

Filed on behalf of: **Junior Party, Broad**

Paper No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF
TECHNOLOGY, and PRESIDENT AND FELLOWS OF
HARVARD COLLEGE,

Patents 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356;
8,889,418; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; and
9,840,713; and Applications 14/704,551 and 15/330,876,

Junior Party,

v.

TOOLGEN, INC.,
Application 14/685,510,

Senior Party.

Patent Interference No. 106,126 (DK)
(Technology Center 1600)

BROAD OPPOSITION 1

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1 **I. PRECISE RELIEF REQUESTED**

2 Junior Party, The Broad Institute, Inc.; Massachusetts Institute of Technology; and
3 President and Fellows of Harvard College (collectively “Broad”) respectfully request that the
4 PTAB defer Senior Party ToolGen, Inc.’s (“ToolGen”) contingent Motion 1 for benefit of U.S.
5 Provisional Appl. No. 61/837,481, filed June 20, 2013 (“P3”) (Ex. 1003) or alternatively,
6 International Appl. No. PCT/KR2013/009488, filed Oct. 23, 2013 (“PCT”) (Exs. 1004-1005).

7 The PTAB has accorded ToolGen priority to its P1 application (U.S. Provisional Appl. No.
8 61/717,324, filed October 23, 2012 (“P1”) (Ex. 1001)), and Broad has not requested to nor filed
9 any motion challenging priority to P1 to date. As such, whether ToolGen is entitled to benefit of
10 its *later-filed* P3 or PCT (*i.e.*, the relief sought in ToolGen’s present Motion) is completely
11 irrelevant at this time. Priority to P3 or the PCT may be potentially relevant only if multiple
12 contingencies in this and other proceedings—that may or may not ever come to pass—do actually
13 arise. These contingencies potentially include that: 1) the PTAB finds ToolGen is not entitled to
14 the benefit of its P1 application in the co-pending 127 Interference, 2) Broad requests and is
15 granted permission to file a motion here challenging ToolGen’s benefit to P1 on the basis of
16 estoppel from that determination in the 127 Interference, and 3) the PTAB grants Broad’s motion,
17 depriving ToolGen here of benefit of its P1. Only then would the question of benefit to P3 or the
18 PCT potentially become relevant, and even this is far from certain.

19 Substantively ruling on ToolGen’s highly contingent motion at this time would waste
20 judicial resources and result in an advisory opinion. 37 C.F.R. § 41.125 provides the PTAB with
21 discretion to determine the order in which motions will be considered, including deferring
22 consideration of a motion. Deferral is proper here. The PTAB should decline to rule on ToolGen’s
23 motion unless and until the multiple contingencies upon which its relevance is based actually arise.

1 **II. DESCRIPTION OF APPENDICES**

2 Appendix A is a List of Exhibits Cited, Appendix B is the Statement of Material Facts and
3 Broad’s Response to ToolGen’s Statement of Material Facts.

4 **III. ARGUMENT**

5 37 C.F.R. § 41.125 provides that the PTAB “may take up motions for decisions in any
6 order, may grant, deny, or dismiss any motion, and may take such other action appropriate to
7 secure the just, speedy, and inexpensive determination of the proceeding.” It further provides that
8 the PTAB may defer a motion to a later point in the proceeding: “A decision on a motion may
9 include deferral of action on an issue until a later point in the proceeding.” 37 C.F.R. § 41.125; *see*
10 *also Berman v. Housey*, 291 F.3d 1345, 1352 (Fed. Cir. 2002) (referring to this as a “sound rule”).
11 In adopting this rule, the PTAB explained that “efficient allocation of Office resources might
12 require deferral of a motion... [g]iven the great cost of contested cases for both parties and the
13 Office.” Ex. 2302 (Rules of Practice Before the BPAI, 68 FR 66648-01). The PTAB further
14 explained that “[n]othing in the rule bars or should even be viewed as discouraging parties from
15 letting the Board know of a party’s opinion on the order in which issues should be considered.”
16 *Id.*

