Filed on behalf of Senior Party ToolGen, Inc. Paper No. _______

Anthony M. Insogna
Timothy J. Heverin
S. Christian Platt
JONES DAY
250 Vesey Street
New York, NY 10281
Tel: (212) 326-3939
Fax: (212) 755-7306
aminsogna@jonesday.com
tjheverin@jonesday.com
cplatt@jonesday.com

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

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; 9,840,713, and Applications 14/704,551 and 15/330,876

v.

TOOLGEN, INC.
Senior Party

Application 14/685,510

Patent Interference No. 106,126 (DK)

TOOLGEN OPPOSITION 3
(opposing motion to designate claims as not corresponding to Count 1 or Proposed Count 2)

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1 Senior Party ToolGen, Inc. requests that the Board deny Broad's Motion 3, seeking to
2 designate certain of Broad's involved claims as not corresponding to Count 1 or Proposed Count
3 2, because Broad has not met its burden to justify de-designating any of its claims from Count 1
4 or not designating such claims to Proposed Count 2. 37 C.F.R. § 41.121(b); 37 C.F.R. § 41.208(b).
5 Appendix 1 is a list of Exhibits cited in this motion. Appendix 2 is the Statement of
6 Material Facts.

7 **I. LEGAL STANDARDS**

8 "A claim corresponds to a count if the subject matter of the count, treated as prior art to the
9 claim, would have anticipated or rendered obvious the subject matter of the claim." 37 C.F.R.
10 § 41.207(b)(2); *see* Standing Order ¶ 208.3.1. The opposite is also true; a claim does not
11 correspond to a count if the claim "would not have been anticipated or rendered obvious by the
12 [c]ount." *Ritzberger v. Durschang*, No. 106,012, 2016 WL 5667730, at *12 (P.T.A.B. Sept. 29,
13 2016). The Board's "initial designation of claim correspondence . . . is presumed correct unless
14 shown otherwise by the moving party." *See Schaenzer v. Knight*, No. 105,058, 2003 WL
15 22521270, at *2 (B.P.A.I. 2003). Broad, the moving party, bears the burden of proving "that it is
16 entitled to the requested relief." 37 C.F.R. § 41.121(b); *see* 37 C.F.R. § 41.208(b).

17 **II. ARGUMENT**

18 Broad has not met its burden of justifying the de-designation of any of its claims from
19 Count 1 or the non-designation of such claims to Proposed Count 2. 37 C.F.R. § 41.121(b); 37
20 C.F.R. § 41.208(b); *see Schaenzer*, 2003 WL 22521270, at *2. Broad's arguments, and those
21 portions of Dr. Seeger's declaration on which it relies, are largely recycled from Broad's Motion
22 3 in Interference No. 106,115 ("the 115 interference"), which the Board denied. Ex. 1101, *Regents*
23 *of the Univ. of California v. Broad Institute, Inc.*, Interference No. 106,115, slip op. at 109
24 (P.T.A.B. Sept. 10, 2020) (Paper No. 877). Broad has provided no reason why those same

1 arguments should not be denied here. Furthermore, Broad's additional arguments are unavailing
2 as a matter of both fact and law.

3 **A. Broad's Claims Requiring The Use Of Vectors For RNA Expression**
4 **Correspond To Count 1 Or Proposed Count 2 Under 37 C.F.R.**
5 **§ 41.207(b)(2)**

6 On page 5, lines 9–12 of Broad's Motion 3, Broad argues that "[m]any of [its] involved
7 claims are limited to use of vectors for delivery and expression of the RNA components"
8 (collectively, "the vector claims") and should therefore "be designated as not corresponding to
9 Count 1 or Proposed Count 2[.]" Mot. 5:9–12 (capitalization normalized); *see id.* at 5:9–9:6. The
10 response is that Broad has failed to meet its burden under § 41.207(b)(2) to establish that Count 1
11 or Proposed Count 2 would not have anticipated or rendered obvious these "vector claims." 37
12 C.F.R. § 41.207(b)(2); *see* 37 C.F.R. §§ 41.121(b), 41.208(b); *Schaenzer*, 2003 WL 22521270, at
13 *2. Here, a POSA would have been motivated to use vectors in the eukaryotic CRISPR-Cas system
14 of Count 1 or Proposed Count 2 with a reasonable expectation of success, and Broad has failed to
15 show otherwise.[1] In fact, as of the priority date, the use of vectors, *e.g.*, plasmid vectors, was well
16 known and widely employed for introducing DNA sequences encoding RNA molecules into
17 eukaryotic cells. Ex. 1420 (Stoddard Decl.), ¶¶143–45; F41. Accordingly, assuming Count 1 or

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[1] Count 1 and Proposed Count 2 recite a CRISPR-Cas9 system in a "eukaryotic cell." 37 C.F.R. § 41.207(b)(2) instructs that in determining claim correspondence, the count is to be "treated as prior art to the claim." Accordingly, in addressing obviousness, ToolGen and its expert have assumed Count 1 or Proposed Count 2 as prior art, which includes "success in eukaryotic cells." *See* Ex. 1101, 66 (holding that "under the framework of 37 C.F.R. § 41.207(b)(2)," "success in eukaryotic cells . . . is assumed").

1 Proposed Count 2 as prior art, using vectors to create the eukaryotic CRISPR-Cas9 system of
2 Count 1 or Proposed Count 2 would have been obvious.

