response: Admitted only to the extent the quoted words appear in ToolGen's P1, Exs. 1001 and 2008.**

17. NC_002737.1 is the accession number for the nucleic acid sequence record of the complete genome of M1 GAS strain of *S. pyogenes* in the NCBI database, which at best includes the nucleotide range of the location of the Cas9 gene in the genome. Ex. 2015, Bailey Decl., ¶59; Ex. 2447; Ex. 2448. **ToolGen's Response: Admitted only to the extent that NC_002737.1 is the accession number for the nucleic acid sequence record of the complete genome of M1 GAS strain of *S. pyogenes* in the NCBI database.**

18. ToolGen's P1 does not disclose a single human codon-usage table. Ex. 2008, ToolGen'sP1; Ex. 2015, Bailey Decl., ¶60. **ToolGen's Response: Denied as incomplete and to**

the extent it implies codon optimization could not be completed without undue experimentation.

19. Without knowing the specific codon-usage table or the process or set of rules for selecting codons from the table, numerous sequences could be reconstituted from acodon-usage table. Ex. 2015, Bailey Decl., ¶¶60, 64. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

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

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

22. Different human codon-usage tables known in the art by October 23, 2012 identified a different codon as the most frequent codon for certain amino acids. Ex. 2015, Bailey Decl., ¶¶41-46, 61; Ex. 2449, Kazusa 2007; Ex. 2077, Jorgensen 2005, Table 8; Ex. 2078, Alff-Steinberger 1987, Table 1. **ToolGen's Response: Denied as the statement is incomplete, vague as to "most frequent" and "certain amino acids" and to the extent it implies codon optimization could not be completed without undue experimentation.**

23. ToolGen's P1 does not provide any human codon-usage information to reconstitute the Cas9 sequence. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶60. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

24. ToolGen's P1 does not indicate which human codon-usage table should be used to reconstitute the Cas9 sequence. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶60. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

25. The codon-usage frequencies for as many as 12 of the 20 possible amino acids differed from table to table. Ex. 2015, Bailey Decl., ¶¶39-46, 61. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

26. If the most frequent codon for each amino acid were picked from multiple possible human codon-usage tables, ToolGen's P1 reconstituted myriad different Cas9 nucleic acids from the native S. pyogenes nucleic acid sequence. Ex. 2015, Bailey Decl., ¶¶39-46,60-61, 63-65. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

27. ToolGen's P1 does not identify a particular codon-optimization program. Ex. 2008, ToolGen's P1; Ex. 2015, Bailey Decl., ¶62. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

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

29. The codon-optimization programs known by October 23, 2012 relied on codon-usage data from different tables. Ex. 2015, Bailey Decl., ¶¶47-49. **ToolGen's Response: Denied as**

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

30. The codon-optimization programs known by October 23, 2012 applied different criteria to select codons to generate a codon-optimized nucleic acid sequence. Ex. 2015, Bailey Decl., ¶¶47-49, 62. **ToolGen's Response: Denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

31. Different codon-optimization programs known in the art by October 23, 2012 would have generated myriad different codon-optimized Cas9 nucleic acid sequences from the native S. pyogenes Cas9 nucleic acid (NC_002737.1) disclosed in ToolGen's P1. Ex. 2015, Bailey Decl., ¶¶47-49, 62-64; Ex. 2008, ToolGen's P1. **ToolGen's Response: Admitted that a POSA could have made "codon-optimized Cas9 nucleic acid sequences from the native S. pyogenes Cas9 nucleic acid (NC_002737.1) disclosed in ToolGen's P1" but otherwise denied as incomplete and to the extent it implies codon optimization could not be completed without undue experimentation.**

32. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is required for CRISPR-Cas9 to function in eukaryotic cells. Ex. 2012, 510 Appl. Pros. History, 8606:5-11 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.**

33. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is required for CRISPR-Cas9 to function in mammalian cells. Id., 8606:5-11 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.**

34. ToolGen argued during prosecution that a codon-optimization is unpredictable. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531 (Reply Br., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.**

35. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in eukaryotic cells due to alleged unpredictability in protein folding. *See, e.g., id*., 6895-6896 (Appeal Br., Jun. 13, 2018) *see also id.*, 6761-6762 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief and response to an office action.**

36. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in eukaryotic cells due to unpredictability in codon optimization. Id., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); see also id., 8531 (ReplyBr., Jan. 8, 2019); see also id., 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.**

37. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in mammalian cells due to unpredictability in protein folding. *See, e.g., id*., 6895-6896 (Appeal Br., Jun. 13, 2018) *see also id.*, 6761-6762 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief and response to an office action.**

38. ToolGen argued during prosecution that a codon-optimized nucleic acid is unlikely to express a functional Cas9 protein in mammalian cells due to unpredictability in codon

optimization. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531 (ReplyBr., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.**

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

40. A skilled artisan reading its P1 would not have been able to know or predict which of the myriad Cas9 nucleic acid sequences reconstituted using human codon-usage tables known by October 23, 2012 would express a functional Cas9 protein in eukaryotic cells. Ex. 2015, Bailey Decl., ¶¶60-61, 63-65; Ex. 2008, ToolGen's P1. **ToolGen's Response: Denied.**

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

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

43. ToolGen argued during prosecution that codon-optimized Cas9 nucleic acid is required for patentability of its involved claims. Ex. 2012, 510 Appl. Pros. History, 8604:24- 8605:25 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.**

44. ToolGen argued during prosecution that a codon-optimized Cas9 nucleic acid is required for CRISPR-Cas9 to function in its claimed invention. Id., 8606:5-11 (Oral Hr., Mar. 11, 2020). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Oral Hearing transcript.**

45. ToolGen argued during prosecution that not all codon-optimized Cas9 nucleic acids would be functional. *Id*., 6895-6896, 6899 (Appeal Br., Jun. 13, 2018); *see also id*., 8531(Reply Br., Jan. 8, 2019); *see also id.*, 6758, 6761-6762, 6767 (Resp., Mar. 3, 2017). **ToolGen's Response: Denied. The statement is inaccurate, incomplete, and taken out of context from a multi-page Appeal Brief, Reply Brief and response to an office action.**

ToolGen's Material Facts 46-88 (with CVC's Reponses)

46. Count 1 does not require a codon-optimized nucleic acid encoding Cas9. Paper 1, 5-7. **CVC's Response: Denied with respect to the scope of admissible proofs on priority ToolGen may submit in view of judicial estoppel and party admission doctrines.**

47. The CVC half of Count 1 does not require a nucleic acid encoding Cas9 or a codon-optimized nucleic acid encoding Cas9. Paper 1, 5-7; Ex. 1550, 124:18-125:1. **CVC's Response: Denied with respect to the scope of admissible proofs on priority ToolGen may submit in view of judicial estoppel and party admission doctrines.**

48. Count 1 does not include the word "enhanced." Paper 1, 5-7. **CVC's Response: Admitted.**

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

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

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

52. ToolGen's P1 does not need to show a codon-optimized nucleic acid encoding Cas9 that results in "enhanced" expression of the Cas9 protein compared to the wild type to show a constructive reduction to practice of Count 1. Ex. 1403 (Cullen Decl.), ¶¶208-210; Paper 1, 5-7. **CVC's Response: Denied on the basis of judicial estoppel and party admission doctrines.**

53. ToolGen's P1 describes a codon-optimized nucleic acid encoding Cas9 that cleaves DNA in a eukaryotic cell. Ex. 2008 (ToolGen's P1), 5-13; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196. **CVC's Response: Denied on the basis of judicial estoppel and party admission doctrines.**

54. CVC's half of Count 1 requires a Cas9 protein or a nucleic acid encoding Cas9. Paper 1, 6. **CVC's Response: Denied with respect to the scope of admissible proofs on priority ToolGen may submit in view of judicial estoppel and party admission doctrines.**