17 The PTAB should defer action on ToolGen Motion 1 under 37 C.F.R. § 41.125 because
18 the multiple contingencies on which the relevance of ToolGen’s motion is based have not yet come
19 to pass and may never come to pass. The PTAB has not yet ruled on—much less granted—CVC’s
20 motion attacking ToolGen’s benefit to P1 in the 127 Interference, and no motion challenging
21 benefit to ToolGen P1 has yet been requested, filed, or granted in this Interference. Unless these
22 contingencies come to pass or ToolGen otherwise loses its benefit to P1, the PTAB would be
23 issuing an advisory opinion on benefit to P3 or the PCT, as ToolGen’s current priority to P1 renders
24 any priority to P3 or the PCT irrelevant at this time.

1 Indeed, at the initial hearing to authorize motions, Judge Katz noted in discussing the
2 current motion that ToolGen was already accorded benefit to its P1. Transcript, Paper 19, 19:9-25.
3 Despite Broad representing that it was not seeking to attack the benefit of P1 through a motion at
4 this time (*id.* at 12:15-12),¹ ToolGen indicated it still sought to file the present motion because it
5 was concerned with the 127 Interference, where CVC is challenging P1 (*id.* at 19:22-20:5). In
6 response to the PTAB’s questioning, ToolGen admitted the present motion was contingent on an
7 attack on P1: “I guess you can consider it a contingent motion, yes.” *Id.* at 20:8-9. Accordingly, in
8 its Order on Motions, the PTAB granted authorization to ToolGen on the basis that its motion was
9 contingent: “ToolGen indicated that this motion would be contingent upon the grant of a motion
10 by Broad to attack the benefit of the filing date of ToolGen’s earlier provisional application
11 61/717,324 accorded to ToolGen upon declaration.” Paper 20 at 7:10-13 (citing Paper 19 at 19:22–
12 20:9).

13 Presumably, ToolGen believes that if it loses its benefit to P1 in the 127 Interference (a
14 contingency that has not and may not arise), then Broad will request to, be authorized to, and file
15 a motion attacking ToolGen’s priority to P1 in this Interference (another contingency that has not
16 and may never arise). Then, the PTAB may grant Broad’s motion (yet another contingency that
17 has not and may never arise), at which point ToolGen’s potential benefit to P3 or the PCT would
18 potentially become relevant. The highly contingent relevance of the benefit to P3 or the PCT shows
19 there is no reason for the PTAB to act on ToolGen’s motion at this time.

¹ Broad preserved the right to bring a motion at an appropriate time based on estoppel if there is a decision in the 127 Interference impacting ToolGen’s benefit to P1. Transcript, Paper 19, 35:14-36:8.

1 Moreover, piling on yet another contingency, if Broad prevails on priority in the co-
2 pending 115 Interference, then the question of whether ToolGen is entitled to priority of its P3 or
3 PCT may *never* become relevant. This is because ToolGen will be unable to beat Broad’s dates of
4 [REDACTED]

5 [REDACTED]
6 [REDACTED]
7 [REDACTED]

8 [REDACTED] As ToolGen itself has
9 argued to the Patent Office the *only thing* that could provide a reasonable expectation of success
10 that CRISPR-Cas9 could work in a eukaryotic cell is demonstration of successfully using the
11 system in a eukaryotic cell:

12 Rather, the *only thing* that would have alleviated the unpredictability in the art
13 and allayed the concerns of one of ordinary skill at this time would have been the
14 *actual demonstration of a Type II Cas9 system successfully introducing site-*
15 *specific double-stranded breaks in a target nucleic acid sequence within a*
16 *eukaryotic, e.g., mammalian, cell....*

17 Ex. 2072 (2015 Response and Amendment) (emphases added). Thus, as ToolGen admits, one
18 cannot have a complete conception of the invention of Count 1—including the requisite
19 expectation of success—before conducting successful work using CRISPR-Cas9 in a eukaryotic
20 cell. *See Hitzeman v. Rutter*, 243 F.3d 1345, 1357-58 (Fed. Cir. 2001) (conception in an
21 unpredictable biological art requires a reasonable expectation of success). [REDACTED]