3 **1. Broad's Arguments Concerning Other Methods Of "Delivery" Are**
4 **Improper And Should Be Ignored**

5 Broad is correct that "[d]elivery of RNA components of a CRISPR-Cas9 system can be
6 accomplished in multiple ways." Mot. 6:18-19. Vectors are molecules that are delivered into a
7 cell for the purpose of RNA expression, Ex. 1420, ¶143; F42. Broad pays lip service to this fact,
8 *see* Mot. 5:9–10, yet proceeds to repeatedly compare vectors to "[o]ther . . . *methods* for delivering
9 the RNA components of the CRISPR-Cas9 system," *id.* at 7:15–16; *see id.* at 7:3–8:6. For
10 example, Lino 2018, cited by Broad, at Mot. 6:20, confirms that among the methods to deliver
11 RNA, the most common is DNA expression of RNA. Broad argues that adding *already translated*
12 *RNA* to cells can lead to cell death. Mot. 7:8-11. The response is use of vectors to deliver RNA
13 via expression was well-known at the time and avoided this problem.

14 **2. A POSA Would Have Been Motivated To Use Vectors/DNA**
15 **Sequences Encoding RNA Molecules In The Eukaryotic CRISPR-Cas**
16 **System Of Count 1 Or Proposed Count 2**

17 On page 6, lines 13–15 of Broad's Motion 3, Broad argues that "there is no teaching or
18 suggestion in either count, or in the prior art, directing a POSA to vector-delivered RNA for use
19 in eukaryotic cells, nor would a 2012 POSA have had a reasonable expectation of success in so
20 doing." Mot. 6:13–15. The response is that as of the priority date, the use of vectors was well-
21 known and widely employed for introducing RNA molecules into eukaryotic cells. *See, e.g.*, Ex.
22 1248 (Paul 2002), Abstract; Ex. 1420, ¶143; F41. In fact, the use of vectors was so widely
23 employed that, almost a decade before the priority date, the Federal Circuit heard cases involving
24 RNA insertion in eukaryotic cells via vectors. *See, e.g.*, *Genzyme Corp. v. Transkaryotic*
25 *Therapies*, 346 F.3d 1094, 1099–1100 (Fed Cir. 2003). Additionally, more than a decade before

1 the priority date, various methods of "introducing cloned genes into cultured mammalian cells,"
2 including vectors, were detailed in J.F. SAMBROOK & D.W. RUSSELL, MOLECULAR CLONING: A
3 LABORATORY MANUAL (3d ed. 2001) ("Sambrook"), including numerous methods employing
4 vectors. Ex. 1243 (Sambrook, Chapter 16); Ex. 1420, ¶143. In describing "different
5 approaches . . . used to transfer DNA into eukaryotic cells[,]" Sambrook teaches that if "[s]table
6 or permanent transfection is used . . . [t]he marker may be present on the recombinant plasmid
7 carrying the target gene, *or it may be carried on a separate vector* and introduced with the
8 recombinant plasmid into the desired cell line[.]" Ex. 1243, 28 (last full paragraph) (emphasis
9 added); Ex. 1420, ¶143. Sambrook describes numerous other such uses. *See, e.g.*, Ex. 1243, 30
10 (first full paragraph) ("Typically, salmon sperm DNA or another inert carrier *such as the vector*
11 *used to construct the recombinant* is transfected into adherent cells[.]"); Ex. 1420 (emphasis
12 added). These are not isolated teachings; the prior art is replete with descriptions of the benefits of
13 using vectors to express RNA in eukaryotic cells. *See, e.g.*, Ex. 1309 (2004), 1229 (right column,
14 first full paragraph) (explaining that "express[ing siRNA] from a plasmid . . . possesses several
15 advantages . . . : (1) The siRNA could be constitutively expressed, allowing for a higher level of
16 silencing; (2) regulatory elements could be added to the promoter region of the plasmid such that
17 tissue-specific silencing occurs with a systemically administered plasmid; and (3) permanent gene
18 'knock-down' cell lines can be established for *in vitro* work, or for generation of 'knock-down'
19 animals through cloning."); Ex. 1310 (Paddison 2002), 956 (right column, first paragraph)
20 (explaining that "shRNAs . . . synthesized in vivo from RNA polymerase III promoters . . .
21 enable[s] the creation of continuous cell lines in which suppression of a target gene is stably
22 maintained by RNAi"); Ex. 1420, ¶143; F43.

1 In fact, as Dr. Stoddard testifies, plasmid vectors were not only well known as of the
2 priority date, but POSAs understood at that time that vectors provided the advantage of continuous
3 and sustained RNA expression and chemical stability within eukaryotic cells. Ex. 1420, ¶144;
4 F44. This benefit is all the more important here because of the presence of sgRNA, which, because
5 of its single-stranded structure, is more susceptible to degradation compared to double-stranded
6 RNA structures, *e.g.*, siRNA and shRNA. Ex. 1420, ¶144; F45. This is a distinction that Broad
7 and Dr. Seeger fail to substantively address. Rather, Broad and Dr. Seeger rely on circular logic,
8 arguing that "[t]here is no prior art that delivered CRISPR-Cas9 systems to eukaryotic cells at all
9 and so, of course, there is none directed to vector delivery of the RNA." Mot. 6:15–17; *see* Ex.
10 2454, ¶215. Aside from its factual inaccuracy, Broad's argument is tantamount to arguing that
11 there was a lack of prior art disclosing methods of using the telephone before the telephone was
12 invented.

13 On page 7, lines 17–18 of Broad's Motion 3, Broad argues that "[t]he prior art does not
14 teach or suggest the use of, or providing [sic] reasons to select . . . a vector for delivery of the
15 RNA." Mot. 7:17–18; *see id.* at 7:3–8:6. The response is that Broad's argument is flawed as a
16 matter of fact and law. All of the claims require RNA for the CRISPR-Cas9 system, expression
17 of RNA using a vector was and is the most common way to do it.