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

56. ToolGen's P1 provides three working examples of the successful use of CRISPR/Cas9 in eukaryotic cells. Ex. 1403 (Cullen Decl.), ¶¶183-194. **CVC's Response: Admitted that ToolGen's P1 provides examples reporting testing the use of CRISPR-Cas9 in eukaryotic cells; otherwise denied.**

57. During prosecution, ToolGen stated that its "claimed invention is ***not obvious*** at least because one of ordinary skill in the art would have doubted whether a Type II CRISPR/Cas9 system could be introduced into a eukaryotic/mammalian cell without toxicity and whether, once introduced, could successfully bring about site-specific double-stranded breaks in a target nucleic acid sequence of the cell." Ex. 2012, 6769 (emphasis in original), 6883, 6896, 8529-8530. **CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6769; otherwise denied.**

58. During prosecution, ToolGen stated that the Examiner offered "only conclusory statements regarding reasonable expectation of success that incorrectly focus[ed] on whether one of ordinary skill in the art would have expected to successfully codon-optimize Cas9 and/or add

an NLS to it[,]" which "fail as a matter of law." Ex. 2012, 6769. **CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6769; otherwise denied.**

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

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

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

62. In prosecution, Dr. Cullen's statements were about the state of the art without the benefit of ToolGen's P1 Disclosure. Ex. 1403 (Cullen Decl.), ¶¶170, 198-200; Ex. 2012, 5645-5654, ¶¶16-18, 29-40 (2016 Cullen Decl.). **CVC's Response: Admitted that Dr. Cullen's prosecution statements that codon optimization had unpredictable effects were about the state of the art before the filing date of ToolGen's P1.**

63. P1's working examples used a Cas9-coding sequence reconstituted using the human codon usage table to express a Cas9 protein. Ex. 2008, 11; Ex. 1403 (Cullen Decl.), ¶¶164, 176-196, 207. **CVC's Response: Admitted that P1 (Ex. 2008, 11) states that "[t]he Cas9-coding sequence (4,104 bp), derived from *Streptococcus pyogenes* strain M1 GAS (NC_002737.1), was reconstituted using the human codon usage table."**

64. ToolGen's P1 discloses the well-known S. pyogenes Cas9 sequence as the sequence being codon-optimized for use in its working examples, and POSA would have understood the

specific Cas9 sequence based on ToolGen's P1 in view of the references known to a POSA. Ex. 1403 (Cullen Decl.), ¶¶176-182; Ex. 2008, 11; see also CVC Substantive Motion 1, Paper 368, 23:24-24:1; Ex. 2013 (Doyon Decl.), ¶150. **CVC's Response: Denied.**

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

66. During prosecution, ToolGen stated that it "was the first to engineer a Type II CRISPR/Cas system to successfully introduce site-specific, double-stranded breaks in target sequences of mammalian cells." Ex. 2012, 6868 (Appeal Brief). **CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6868; otherwise denied.**

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

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

> The Examiner either summarily dismissed or failed to address the evidence presented by Applicant in the Cullen Declaration, showing that one of ordinary skill in the art would not have had a reasonable expectation of success, based on [CVC's] '797 Pl/P2, Gustafsson and Chiu, for a method of introducing a site-specific, double-

> stranded break at a target nucleic acid sequence in a mammalian cell using a Type II CRISPR/Cas system."

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6893; otherwise denied.

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6894; otherwise denied.

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

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 5646; otherwise denied.

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 6895-96; otherwise denied.

72. In prosecution, Dr. Cullen stated that his primary concerns were related to the differences between prokaryotic and eukaryotic environments and that codon optimization can affect protein

folding: "[T]he importance of native codon organization to proper folding was known by one of ordinary skill in the art by October 23, 2012." Ex. 2012, 5653-5654, ¶39-40 (2016 Cullen Decl.).

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 5653-54; otherwise denied.

73. During prosecution, ToolGen stated:

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

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 5653-54; otherwise denied.