22 [REDACTED]
23 [REDACTED]

24 [REDACTED]. Thus, if Broad is awarded priority in the 115 Interference [REDACTED]

1 [REDACTED], ToolGen cannot win this Interference regardless of whether its earliest priority
2 application is P1, P3, or the PCT.²

3 Thus, should Broad prevail in the 115 Interference, it is unlikely Broad would need to
4 attack ToolGen’s benefit to P1 at all, because Broad can establish priority to Count 1 [REDACTED]
5 [REDACTED] regardless of whether ToolGen is entitled to benefit of P1, P3, or the PCT.
6 And it is well-established that once the PTAB has determined priority in an interference, it has
7 discretion to terminate the interference without further action on pending motions. *See In re*
8 *Sullivan*, 362 F.3d 1324, 1327 (Fed. Cir. 2004); *In re Sullivan*, 84 F. App’x 86, 88 (Fed. Cir. 2003)
9 (“[T]he statute mandates only that the issue of priority be decided; the Board has discretion to
10 terminate an interference once priority is determined.”). ToolGen’s present motion would be
11 mooted if the PTAB awarded Broad priority, and the PTAB could then terminate the Interference
12 without ruling on benefit to P3 or the PCT.

13 In sum, ToolGen’s motion is premature because its relevance depends on multiple
14 contingencies that may or may not arise. Deferral under 37 C.F.R. § 41.125 is the proper course
15 and will help “secure the just, speedy, and inexpensive determination of the interference.” *Berman*,
16 291 F.3d at 1352.

17 **IV. CONCLUSION**

18 For the foregoing reasons, the PTAB should defer ruling on ToolGen’s Motion 1.

² Should Broad be awarded priority in the 115 Interference, Broad respectfully submits that the PTAB should issue an Order to Show Cause to ToolGen as to why priority should not be awarded to Broad here. *See In re Sullivan*, 362 F.3d at 1326 (Board can *sua sponte* issue show cause order).

1 Dated: August 6, 2021
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APPENDIX A: LIST OF EXHIBITS CITED

EX.	DESCRIPTION
1001	U.S. Provisional Application No. 61/717,324, filed October 23, 2012.
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.
1005	International Publication WO 2014/065596 A1, published on May 1, 2014.
2072	Excerpt of U.S. Patent Application 14/685,510, Kim et al., April 13, 2015 (the '510 Application)
2302	Rules of Practice Before the Board of Patent Appeals and Interferences, 68 Fed. Reg. 66648-01.

1 **APPENDIX B: TO STATEMENT OF MATERIAL FACTS**

2 **Broad's Responses to ToolGen's Material Facts:**

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

5 **RESPONSE:** Admitted.

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

8 **RESPONSE:** Admitted.

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

11 **RESPONSE:** Admitted.

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

15 **RESPONSE:** Admitted.

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

18 **RESPONSE:** Admitted.

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

21 **RESPONSE:** Admitted.

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

1 **RESPONSE:** Admitted.

2 8. Each of PCT and the '510 Application was timely filed in accordance with 35 U.S.C.
3 §§ 119-120. F5-7.

4 **RESPONSE:** Admitted.

5 9. The specification of the '510 Application states that “the entire contents of each” of P1, P2,
6 P3, and PCT “are incorporated herein by reference.” Ex. 1006, 15.

7 **RESPONSE:** Admitted.

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

10 **RESPONSE:** Denied.

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

13 **RESPONSE:** Denied.

14 12. Example 3 of P3 describes a Type II CRISPR-Cas system comprising a Cas9 protein and
15 a guide RNA. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402, ¶¶ 55-75.

16 **RESPONSE:** Denied.

17 13. Example 3 of P3 describes a guide RNA that targets and hybridizes to a target sequence
18 of a DNA molecule in a eukaryotic cell, wherein the guide RNA comprises a guide sequence
19 fused to a tracr sequence. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 69-75,
20 114-18.

21 **RESPONSE:** Denied.