18 Broad's citation to *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed.
19 Cir. 2008), for the proposition that "[w]here . . . the prior art provides a number of choices, without
20 any reason to make a particular selection, the selection is not obvious," Mot. 7:18–20, is likewise
21 unhelpful to its cause. *Ortho-McNeil* concerned a factually distinct scenario in which there existed
22 no "finite, and in the context of the art, small or easily traversed, number of options" from which
23 a POSA might choose. *Ortho-McNeil Pharm.*, 520 F.3d at 1364. Here, again, the use of vectors,

1 as well as their numerous benefits, were well known as of the priority date. Ex. 1248, 505
2 (Abstract); Ex. 1243, 28, 30, 64; Ex. 1309, 1229 (right column, first full paragraph); Ex. 1310, 956
3 (right column, first paragraph); Ex. 1420, ¶145; F46; *see Bestway (USA), Inc. v. Intex Marketing*
4 *Ltd.*, 2017 WL 1969760, at *6 n.2 (P.T.A.B 2017) (distinguishing *Ortho-McNeil* as being related
5 to an invention with "unpredictable alternatives"). Additionally, a POSA would not have been
6 faced with an infinite spectrum of possibilities, as Broad would have the Board believe; rather,
7 even Broad's own reference teaches that vectors were the first among "*three* . . . commonly
8 reported" "CRISPR/Cas9 cargoes." Ex. 2648, 1241 (right column, first full paragraph); Ex. 1420,
9 ¶145. Accordingly, a POSA would have been motivated to use vectors in the CRISPR-Cas9
10 system of Count 1 or Proposed Count 2. Ex. 1420, ¶¶143–45.

11 **3. Broad Has Failed To Establish Any Objective Indicia Of Non-**
12 **Obviousness**

13 On page 8, lines 7–10 of Broad's Motion 3, Broad argues that "vector-delivered RNA was
14 shown by Broad to have unexpectedly positive results, supporting a finding of non-obviousness"
15 as "demonstrated by the fact that the eukaryotic vector-based CRISPR-Cas9 system developed by
16 Dr. Zhang is one of the most requested CRISPR vectors of all time from Addgene." Mot. 8:7–10;
17 *see id.* at 8:7–14. The response is that even if one were to overlook the underwhelming nature of
18 Broad's purported evidence, Broad fails to prove *any* nexus between its asserted secondary
19 considerations of non-obviousness and the allegedly inventive feature, *i.e.*, the use of vectors for
20 RNA expression. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

21 Neither Broad nor Dr. Seeger offer *any* evidence of unexpected results, and though Broad's
22 evidence purports to show Broad's plasmid as one of "[t]he top 15 plasmids requested from
23 Addgene," Ex. 2504, 1–2, nowhere does this evidence prove the actual number of Broad plasmids
24 sold or, more importantly, that even a single one of those sales is attributable to the use of vectors

1 for RNA expression in connection with CRISPR-Cas9 in eukaryotes, *see Geo. M. Martin Co. v.*
2 *All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) ("The commercial success of a
3 product is relevant to the non-obviousness of a claim only insofar as the success of the product is
4 due to the claimed invention."); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed.
5 Cir. 2006). Not addressed by Broad or Dr. Seeger, Broad's purported sales could be attributed to
6 any number of features, including external factors "such as marketing and advertising." *Apple Inc.*
7 *v. Samsung Elecs. Co.*, 839 F.3d 1034, 1055 n.17 (Fed. Cir. 2016).[2]

8 Further, Dr. Seeger relies on "considerable evidence of the commercial success of the
9 vector-delivery CRISPR invention," but cites only a *single* clinical study, Ex. 2454, ¶225
10 (emphasis added), and the purported "recent[] use[] in *two* patients," *id.* at ¶226 (emphasis added).
11 This showing is insufficient on its face, but more importantly, Dr. Seeger testifies that this same
12 alleged evidence of commercial success is also attributable to other features, namely, SaCas9. *Id.*
13 at ¶246 (offering the same evidence as "considerable evidence of the commercial success of the
14 SaCas9 invention"). Thus, Broad's own expert offers proof against the finding of a nexus in this
15 case.

16 Accordingly, Broad has not met its burden as the movant to justify de-designating any of
17 the vector claims from Count 1 or Proposed Count 2. 37 C.F.R. § 41.121(b); 37 C.F.R. § 41.208(b).

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[2] But even if this evidence did show the vector was highly sold, that would only prove the interest in CRISPR-Cas9 and the most well-known way to introduce RNA into a eukaryotic cell, not any unexpected property or result of the system.

1 **B. Broad's Claims Requiring *Staphylococcus Aureus* Cas9 Protein (SaCas9)**
2 **Correspond To Count 1 Or Proposed Count 2 Under 37 C.F.R.**
3 **§ 41.207(b)(2)**

4 On page 9, lines 7–11 of Broad's Motion 3, Broad argues that certain of its involved claims
5 "are limited to using the *Staphylococcus aureus* Cas9 [(SaCas9)] protein or a nucleotide sequence
6 encoding such a protein" (collectively, "the SaCas9 claims") and should therefore "be designated
7 as not corresponding to Count 1 or Proposed Count 2[.]" Mot. 9:7–11 (capitalization normalized);
8 *see id.* at 9:7–13:17. The response is that Broad has failed to meet its burden under § 41.207(b)(2)
9 to establish that Count 1 or Proposed Count 2 would not have anticipated or rendered obvious the
10 SaCas9 claims. 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R. §§ 41.121(b), 41.208(b); *Schaenzer*, 2003
11 WL 22521270, at *2. Here, given Count 1 or Proposed Count 2 as prior art, a POSA would have
12 been motivated to use SaCas9 in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count
13 2 with a reasonable expectation of success, and Broad has failed to show otherwise. Broad's
14 arguments, and those portions of Dr. Seeger's declaration on which it relies, are again recycled
15 from its Motion 3 from the 115 interference. The Board found Broad's arguments unpersuasive
16 then, Ex. 1101, 53:6–62:6, and they have not improved with age. Broad fails to show why the
17 Board should reach a different result here.

