Interference No. 106,126

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 BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND PRESIDENT AND FELLOWS OF HARVARD COLLEGE
Junior Party

Patent Nos. 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; 9,840,713; and Application Nos. 14/704,551 and 15/330,876

v.

TOOLGEN, INC.
Senior Party

Application 14/685,510

Patent Interference No. 106,126 (DK)

TOOLGEN, INC. REPLY 1
(for accorded benefit)

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OTHER AUTHORITIES

In its Opposition ("Opp."), Broad speculates as to various potential outcomes of this and other interferences, but loses sight of the single contingency to which ToolGen Substantive Motion 1 is subject. Motion 1 argues that ToolGen is entitled to the benefit of its P3 or PCT application *if* the Board grants a Broad motion attacking ToolGen's P1. Broad has not so moved (or otherwise attacked) ToolGen's P1. Thus, the sole contingency has not been met.

Broad's Opposition does not address the substantive merits of Motion 1, but asks only that the Board *defer* action because Motion 1 is based on "multiple contingencies" that "have not yet come to pass and may never come to pass." Opp. 2:17–19. But contingencies are the very nature of a contingent motion and do not warrant deferral. If the contingency here is not met when the Board decides motions, the Board should not *defer* but rather *dismiss* Motion 1 as moot. In the unlikely event that the contingency somehow becomes realized before the Board's decision on motions, the Board then should grant Motion 1, which is unopposed on the merits, without further briefing.

I. THE BOARD SHOULD DISMISS MOTION 1 AS MOOT IF THE CONTINGENCY DOES NOT OCCUR OR RULE ON THE MERITS IF THE CONTINGENCY DOES OCCUR BEFORE THE DECISION ON MOTIONS

A. The Board Should Dismiss, Not Defer, Motion 1 As Moot If the Contingency Does Not Occur Before the Decision On Motions Because Benefit Must Be Decided Before The Priority Phase

Motion 1 is contingent upon the grant of a motion by Broad attacking ToolGen's P1 application. *See* Motion 1, n. 1 ("This motion is contingent upon the Board finding ToolGen not entitled to the benefit of ToolGen P1."); Order Authorizing Motions and Setting Times, Paper 20 (hereinafter, "Order"), 7:10-15 ("On the conference call, ToolGen indicated that this motion would be contingent upon the grant of a motion by Broad to attack the benefit of the filing date of ToolGen's earlier provisional application 61/717,324 accorded to ToolGen upon declaration.

(Transcript, Paper 19, 19:22–20:9.) Authorization for this motion is GRANTED."); F77. Broad has not brought such a motion or made such an argument. F74, F75. Therefore, unless that changes, and it should not,[1] the Board should *dismiss* Motion 1 as moot because the contingency has not been met. The motion should not be "deferred" as Broad argues.

It is during the motions phase that the Board adjudicates accorded benefit, which determines the schedule and the burdens in the priority phase. The Board explained that "[i]n this phase of the interference, we authorize substantive motions that may change the original status quo of the interference, in order to set up a priority contest in the second phase, if one is necessary." Order, 2:13–16; *see also id.* 6:22–24 ("Thus, deciding these issues will prepare the proceeding for judgment on priority"); *see also Hum. Genome Scis., Inc. v. Genentech, Inc.*, 589 F. Supp. 2d 512, 514 (D. Del. 2008), dismissed, 368 F. App'x 116 (Fed. Cir. 2009) ("The first phase in an interference is the preliminary motions phase. [A] party may not raise any issue at a final hearing that was not, but could have been, raised by a preliminary motion…. Preliminary motions generally are filed to redefine the scope of a contested case, to change the benefit date accorded for the contested subject matter, or for judgment in the contested case. 37 C.F.R. § 41.121(a)(1)."). The issue that could have triggered the contingency and which is presented in Motion 1—ToolGen's accorded benefit—is an issue to be resolved before the priority phase.

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[1] Broad states that it "preserved the right" to bring at a motion "at an appropriate time" based on estoppel if there is a decision in the 127 Interference impacting ToolGen's benefit to P1. Opp. 3, n. 1. ToolGen disagrees. Broad could have, but did not, identify any such motion in its Motions List and therefore has not preserved any such right. *See* Standing Order, Paper 20, ¶ 204 ("All substantive and anticipated responsive motions must be listed on the motions list."); F78.