1 14. Example 3 of P3 describes a CRISPR/Cas9 system targeting a DNA molecule in a
2 eukaryotic cell, wherein the DNA molecule encodes, and the eukaryotic cell expresses, a gene
3 product. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 69-80.

4 **RESPONSE:** Denied.

5 15. Example 3 of P3 describes a CRISPR/Cas9 system in which the Cas9 protein cleaves a
6 target DNA molecule in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402, ¶¶ 81-90.

7 **RESPONSE:** Denied.

8 16. Example 3 of P3 describes a CRISPR/Cas9 system in which the Cas9 protein cleaves a
9 target DNA resulting in altered expression of a gene product encoded by the target DNA in a
10 eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 91-108.

11 **RESPONSE:** Denied.

12 17. Example 3 of P3 describes how to make a single-chain guide RNA (“sgRNA”) that targets
13 a sequence of a DNA molecule. Ex. 1003, 36-37, 63 (Fig. 5(a)); *id.* at 10-13, 28; Ex. 1402, ¶ 74.

14 **RESPONSE:** Denied.

15 18. Example 3 of P3 describes how to use an sgRNA that targets a sequence of a DNA
16 molecule in a eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶ 74.

17 **RESPONSE:** Denied.

18 19. Before June 20, 2013, the Cas9-encoding sequence derived from *Streptococcus pyogenes*
19 strain M1 GAS (NC_002737.1) was known. Ex. 1203; Ex. 1204; Ex. 1402, ¶¶ 27, 43-45.

20 **RESPONSE:** Admitted.

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

1 **RESPONSE:** Admitted.

2 21. P3 describes that the Cas9 protein in the Type II CRISPR-Cas9 system can be Cas9 from
3 *S. pyogenes*. Ex. 1003, 36-37; *see also id.* at 9-10, 26; Ex. 1402, ¶¶ 27, 43-45, 64-68.

4 **RESPONSE:** Admitted to the extent that P3 refers to a Cas9 from *S. pyogenes*.

5 22. P3 describes how to make a recombinant Cas9 protein, with a nuclear localization signal
6 (“NLS”) attached. Ex. 1003, 36-37; *see also id.* at 9-10, 26; Ex. 1402, ¶¶ 27, 43-45, 64-68.

7 **RESPONSE:** Denied.

8 23. P3 describes how to make an mRNA encoding Cas9 protein with an NLS, including codon
9 optimization. Ex. 1003, 36-37; *see also id.* at 9-10, 26; Ex. 1402, ¶¶ 27, 43-45, 64-68.

10 **RESPONSE:** Denied.

11 24. P3 describes how to use a recombinant Cas9 protein or mRNA encoding the Cas9 protein
12 with an sgRNA that targets and hybridizes to a target sequence of a DNA molecule in a
13 eukaryotic cell. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 64-68.

14 **RESPONSE:** Denied.

15 25. Example 3 of P3 describes that *Cas9* mRNA and sgRNA can be delivered into a mouse
16 embryo cell by microinjection. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402 ¶¶ 64-75.

17 **RESPONSE:** Admitted to the extent that P3 refers to *Cas9* mRNA and sgRNA that can
18 allegedly be delivered into a mouse embryo cell by microinjection; otherwise denied.

19 26. Example 3 of P3 describes the cleavage of a target DNA molecule by a Cas9 protein in
20 mouse embryo cells after the injection of *Cas9* mRNA and sgRNA, resulting in altered
21 expression of a gene product in mouse cells. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402, ¶¶ 81-
22 108.

23 **RESPONSE:** Denied.

1 27. Example 3 of P3 describes that a recombinant Cas9 protein and sgRNA can be delivered
2 into a mouse embryo cell by microinjection. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402, ¶¶ 64-75.

3 **RESPONSE:** Admitted to the extent that P3 refers to a recombinant Cas9 protein and
4 sgRNA that allegedly can be delivered into a mouse embryo cell by microinjection; otherwise
5 denied.