18 **1. A POSA Would Have Been Motivated To Use SaCas9 In The**
19 **Eukaryotic CRISPR-Cas System Of Count 1 Or Proposed Count 2**

20 **(a) A POSA would have been motivated to use the small Cas9**
21 **protein, SaCas9**

22 SaCas9 was known in the art to be a small Cas9 protein, and, because of its small size, a
23 POSA would have been motivated to use it in the eukaryotic CRISPR-Cas system of Count 1 or
24 Proposed Count 2, particularly for human therapeutics—*e.g.*, with Adeno-associated virus
25 ("AAV") vectors, as the Board found in the '115 interference. Ex. 1420, ¶¶84–90. In fact, before
26 the priority date, *S. aureus* had been established as one of "[a] few *model* systems . . . in the study

1 of CRISPR/Cas functionality[.]" Ex. 1311 (Sapranaukas 2011), 9276 (left column, first full
2 paragraph) (emphasis added); Ex. 1101, 56:10–11 ("We are persuaded that Sapranauskas indicates
3 what systems those of ordinary skill in the art were using as model systems because of its plain
4 language."); Ex. 1420, ¶84. Moreover, as of the priority date, at least one commonly used public
5 database, the European Nucleotide Archive, had identified SaCas9 as a Cas9 protein and disclosed
6 its amino acid and cDNA sequences, its location on the genome, and *S. aureus* genomic sequences.
7 Ex. 1312; Ex. 1313. Thus, SaCas9 and its sequence were known in the art before the priority date.
8 Ex. 1420, ¶84. Once SaCas9 was identified as a Cas9 protein, with the characteristic RuvC and
9 HNH domains that characterize a functional Cas9 protein, a POSA would have expected it to
10 function as a Cas9 protein. Ex. 1420, ¶85; *see* Ex. 1312; Ex. 1313; *see also* Ex. 1206. Further, a
11 POSA would have known that SaCas9 is 1,053 amino acids in length and encoded by a 3.16
12 kilobase (kb) DNA. Ex. 1420, ¶86. A POSA would have readily recognized that SaCas9 is smaller
13 than even the other relatively small Cas9 proteins such as *S. pyogenes* Cas9 protein ("SpCas9")
14 (1,368 amino acids; 4.1 kb DNA) and *S. thermophilus* Cas9 protein ("StCas9") (1,121 amino acids;
15 3.4 kb DNA). Ex. 1420, ¶86.

16 Moreover, a POSA would have been motivated to use AAV vectors to heterologously
17 express a Cas9 protein in certain applications of the CRISPR system, including human
18 therapeutics. Ex. 1420, ¶¶87–88. Before the priority date, AAV vectors were available and
19 commonly used in the art—particularly for "human therapeutics," because they were known to
20 "mediate long-term gene expression" and had "no known pathology in humans." Ex. 1314 (Wu
21 2010), 80; Ex. 1420, ¶87. Further, due to easier manipulation of the smaller components and
22 limitations on the size of the DNA that can be inserted into a vector for expression, a POSA would
23 have been motivated to use a smaller Cas9 protein like SaCas9. Ex. 1314, 80 ("A substantial

limitation of AAV vectors is their small packaging capacity that is generally considered to be <5 kb. This limitation makes vector design for diseases involving larger genes challenging or impossible."); Ex. 1420, ¶88. For example, for AAV vectors, a POSA would have preferred to use <5 kb total DNA to maximize efficiency. *Id.* Thus, a POSA seeking to use a CRISPR-Cas system for human therapeutics would have been motivated to express SaCas9 from an AAV vector, at least because: (1) AAV vectors were known to "mediate long-term gene expression" and had "no known pathology in humans"; (2) SaCas9's 3.16 kb DNA would fit well within an AAV vector and would be expected to be expressed more efficiently than larger Cas9 proteins; and (3) the SaCas9 DNA, the smallest of the small DNAs, would allow the POSA to include the maximum of additional desired elements in the vector. Ex. 1420, ¶¶87–90.

A POSA would have been further motivated to use the smaller SaCas9 in tissue-specific therapeutics applications using AAV vectors, as that would allow the artisan to include additional regulatory elements such as tissue-specific promoters, *e.g.*, liver-specific Liver Fatty Acid Binding Protein (L-FABP) promoter and red blood cell-specific GATA1 promoter. Ex. 1315 (Her 2003); Ex. 1316 (Zon and Orkin 1992). As the Board previously recognized, Dr. Seeger's declaration supports this argument. Ex. 1101, 58:6–9 ("Dr. Seeger's statements tend to support [the] argument that those of ordinary skill in the art would have been motivated to use a smaller sized Cas9 protein to be able to fit desired elements into an AAV delivery vehicle."); *see* Ex. 2454, ¶237 ("This combination of efficient indel production and small size is key for many basic research and therapeutic applications that employ the highly versatile adeno-associated virus (AAV) as the delivery vehicle."). Another motivation for using SaCas9, such as when using AAV vectors, is that its smaller size would permit a POSA to include nucleotide sequences encoding SaCas9, the RNA guide and promoter elements on the same vector, which is desirable to reduce the number of

components to be delivered into a cell. Ex. 1420, ¶90. These additional reasons would have motivated a POSA to use SaCas9 in the system of Count 1 or Proposed Count 2. Ex. 1420, ¶90.