Broad presents no basis for why Motion 1 should be deferred past the motions phase other than because it is based on "multiple contingencies" that "have not yet come to pass and may never come to pass." Opp. 2:17–19. The response is that this is true of all contingent motions. Broad fails to identify any authority to support why the purported "contingencies" warrant *deferral* past the motions phase. While Broad appeals to the purported number of contingencies on which Motion 1 is based (Opp. 1:11–12, 22–23, 2:17–19, 3:15–17, 4:1–3, 5:13–14), there is only one contingency that triggers Motion 1: the Board granting a Broad motion attacking ToolGen's benefit to its P1 application. Order, 7:10-15.

All other Broad-stated "contingencies" are either speculative or irrelevant. For example, Broad argues at Opp. 5:3–5 that "should [it] prevail in the 115 Interference, it is unlikely Broad would need to attack ToolGen's benefit to P1 at all, because Broad can establish priority to Count 1 … regardless of whether ToolGen is entitled to benefit of P1, P3, or the PCT." The response is that ToolGen disagrees with Broad's premise and will demonstrate ToolGen's earlier priority at the appropriate time—during the priority phase—and in view of the parties' respective burdens of proof, which are determined at the end of the motions phase.

B. If The Contingency Occurs Before The Decision On Motions, The Board Should Rule On The Merits And Grant ToolGen's Motion 1, Because Broad Did Not Oppose On The Merits

Broad's Opposition requested only that the Board defer ruling on Motion 1, and failed to oppose Motion 1 on the merits. *See* Opp. 1:22–23 ("The PTAB should decline to rule on ToolGen's motion unless and until the multiple contingencies upon which its relevance is based actually arise."); *id.* 5:18 ("[T]he PTAB should defer ruling on ToolGen's Motion 1."). As such, subject to the contingency being met, ToolGen's Motion 1 stands unopposed on the merits. The Motion 1 briefing is complete. In the unlikely event the contingency becomes met and the Board

reaches Motion 1, the Board should grant Motion 1 for the reasons stated therein and without additional briefing.

II. CONCLUSION

For the foregoing reasons, the Board should dismiss Motion 1 as moot if the contingency is not met at the time of the decision on motions, or grant Motion 1 if the contingency is met at that time.

Respectfully submitted,

Dated: September 24, 2021

/Timothy J. Heverin/

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APPENDIX 1: STATEMENT OF MATERIAL FACTS

Senior Party ToolGen's Material Facts 1-73 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: Denied.

11. All of the disclosures of the PCT, incluing 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: Denied.

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

Response: Denied.

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

Response: Denied.

14. Example 3 of P3 describes a CRISPR/Cas9 system targeting a DNA molecule in a eukaryotic cell, wherein the DNA molecule encodes, and the eukaryotic cell expresses, a gene

product. Ex. 1003, 22-24, 36-45, 63-65 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 69-80.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 27, 43-45.

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. 1402, ¶¶ 27, 43-45, 64-68.

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

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. 1402, ¶¶ 27, 43-45, 64-68.

Response: Denied.

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. 1402, ¶¶ 27, 43-45, 64-68.

Response: Denied.

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

Response: Denied.

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. 1402 ¶¶ 64-75.

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

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

Response: Denied.

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. 1402, ¶¶ 64-75.

Response: Admitted to the extent that P3 refers to a recombinant Cas9 protein and sgRNA

that allegedly can be delivered into a mouse embryo cell by microinjection; otherwise denied.

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

Response: Denied.

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. 1402, ¶¶ 81-108.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Fig. 5(a)); Ex. 1402, ¶¶ 184-98.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 27, 122-25, 154-59.

Response: Denied.

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. 1402, ¶¶ 27, 122-25, 154-59.

Response: Denied.

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. 1402, ¶¶ 27, 122-25, 154-59.

Response: Denied.

40. Examples 3 and 4 of PCT each describe how to use a recombinant Cas9 protein or mRNA

encoding the Cas9 protein with an sgRNA that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell. Ex. 1004, 13-16, 37-52, 81-86, 90-91 (*e.g.*, Fig. 5(a)); Ex. 1402, ¶¶ 154-59.

Response: Denied.