6 28. Example 3 of P3 describes the cleavage of a target DNA molecule by a Cas9 protein in
7 mouse embryo cells after injection of a recombinant Cas9 protein and sgRNA, resulting in
8 altered expression of a gene product in mouse cells. Ex. 1003, 22-24, 36-45, 63-65; Ex. 1402,
9 ¶¶ 81-108.

10 **RESPONSE:** Denied.

11 29. Example 3 of P3, including Figure 5(a), discloses that an sgRNA complexed with a Cas9
12 protein cleaved a target DNA molecule in Exon 2 of the *Foxn1* gene. Ex. 1003, 22-24, 36-45,
13 63- 65; Ex. 1402, ¶¶ 81-108.

14 **RESPONSE:** Denied.

15 30. Examples 3 and 4 of PCT each describe a Type II CRISPR-Cas system comprising a Cas9
16 protein and a guide RNA. Ex. 1004, 13-16, 37-52, 81-86, 90-91; Ex. 1402, ¶¶ 138-75.

17 **RESPONSE:** Denied.

18 31. Examples 3 and 4 of PCT each describe a guide RNA that targets and hybridizes to a target
19 sequence of a DNA molecule in a eukaryotic cell, wherein the guide RNA comprises a guide
20 sequence fused to a tracr sequence. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (e.g., Fig. 5(a)); Ex. 1402,
21 ¶¶ 161-75, 237-44.

22 **RESPONSE:** Denied.

1 32. Examples 3 and 4 of PCT each describe a CRISPR/Cas9 system targeting a DNA molecule
2 in a eukaryotic cell, wherein the DNA molecule encodes, and the eukaryotic cell expresses, a
3 gene product. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 161-83.

4 **RESPONSE:** Denied.

5 33. Examples 3 and 4 of PCT each describe a CRISPR/Cas9 system in which the Cas9 protein
6 cleaves a target DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*,
7 Fig. 5(a)); Ex. 1402, ¶¶ 184-98.

8 **RESPONSE:** Denied.

9 34. Examples 3 and 4 of PCT each describe a CRISPR/Cas9 system in which the Cas9 protein
10 cleaves a target DNA resulting in altered expression of a gene product encoded by the target
11 DNA in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶
12 199-228.

13 **RESPONSE:** Denied.

14 35. PCT describes how to make an sgRNA that targets a sequence of a DNA molecule.
15 Ex. 1004, 37-39, 81 (*e.g.*, Fig. 5(a)); *see also id.* at 22-23, 32; Ex. 1402, ¶¶ 166, 174.

16 **RESPONSE:** Denied.

17 36. Examples 3 and 4 of PCT each describe how to use an sgRNA that targets a sequence of a
18 DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*, Fig. 5(a)); Ex.
19 1402, ¶¶ 166, 174.

20 **RESPONSE:** Denied.

21 37. PCT describes that the Cas9 protein in the Type II CRISPR-Cas9 system can be Cas9 from
22 *S. pyogenes*. Ex. 1004, 22, 31, 38, 130-33, 160-83; Ex. 1402, ¶¶ 27, 122-25, 154-59.

23 **RESPONSE:** Denied.

1 38. PCT describes how to make a recombinant Cas9 protein, with an NLS attached. Ex. 1004,
2 37-38; *see also id.* at 22, 31, 130-33, 160-83; Ex. 1402, ¶¶ 27, 122-25, 154-59.

3 **RESPONSE:** Denied.

4 39. PCT describes how to make an mRNA encoding Cas9 protein with an NLS, including
5 codon optimization. Ex. 1004, 22, 31, 37-38, 130-33, 160-83; Ex. 1402, ¶¶ 27, 122-25, 154-59.

6 **RESPONSE:** Denied.

7 40. Examples 3 and 4 of PCT each describe how to use a recombinant Cas9 protein or mRNA
8 encoding the Cas9 protein with an sgRNA that targets and hybridizes to a target sequence of a
9 DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*, Fig. 5(a));
10 Ex. 1402, ¶¶ 154-59.

11 **RESPONSE:** Denied.