Broad erroneously argues that "[a]s of 2012, there were more than 600 bacterial Cas9 orthologs that had been identified," and that "[a]lthough SaCas9 was known as one of those orthologs," a POSA would have had no reason to select "SaCas9 for use in eukaryotes over any of the other orthologs." Mot. 10:14–17. Neither Broad nor Dr. Seeger, however, provide *any* evidence showing that there were more than 600 Cas9 orthologs known before the priority date. *See id.* at 10:14–11:4; Ex. 2454, ¶234. Rather, Broad and Dr. Seeger rely on Ran (Ex. 2226), *id.* at 10:14–15; Ex. 2454, ¶234, which published in April 2015, and cites to studies published in 2014—years *after* the priority date. Moreover, Broad once again cites to *Ortho-McNeil*, but that case concerned a factually distinct scenario in which there existed no "finite, and in the context of the art, small or easily traversed, number of options" from which a POSA might choose. *Ortho-McNeil Pharm.*, 520 F.3d at 1364. Here, as noted above, *S. aureus* was known to be one of "[a] *few model systems* . . . in the study of CRISPR/Cas functionality[.]" Ex. 1311, 9276 (emphasis added); *see Bestway (USA), Inc.*, 2017 WL 1969760, at *6 n.2. In fact, SaCas9 was known in the art as a Cas9 protein, and so a POSA would have understood SaCas9 to function as such in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2 to obtain predictable results, *i.e.*, it would cleave, edit, or modulate transcription of the target DNA. Ex. 1420, ¶94. Thus, a POSA would have been motivated to use SaCas9 in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2. Ex. 1420, ¶¶92–98.

(b) Broad's arguments as to why a POSA would not have selected SaCas9 are unavailing

As they were found in the 115 interference, Broad's arguments about why a POSA would not have selected SaCas9 from the alleged 600 Cas9 orthologues are unavailing. *First*, Broad

1 asserts that SpCas9 was "the most commonly studied Cas9 ortholog in prokaryotes[,]" and thus,
2 impliedly demands proof of a reason to switch from SpCas9 to SaCas9. Mot. 11:6–7. Neither
3 Count 1 nor Proposed Count 2 recite the use of SpCas9. In fact, as Broad admits, "neither count
4 recites that the Cas9 be . . . any particular Cas9 protein[.]" *Id.* at 10:3–4. Thus, the test for claim
5 correspondence here is whether a POSA would have been motivated to use SaCas9 as the recited
6 Cas9 protein when considering Count 1 or Proposed Count 2 as prior art, and not whether a POSA
7 would have been motivated to use SaCas9 *over* SpCas9. Therefore, Broad errs in requiring a
8 reason to switch from SpCas9. Moreover, Broad's cited references are not probative of a POSA's
9 motivations to use SaCas9 as of the priority date. Rather, Broad, like Dr. Seeger, cites to "*later*
10 disclosed . . . tests" and "the *later* study of Cas9 proteins," *id.* at 11:6–13 (emphasis added) (citing
11 Ex. 2201 (Cong 2013)); *see* Ex. 2454, ¶¶230, 234–39, none of which concern the knowledge of a
12 POSA as of the priority date. Additionally, Broad's cited references do not disclose the number
13 of Cas9 proteins known as of the priority day, nor are they directed to developing the CRISPR
14 systems for applications where the Cas9 protein size would have been an important consideration,
15 such as in human therapeutics using AAV vectors. Ex. 1420, ¶92. Nor do those references teach
16 away from using SaCas9 because of its small size, as the Board previously found. Ex. 1101, 57:8–
17 13.

18 *Second*, Broad erroneously argues that even if a POSA would have been focused on a small
19 Cas9 protein, they would not have had a reason to select "SaCas9 out of the many known 'small'
20 Cas9 orthologs that are similar in size to, or smaller than, SaCas9." Mot. 11:17–20. Again, Broad
21 fails to provide any evidence that the number of "small" Cas9 proteins was known as of the priority
22 date. Broad instead cites Dr. Seeger's declaration, which cites later-issued references for support,
23 Ex. 2454, at ¶¶234–39, including Figs. 4A–D of Broad's own U.S. Patent No. 8,865,406 ("the

1 ’406 patent”), *id.* at ¶239. As with Dr. Seeger’s other cited references, however, the ’406 patent
2 does not disclose that this number was known before the priority date. In fact, the ’406 patent only
3 describes what was known as of its later filing date, *i.e.*, March 24, 2014. Moreover, Dr. Seeger
4 in paragraph 239 articulates the number of “Cas9 orthologues smaller than SpCas9,” not SaCas9;
5 and the cited Figs. 4A–D do not identify the proteins that were as small or smaller than SaCas9 or
6 SpCas9. Ex. 2017, Figs. 4A–D; Ex. 1420, ¶97; F47.

7 *Third*, Broad’s argument, that the “particularly low” sequence identity and differences in
8 size and certain domains between SaCas9 and SpCas9 would have steered a POSA away from
9 SaCas9, also fails. Mot. 12:4–5; *see* Ex. 1101, 57:5–8 (“Again, in light of the express teaching in
10 Sapranauskas that SaCas9 was known to be a model system, we are not persuaded that its sequence
11 homology or any other differences would have indicated it would not be a potential protein for the
12 system of Count 1.”). Here, again, Broad improperly requires switching from SpCas9 to SaCas9,
13 even though SpCas9 is neither part of Count 1 nor of Proposed Count 2. In any event, a POSA
14 would have found the sequence identity of SaCas9 overall, and within its catalytic domains, to be
15 typical for Cas9 orthologs. Ex. 2002, Fig. 10; Ex. 1420, ¶¶93–94. SaCas9 would have been
16 expected to function as a Cas9 protein in the eukaryotic CRISPR-Cas system of Count 1 or
17 Proposed Count 2 and cleave, edit, or modulate transcription of the target DNA. Ex. 1420, ¶94.
18 Accordingly, because of its small size, a POSA would have been motivated to use SaCas9 in the
19 eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2, *e.g.*, for human therapeutics with
20 AAV vectors.