74. During prosecution, Dr. Cullen stated that a POSA would have appreciated that "codon optimization of a nucleic acid encoding Cas9 could result in a Cas9 exhibiting inactive or aberrant function, likely due to inappropriate Cas9 folding. So, the failure to successfully use a Type II CRISPR/Cas9 in a eukaryotic cell [and] the expectation of success at the time would have been diminished even further." Ex. 2012, 5654, ¶40 (2016 Cullen Decl.); Ex. 1403 (Cullen Decl.), ¶201. **CVC's Response: Admitted that Ex. 2012, 5654, ¶ 40 stated that "codon optimization of a nucleic acid encoding Cas9 could result in a Cas9 exhibiting inactive or aberrant function, likely due to inappropriate Cas9 folding, and, as such, failure to successfully use a Type II CRISPR/Cas9 in a eukaryotic cell. In situations where Cas9 was both NLS-tagged and its expression was codon-optimized, the expectation of success at the time would have been diminished even further." Otherwise, denied.**

75. During prosecution, Dr. Cullen stated that the references used by the Examiner to show codon optimization "serve as verifications that . . . the technique of codon optimization [was] known by October 23, 2012." Ex. 2012, 5646, ¶17 (2016 Cullen Decl.). **CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 5646; otherwise denied.**

76. During prosecution, Dr. Cullen stated:

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

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 5646; otherwise denied.

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

CVC's Response: Denied.

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 8638; otherwise denied.

79. At the time ToolGen's P1 was filed, a POSA would understand that reconstitution of a sequence using a human codon usage table is codon optimization. Ex. 1403 (Cullen Decl.),

¶¶173, 176; Ex. 1550 (Bailey Tr.), 108:7-10; Ex. 2015 (Bailey Decl.) ¶¶38-49. **CVC's Response: Denied.**

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

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

CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2012, 8645; otherwise denied.

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

CVC's Response: Denied.

82. Dr. Bailey was provided assumptions that a POSA would believe to be true by CVC's lawyers and was instructed not to answer questions about the basis for any of these assumptions. Mot. 11:19-20; Ex. 2015 (Bailey Decl.), ¶38; Ex. 1550 (Bailey Tr.), 102:11-105:7. **CVC's Response: Admitted that Dr. Bailey was provided assumptions as described in his declaration, and was instructed not to reveal the substance of privileged communications with counsel; otherwise denied.**

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

84. At the time ToolGen's P1 was filed, a POSA would know "codon-optimization was a well-known, routine technique that was used frequently and successfully in the field to achieve enhanced protein expression of a foreign gene." Ex. 2015 (Bailey Decl.), ¶63, n.1. **CVC's Response: Admitted to the extent that the quoted words appear at Ex. 2015, ¶ 38, n1; otherwise denied.**

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

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

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

known, routine technique in the art before the filing date of ToolGen's P1; otherwise denied.

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

CVC's Additional Material Facts 89-94

89. ToolGen admits that its prosecution statements about codon optimization "were about its pending claims that included, *inter alia*, a codon optimization limitation." Opp., 6:17-19.

90. Dr. Cullen does not deny that ToolGen argued during prosecution that codon optimization is required for CRISPR-Cas9 to function in eukaryotic cells. Ex. 1403, ¶ 206.

91. ToolGen agrees that during prosecution it distinguished its claimed invention from the prior art based on codon optimization. Opp., 7:9-12.

92. ToolGen admits that it and Dr. Cullen argued during prosecution that it was unpredictable in the art before P1's filing to obtain a functional Cas9 protein in eukaryotic cells from a codon-optimized nucleic acid. Opp., 10:12-11:2, 11:32-12:1; Ex. 1403, ¶¶ 201, 204.

93. Dr. Cullen admits that enhanced protein expression is a goal for codon optimization, which he believes was unpredictable to achieve. Ex. 1403, ¶¶ 171, 172; Ex. 2538, 51:6-22.

94. Dr. Cullen testified that "codon optimization is a technique that certainly seeks to enhance protein expression, but of course there is no guarantee that it will work" and he applied this understanding when he submitted his prosecution 2016 declaration. Ex. 2538, 51:6-52:5.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **CVC REPLY 2 (to deny ToolGen P1 benefit)** and the related exhibits were filed via the Interference Web Portal by 8:00 PM Eastern Time on August 27, 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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