12 41. Example 3 of PCT describes that *Cas9* mRNA and sgRNA can be delivered into a mouse
13 embryo cell by microinjection. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1402, ¶¶ 153-75.

14 **RESPONSE:** Denied.

15 42. Example 3 of PCT describes the cleavage of a target DNA molecule by a Cas9 protein in
16 mouse embryo cells after the injection of *Cas9* mRNA and sgRNA, resulting in altered expression
17 of a gene product in mouse cells. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1402, ¶¶ 184-228.

18 **RESPONSE:** Denied.

19 43. Example 3 of PCT describes that a recombinant Cas9 protein and sgRNA can be delivered
20 into a mouse embryo cell by microinjection. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1402, ¶¶ 153-75.

21 **RESPONSE:** Denied.

22 44. Example 3 of PCT describes cleavage of a target DNA molecule by a Cas9 protein in mouse
23 embryo cells after injection of a recombinant Cas9 protein and sgRNA, resulting in altered

1 expression of a gene product in mouse cells. Ex. 1004, 13-16, 37-50, 81-86; Ex. 1402, ¶¶ 184-
2 228.

3 **RESPONSE:** Denied.

4 45. Example 3 of PCT, including Figure 5(a), discloses that an sgRNA complexed with a Cas9
5 protein to cleave a target DNA molecule in Exon 2 of the *Foxn1* gene. Ex. 1004, 13-16, 37-50,
6 81-86; Ex. 1402, ¶¶ 184-228.

7 **RESPONSE:** Denied.

8 46. The mouse embryo cells described in Example 3 of P3 and PCT are eukaryotic cells that
9 contain the *Foxn1* gene that encodes a gene product, the forkhead box N1 (Foxn1) protein. Ex.
10 1003, 36-45; Ex. 1004, 37-50; Ex. 1402, ¶¶ 70-71, 162-63.

11 **RESPONSE:** Denied.

12 47. Exon 2 of the *Foxn1* gene described in Example 3 of P3 and PCT is a DNA molecule in
13 mouse embryo cells. Ex. 1003, 36-45; Ex. 1004, 37-50; Ex. 1402, ¶¶ 70-71, 162-63.

14 **RESPONSE:** Denied.

15 48. Figure 5(a) of P3 and PCT depicts Exon 2 of the *Foxn1* gene as containing a target sequence
16 of a DNA molecule. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1402, ¶¶
17 70-71, 162-63.

18 **RESPONSE:** Denied.

19 49. The sgRNAs described in Example 3 of P3 and PCT are engineered, programmable, and
20 non-naturally occurring. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1402 ¶¶ 55-
21 63, 109-113, 139-45, 230-32.

22 **RESPONSE:** Denied.

1 50. Figure 5(a) of P3 and PCT depicts an sgRNA that is a guide RNA that targets and
2 hybridizes to a target sequence of a DNA molecule. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-
3 50 & Fig. 5(a); Ex. 1402, ¶¶ 72, 164.

4 **RESPONSE:** Denied.

5 51. Figure 5(a) of P3 and PCT depicts an sgRNA containing a sequence complementary to,
6 and that targets and hybridizes to, a 20-nucleotide (“nt”) sequence from Exon 2 of the *Foxn1* gene
7 in mice. Ex. 1003, 36-45 & Fig. 5(a); Ex. 1004, 37-50 & Fig. 5(a); Ex. 1402, ¶¶ 72, 164.

8 **RESPONSE:** Denied.

9 52. Figure 5(a) of P3 and PCT depicts an sgRNA containing intervening nucleotides linking
10 two portions of the sgRNA (the guide sequence and the tracr sequence) to each other. Ex. 1003,
11 Fig. 5(a); Ex. 1004, Fig. 5(a); Ex. 1402, ¶¶ 72, 115, 164, 238.

12 **RESPONSE:** Denied.

13 53. Figure 5(a) of P3 and PCT depicts an sgRNA capable of forming a double-stranded RNA
14 duplex. Ex. 1003, Fig. 5(a); Ex. 1004, Fig. 5(a); Ex. 1402, ¶¶ 115, 238.