21 Once SaCas9 was identified as a Cas9 protein, with its characteristic RuvC and HNH
22 domains, as noted above, and given Count 1 or Proposed Count 2 as assumed prior art, a POSA
23 would have expected it to function as a Cas9 protein to cleave, edit, or modulate transcription of

1 the target DNA, *e.g.*, when provided on an AAV vector. Ex. 1312; Ex. 1313; Ex. 1420, ¶94. The
2 entire CRISPR locus region of *S. aureus*, including the crRNA and tracrRNA sequences, had been
3 identified and sequenced. Ex. 1312; Ex. 1313. To identify the PAM sequence for SaCas9, a POSA
4 would have used processes routinely applied in the art. Ex. 1420, ¶96. Thus, in view of the success
5 of SpCas9, a POSA would have had a reasonable expectation of successfully using SaCas9 in the
6 eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2. Ex. 1420, ¶¶96–98. Broad fails
7 to establish a lack of a reasonable expectation of success, and so has failed to meet its burden under
8 § 41.208(b).

9 **2. Broad Has Failed To Establish Any Objective Indicia Of Non-**
10 **Obviousness**

11 Broad's argument that "surprising" or "unexpected" results arise from using SaCas9 is
12 based on multiple inferences and untenable leaps of logic. Mot. 12:18–13:6. Broad does not try
13 to argue that SaCas9 had unexpectedly superior results compared to SpCas9. Rather, it argues that
14 SaCas9 unexpectedly had an efficiency comparable to SpCas9 with low off-target activity, in
15 contrast to the alleged poorer efficiency of other smaller sized Cas9 proteins, such as StCas9. *Id.*
16 at 12:20–22. Thus, Broad alleges that SaCas9 demonstrated unexpected results because it had
17 comparable efficiency to SpCas9. This argument flounders on the facts and on the law.

18 *First*, unexpected results "must be shown to be unexpected compared with the closest prior
19 art." *Millennium Pharms, Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017). Here,
20 however, Broad and Dr. Seeger do not compare the results obtained from using SaCas9 with the
21 closest prior art at the time. Rather, both rely on references published after the priority date,
22 specifically, the '406 patent. Mot. 12:20–23 (citing Ex. 2454, ¶245 (citing Ex. 2017, 83:25–
23 84:23)).

1 *Second*, "[a]n applicant may make this showing [of unexpected results] with evidence that
2 the claimed invention exhibits some superior property or advantage that a [POSA] would find
3 surprising or unexpected." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (emphasis added).
4 Here, however, each of Broad's underlying factual assertions is contradicted by the evidence.
5 Contemporaneous studies contradict the assertion that StCas9 was less efficient than SpCas9, Ex.
6 1420, ¶103, and the data Broad cites show that SaCas9 and StCas9 have comparable activity, Ex.
7 1420, ¶105. Finally, as in the 115 interference, neither Broad nor Dr. Seeger have provided
8 "evidence that StCas9 is inefficient because of its small size or that those of ordinary skill would
9 have considered all small Cas9 proteins to be similarly inefficient." Ex. 1101, 59:15–17.

10 *Third* and finally, Broad's argument that "the commercial success of systems using SaCas9
11 is powerful objective evidence" is unsupported. Mot. 13:7. Broad cites to Dr. Seeger's
12 declaration, which, as noted above, claims a single clinical study as "considerable evidence of the
13 commercial success of . . . SaCas9," Ex. 2454, ¶225 (emphasis added), along with the purported
14 "recent[] use[] in *two* patients," *id.* at ¶226 (emphasis added). Moreover, as also noted above, Dr.
15 Seeger testifies that this same alleged evidence of commercial success is attributable to *other*
16 features, namely, "vector-delivery." *Id.* at ¶¶225–26. Thus, even Broad's own expert testifies that
17 there is no nexus between the alleged success and the invention itself. *See Geo. M. Martin Co.*,
18 618 F.3d at 1304; *Ormco Corp.*, 463 F.3d at 1311–12.

19 Accordingly, Broad's SaCas9 claims would have been obvious over Count 1 in view of the
20 prior art, and so they correspond to Count 1 or Proposed Count 2. Ex. 1420, ¶¶100–110.

21 **C. Broad's Claims Requiring A Chimeric Cas9 Correspond To Count 1 Or**
22 **Proposed Count 2 Under 37 C.F.R. § 41.207(b)(2)**

23 On page 13, lines 18–22 of Broad's Motion 3, Broad argues that "[a]ll of the involved
24 claims . . . are limited to a Cas9 that is a chimeric enzyme . . . wherein each of the first and second

fragments are from a different Cas9 protein" and should therefore "be designated as not corresponding to Count 1 or Proposed Count 2." Mot. 13:18–22 (capitalization normalized); *see id.* at 13:18–15:5. The response is that Broad has failed to meet its burden under § 41.207(b)(2) to establish that Count 1 or Proposed Count 2 would not have anticipated or rendered obvious the use of a chimeric Cas9 protein. 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R. §§ 41.121(b), 41.208(b); *Schaenzer*, 2003 WL 22521270, at *2. Here, given Count 1 or Proposed Count 2 as prior art, a POSA would have been motivated to use a chimeric Cas9 protein in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2 with a reasonable expectation of success, and Broad has failed to show otherwise. In fact, as of the priority date, the use of chimeric proteins was both well-known and widely employed.

1. Broad Has Waived Its Argument

As the Federal Circuit has made clear, where a party "only mentions [a] point in passing, with no development of an argument in support of it, . . . [the argument] has not been properly raised," and is therefore waived. *Oracle Am., Inc. v. Google Inc.*, 750 F.3d 1339, 1377 n.17 (Fed. Cir. 2014). Here, even giving Broad's obviousness argument the most generous construction possible, it still consists of only three conclusory sentences, Mot. 14:17–15:1, none of which substantively address the merits of Broad's claim. Broad has waived its argument.