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. 1402, ¶¶ 153-75.

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 153-75.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 70-71, 162-63.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 115, 238.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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. 1402, ¶¶ 159, 174.

Response: Denied.

58. Example 4 of PCT describes the cleavage of a target DNA molecule by a Cas9 protein in plant protoplast cells after the transfection of a recombinant Cas9 protein and sgRNA, resulting in

altered expression of a gene product in plant cells. Ex. 1004, 50-52, 90-91 (*e.g.*, Fig. 12); Ex. 1402, ¶¶ 193-97, 216-27.

Response: Denied.

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. 1402, ¶¶ 167-68.

Response: Denied.

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. 1402, ¶¶ 167-68.

Response: Denied.

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

Response: Denied.

62. The sgRNAs described in Example 4 of PCT contain a sequence complementary to, and that targets and hybridizes to, a 20-nt sequence from an exon of the *BRI1* gene in protoplast cells. Ex. 1004, 50-52; Ex. 1402, ¶¶ 170-72.

Response: Denied.

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

Response: Denied.

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

Response: Denied.

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

Response: Denied.

66. Example 4's CRISPR/Cas9 systems are programmable because the sequence of the sgRNA can be adjusted to target different sequences in an exon of the Arabidopsis *BRI1* gene. Ex. 1004, 50-52, 91; Ex. 1402, ¶ 149.

Response: Denied.

67. Figure 12 of PCT depicts cleavage and editing of one or more sequences in the *BRI1* gene of Arabidopsis resulting in altered gene product expression. Ex. 1004, 50-52, 90-91; Ex. 1402, ¶¶ 193-97, 216-27.

Response: Denied.

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

Response: Denied.

69. Insertions or deletions of nucleotides from a DNA sequence in Exon 2 of the *Foxn1* gene or from a DNA sequence in an exon of the *BRI1* gene would cause altered gene product expression. Ex. 1402, ¶¶ 92-105, 200-13, 216-25.

Response: Denied.

70. In Example 3 of P3 and PCT, CRISPR/Cas9 mediated cleavage and editing of a target DNA sequence from Exon 2 of the *Foxn1* gene results in altered expression of the Foxn1 protein (a gene product), because that gene product is expressed as a mutant and/or at low

levels. Ex. 1402, ¶¶ 77, 82-87, 92-105, 177, 185-90, 200-13.

Response: Denied.

71. The eukaryotic Arabidopsis cells express a putative leucine-rich repeat (LRR) receptor kinase (gene product) encoded by the *BRI1* gene (DNA molecule). Ex. 1402, ¶¶ 134, 180.

Response: Denied.

72. In Example 4 of PCT, CRISPR/Cas9 mediated cleavage and editing of a target DNA sequence from an exon of the *BRI1* gene results in altered expression of the putative LRR receptor kinase (a gene product), because that gene product is expressed as a mutant and/or at low levels. Ex. 1402, ¶¶ 180-82, 193-97, 216-27.

Response: Denied.

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

Response: Denied.

Junior Party's Alleged Facts 74-76 and Senior Party ToolGen's Answers

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

Response: Admitted.

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

Response: Admitted.

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

Response: Admitted only that the quoted language appears in Transcript, Paper 19, 35:14-36:8; otherwise, denied. Broad could have, but did not, identify any such motion in its Motions List and therefore has not preserved any such right. *See* Standing Order ¶ 204 ("All substantive and anticipated responsive motions must be listed on the motions list.").

Senior Party ToolGen's Additional Facts 77-78

77. Motion 1 is contingent upon the grant of a motion by Broad attacking ToolGen's P1 application. *See* Motion 1, n. 1; Order Authorizing Motions and Setting Times, Paper 20, 7:10-15.

78. Broad has not preserved the right to attack ToolGen's priority to P1 because Broad could have, but did not, identify any such motion in its Motions List. *See* Broad List of Proposed Motions, Paper 17; Standing Order ¶ 204 ("All substantive and anticipated responsive motions must be listed on the motions list.")

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **TOOLGEN, INC. REPLY 1** was filed via the Interference Web Portal on September 24, 2021 by 5:00 PM ET, and thereby served on the attorneys of record for the Junior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to agreement of the parties, service copies are being sent by email by counsel for Junior Party as follows:

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