15 **RESPONSE:** Denied.

16 54. Figure 5(a) of P3 and PCT depicts a CRISPR/Cas9 system comprising a Cas9 protein and
17 an sgRNA targeting a target sequence in a DNA molecule. Ex. 1003, Fig. 5(a); Ex. 1004, Fig. 5(a);
18 Ex. 1402, ¶¶ 55-75, 139-45, 154-56, 162-66.

19 **RESPONSE:** Denied.

20 55. Figures 5(c), 6(c) and 7(c), and Table 7 of P3 and PCT depicts cleavage and editing of a
21 sequence in Exon 2 of the *Foxn1* gene. Ex. 1003, 36-45; Ex. 1004; Ex. 1402, ¶¶ 82-87, 185-90.

22 **RESPONSE:** Denied.

1 56. Figures 5(c), 6(c) and 7(c), and Table 7 of P3 and PCT depicts cleavage and editing of a
2 sequence in Exon 2 of the *Foxn1* gene resulting in altered expression of a gene product. Ex.
3 1003, 36-45; Ex. 1004; Ex. 1402, ¶¶ 82-87, 92-105, 185-90, 200-13.

4 **RESPONSE:** Denied.

5 57. Example 4 of PCT describes that a recombinant Cas9 protein and sgRNA can be delivered
6 into a protoplast cell of Arabidopsis by transfection. Ex. 1004, 50-52; Ex. 1402, ¶¶ 159, 174.

7 **RESPONSE:** Denied.

8 58. Example 4 of PCT describes the cleavage of a target DNA molecule by a Cas9 protein in
9 plant protoplast cells after the transfection of a recombinant Cas9 protein and sgRNA, resulting
10 in altered expression of a gene product in plant cells. Ex. 1004, 50-52, 90-91 (*e.g.*, Fig. 12); Ex.
11 1402, ¶¶ 193-97, 216-27.

12 **RESPONSE:** Denied.

13 59. The Arabidopsis protoplast cells described in Example 4 of PCT are eukaryotic cells that
14 contain the *BRI1* gene. Ex. 1004, 50-52, 90-91; Ex. 1402, ¶¶ 167-68.

15 **RESPONSE:** Denied.

16 60. The *BRI1* gene described in Example 4 of PCT is a DNA molecule in Arabidopsis
17 protoplast cells. Ex. 1004, 50-52, 90-91; Ex. 1402, ¶¶ 167-68.

18 **RESPONSE:** Denied.

19 61. The sgRNAs described in Example 4 of PCT are engineered, programmable, and non-
20 naturally occurring. Ex. 1004, 50-52; Ex. 1402, ¶¶ 146-51.

21 **RESPONSE:** Denied.

1 62. The sgRNAs described in Example 4 of PCT contain a sequence complementary to, and
2 that targets and hybridizes to, a 20-nt sequence from an exon of the *BRII* gene in protoplast
3 cells. Ex. 1004, 50-52; Ex. 1402, ¶¶ 170-72.

4 **RESPONSE:** Denied.

5 63. The sgRNAs described in Example 4 of PCT contain intervening nucleotides linking two
6 portions of the sgRNA (the guide sequence and the tracr sequence) to each other. Ex. 1004, 50-
7 52; Ex. 1402, ¶¶ 170-72, 241.

8 **RESPONSE:** Denied.

9 64. The sgRNAs described in Example 4 of PCT are capable of forming a double-stranded
10 RNA duplex. Ex. 1004, 50-52; Ex. 1402, ¶ 241.

11 **RESPONSE:** Denied.

12 65. Example 3's CRISPR/Cas9 systems are programmable because the sequence of the
13 sgRNA can be adjusted to target different sequences in Exon 2 of the mouse *Foxn1* gene. Ex.
14 1003, 37; Ex. 1004, 32-33; Ex. 1402, ¶¶ 60, 143.

15 **RESPONSE:** Denied.