2. A POSA Would Have Been Motivated To Use Chimeric Proteins In The Eukaryotic CRISPR-Cas System Of Count 1 Or Proposed Count 2

Aside from Broad's waiver, on page 14, lines 17–19 of Broad's Motion 3, Broad argues that "nothing in either count or the prior art teaches, suggests, or provides motivation to a POSA to design a chimeric Cas9 that is comprised of two fragments from different organisms." Mot. 14:17–19. The response is that Broad's argument fails to even acknowledge, let alone address, the vast array of prior-art references disclosing the use and numerous benefits of chimeric proteins.

Contrary to Broad's assertion, as of the priority date—indeed, *more than a decade before* December 2012—it was well known in the art to design chimeric proteins in both prokaryotic and eukaryotic cells. Ex. 1317 (Hamamoto 1992), Abstract; Ex. 1318 (Matsui 1987), Abstract; F48. Relevant here, several naturally occurring chimeric variants of Cas proteins were well known in the art. Ex. 1207 (Makarova 2011), Abstract; Ex. 1420, ¶148; F49. Among other reasons, a POSA would have been motivated to design a chimeric Cas9 protein because of the known ability to alter the functions of the wild-type Cas9 protein. Ex. 1420, ¶148; F50. PAM sequences, for example, were known to differ between Cas proteins, and thus a POSA would have been motivated to design a chimeric Cas protein to modify target PAM sequences. Ex. 1207, 467 (third column, last full paragraph); Ex. 1420, ¶148; F51. Such a modification would have been routine for a POSA as of the priority date. Ex. 1420, ¶148; F52. Thus, given Count 1 or Proposed Count 2 as prior art, a POSA would have been motivated to design a chimeric Cas9 protein with a reasonable expectation of successfully creating a chimeric Cas9 to function in the eukaryotic CRISPR system of Count 1 and Proposed 2. Ex. 1420, ¶148. Accordingly, Broad has failed to meet its burden under § 41.208(b).

3. Broad Has Failed To Establish Any Objective Indicia Of Non-Obviousness

Broad's argument that "unexpected benefits" arise from using chimeric Cas9 is based on unsubstantiated evidence. Mot. 14:22–15:1. Broad argues that chimeric Cas9 has "unexpected benefits" compared to wild-type Cas9 because its own patent specification says so. Mot. 14:22–15:1 (citing Ex. 2060, 83:45–52). This argument is legally and factually flawed. To begin, it is well settled that "conclusory statements in a patent's specification cannot constitute evidence of unexpected results in the absence of factual support," *Sud-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1009 (Fed. Cir. 2009); and U.S. Patent No. 8,889,418 ("the '418 patent") provides

1 *no* data or testing results to support Broad's argument, Ex. 2060, 83:45–52; F53. Broad cites none.
2 Additionally, unexpected results must show "that the claimed invention exhibits some superior
3 property or advantage that a [POSA] would find surprising or unexpected." *In re Mayne*, 104 F.3d
4 1339, 1343 (Fed. Cir. 1997). Here, Broad provides no "surprising" or "unexpected" results,
5 relying instead on benefits that a POSA would have expected to achieve using a chimeric Cas9
6 protein. Ex. 1420, ¶149. In fact, a POSA would have *expected* a chimeric Cas9 protein to have
7 altered results in areas such as specificity and the ability to target specific PAM sequences, which
8 are the exact results Broad claims to be "unexpected." Ex. 1317, 477 (second column, last
9 paragraph); Ex. 1207, 467 (third column, last full paragraph).

10 Dr. Seeger's testimony fails to bridge the gaps in Broad's argument. Unexpected results
11 "must be shown to be unexpected compared with the closest prior art." *Millennium Pharms, Inc.*,
12 862 F.3d at 1368. Here, however, Dr. Seeger fails to compare the results obtained from using
13 chimeric Cas9 with the closest prior art, *i.e.*, known chimeric variants of the Cas protein in
14 combination with Count 1 or Proposed Count 2 as prior art. Rather, he relies on only two articles,
15 Ma 2019 (Ex. 2683) and Liu 2019 (Ex. 2654)—both published after the priority date—to support
16 the benefits of chimeric Cas9. Ex. 2454, ¶¶255–56. Accordingly, Broad has failed to meet its
17 burden under § 41.208(b).

18 **D. Broad's Claims Requiring Two Or More Nuclear Localization Sequences**
19 **(NLSs) Correspond To Count 1 Or Proposed Count 2 Under 37 C.F.R.**
20 **§ 41.207(b)(2)**

21 On page 15, lines 6–9 Broad's Motion 3, Broad argues that its NLS claims—those
22 "requiring the use of 'two or more' [NLSs]"—should be designated as not corresponding to Count
23 1 or Proposed Count 2. Mot. 15:6–9; *see id.* at 15:6–18:19. The response is that Broad has failed
24 to meet its burden under § 41.207(b)(2) to establish that Count 1 or Proposed Count 2 would not
25 have anticipated or rendered obvious the NLS claims. 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R.

1 §§ 41.121(b), 41.208(b); *Schaenzer*, 2003 WL 22521270, at *2. Here, given Count 1 or Proposed
2 Count 2 as prior art (a fact that Broad missed, Mot. at MF 22), a POSA would have been motivated
3 to use two or more NLSs in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2
4 with a reasonable expectation of success, Ex. 1420, ¶¶111–12, and Broad has failed to show
5 otherwise. In fact, as with other of its arguments, Broad's arguments, and those portions of Dr.
6 Seeger's declaration on which it relies, are repeated from its denied Motion 3 from the 115
7 interference. The Board found Broad's arguments unpersuasive then, Ex. 1101, 61:7–67:4, and
8 Broad has failed to provide any arguments or evidence showing why it should now succeed.