16 66. Example 4's CRISPR/Cas9 systems are programmable because the sequence of the
17 sgRNA can be adjusted to target different sequences in an exon of the *Arabidopsis BRII* gene.
18 Ex. 1004, 50-52, 91; Ex. 1402, ¶ 149.

19 **RESPONSE:** Denied.

20 67. Figure 12 of PCT depicts cleavage and editing of one or more sequences in the *BRII* gene
21 of *Arabidopsis* resulting in altered gene product expression. Ex. 1004, 50-52, 90-91; Ex. 1402,
22 ¶¶ 193-97, 216-27.

23 **RESPONSE:** Denied.

1 68. Each sgRNA described in Example 3 of P3 and PCT and in Example 4 of PCT is guide
2 RNA that targets and hybridizes to a target sequence of a DNA molecule. Ex. 1003, Figs. 5(a)
3 & 12; Ex. 1004, Fig. 5(a) & 12; Ex. 1402, ¶¶ 72, 164, 170-72.

4 **RESPONSE:** Denied.

5 69. Insertions or deletions of nucleotides from a DNA sequence in Exon 2 of the *Foxn1* gene
6 or from a DNA sequence in an exon of the *BRII* gene would cause altered gene product
7 expression. Ex. 1402, ¶¶ 92-105, 200-13, 216-25.

8 **RESPONSE:** Denied.

9 70. In Example 3 of P3 and PCT, CRISPR/Cas9 mediated cleavage and editing of a target
10 DNA sequence from Exon 2 of the *Foxn1* gene results in altered expression of the Foxn1 protein
11 (a gene product), because that gene product is expressed as a mutant and/or at low levels. Ex.
12 1402, ¶¶ 77, 82-87, 92-105, 177, 185-90, 200-13.

13 **RESPONSE:** Denied.

14 71. The eukaryotic Arabidopsis cells express a putative leucine-rich repeat (LRR) receptor
15 kinase (gene product) encoded by the *BRII* gene (DNA molecule). Ex. 1402, ¶¶ 134, 180.

16 **RESPONSE:** Denied.

17 72. In Example 4 of PCT, CRISPR/Cas9 mediated cleavage and editing of a target DNA
18 sequence from an exon of the *BRII* gene results in altered expression of the putative LRR
19 receptor kinase (a gene product), because that gene product is expressed as a mutant and/or at
20 low levels. Ex. 1402, ¶¶ 180-82, 193-97, 216-27.

21 **RESPONSE:** Denied.

1 73. Nonsense-mediated mRNA decay (“NMD”) destroys mRNA transcripts with premature
2 stop codons, which can result in entire mRNA transcripts being destroyed and only low levels of
3 a truncated protein being expressed. Exs. 1222-1224, 1226; Ex. 1402, ¶¶ 94, 202, 219.

4 **RESPONSE:** Denied.

5
6 **Broad’s Additional Material Facts:**

7 74. To date, Broad has not requested authorization to file a motion challenging ToolGen’s
8 priority to P1.

9 75. To date, Broad has not filed any motion challenging ToolGen’s priority to P1.

10 76. Broad preserved the right to bring at a motion at an appropriate time based on estoppel if
11 there is a decision in the 127 Interference impacting the benefit to P1. Transcript, Paper 19,
12 35:14-36:8. (“Your Honor, if I can raise one more issue, and that is we did look and see, you
13 know, the motions that were filed in 127 interference, and there are certain motions that are
14 sought there by CVC that could result, for example, in a determination of unpatentability on
15 grounds that are different than the ones we have alleged, and we just want to make sure that, you
16 know, we indicate that we're preserving rights to bring at an appropriate time a motion that might
17 be based upon estoppel if there are decisions contrary to the patentability of ToolGen's claims or
18 their benefit made in that additional interference as well.”)

CERTIFICATE OF FILING AND SERVICE

I hereby certify that on August 6, 2021, a true and complete copy of the foregoing **BROAD OPPOSITION 1** is being filed and served by 5:00 pm PT /8:00 pm ET via the Interference Web Portal and by agreement served by email on the Senior Party by 8:00 pm PT / 11:00 pm ET to:

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