9 10 11 **1. A POSA Would Have Been Motivated To Use The Cas9 Protein With Two Or More NLSs In The Eukaryotic CRISPR-Cas System Of Count 1 Or Proposed Count 2**

12 Before the priority date, POSAs routinely used NLSs—including two or more NLSs—to
13 successfully direct the nuclear localization of proteins, including prokaryotic proteins. Ex. 1420,
14 ¶¶113–114. For example, before the priority date, POSAs knew to attach, and had attached, NLSs
15 to Cas proteins of Type I and III CRISPR systems, and to proteins of Zinc Finger Nucleases,
16 TALENs, Rec A, Lac, and HaloTag™ proteins. Ex. 1022, ¶¶[0054], [0058] (instructing to attach
17 "NLSs" to "Cas/Cse protein[s]" of Type I and III CRISPR system); Ex. 1319 (Rebar 2002),
18 Abstract; Ex. 1320 (Cermak 2011), Fig. 1(b) (depicting a TALEN with two NLSs); Ex. 1321
19 (Reiss 1996), 3095; Ex. 2258 (Fieck 1992), 1785 (last paragraph) ("study[ing] the effects of
20 nuclear localization sequences" on Lac repressor proteins); Ex. 1322 (Los 2006), 11 (first column,
21 last paragraph) (disclosing that three NLSs "were added to the C-terminus of both [a] HaloTag™
22 Protein and hMGFP"); Ex. 1420, ¶115; F54. POSAs also knew that attaching additional NLSs to
23 a protein had further increased nuclear localization. Ex. 2268 (Luo 2004), 849–50; Ex. 1324
24 (Fischer-Fantuzzi and Vesco 1988), 5496 (disclosing that "nuclear localization was always
25 improved by . . . reiterating the [nuclear localization] signal"); Ex. 1420, ¶120. Even the references

1 that Dr. Seeger cites in paragraph 277 of his declaration show that the nuclear localization of a
2 protein increases when additional NLSs are attached to the protein. Ex. 2262 (Park 2002), 31427–
3 28; Ex. 2267 (Lyssenko 2007), 597–98; Ex. 2268, 847; Ex. 1420, ¶121. For example, Park notes
4 that the degree of nuclear localization corresponded to the number of NLSs present. Ex. 2262,
5 31427; Ex. 1420, ¶122; F55. Similarly, before the priority date, several well-known and readily
6 available commercial eukaryotic expression vectors attached two or more NLSs to proteins
7 expressed from the vector. Ex. 1323 (Dai 2002), 24391; Ex. 1325 (Planey 2002), 42189; Ex. 1420,
8 ¶127; F56. Thus, a POSA would have had a reason to use two or more NLSs in the CRISPR system
9 of Count 1 or Proposed Count 2. Ex. 1420, ¶¶113–15, 120–29.

10 Before the priority date, POSAs routinely used NLSs to localize prokaryotic and eukaryotic
11 proteins, with different sequence and three-dimensional structure, to the nucleus. Ex. 1420, ¶130;
12 F57. POSAs also routinely attached two or more NLSs to proteins to increase nuclear localization
13 while maintaining protein function. Ex. 1420, ¶¶130–31; F58. Thus, given Count 1 or Proposed
14 Count 2 as prior art, a POSA would have had a reasonable expectation of successfully attaching
15 two or more NLSs to Cas9. Ex. 1420, ¶134. For example, Jinek 2012 (Ex. 2202) attached a four-
16 amino-acid tag to a Cas9 while retaining function, thereby providing further reasonable
17 expectation for successfully attaching two or more NLSs. Ex. 1420, ¶¶131–33; F59.

18 And, while Broad argues that there was no reasonable expectation of successfully using
19 two or more NLSs in a CRISPR-Cas system, based on its speculation that protein folding may
20 impair the function of Cas9, Mot. 17:19–18:5, both Broad and Dr. Seeger rely on a selective
21 citation of a few instances where an NLS affected the protein's function, all the while ignoring the
22 extensive evidence in the art that NLSs were routinely attached to heterologously expressed
23 proteins to successfully increase their nuclear localization while maintaining the protein's

1 function. Ex. 2258, Abstract; Ex. 2263 (Brothers 2003), Abstract, 6111; Ex. 2264 (Turner 1996),
2 7738, 7744; Ex. 2265 (Song and Markley 2007), 265, 268; Ex. 1420, ¶135.

3 As in the in the 115 interference, Broad and Dr. Seeger rely on Fieck (Ex. 2258). Mot.
4 18:3–5. But the Board found in that interference that "Fieck teaches that one NLS position
5 produced 'efficient nuclear accumulation, strong repressor activity and greater sensitivity to IPTG
6 induction.'" Ex. 1101, 64:2–4 (quoting Ex. 2258, Abstract); F60. And neither Broad nor Dr.
7 Seeger here provide argument or evidence even addressing—let alone rebutting—this finding.
8 Here, as in the 115 interference, "Broad does not direct [the Board] to a teaching in the art that for
9 some proteins, there is no position of the NLS that will successfully locate a functional protein
10 into the nucleus." Ex. 1101, 64:9–11 (quoting Ex. 2258, Abstract). Rather, in the context of the
11 art as a whole, Broad's references show that a POSA would have expected that routine
12 experimentation would provide an optimal configuration. Ex. 2258, 1785; Ex. 2263, Abstract,
13 6111; Ex. 2264, 7738, 7744; Ex. 2265, 265, 268; Ex. 1420, ¶¶137–39. Moreover, each reference
14 shows successful attachment of peptide tags to proteins after routine experimentation. Ex. 2258,
15 1785; Ex. 2263, Abstract, 6111; Ex. 2264, 7738, 7744; Ex. 2265, 265, 268; Ex. 1420, ¶¶137–39;
16 F61. In view of all of this contrary evidence and prior Board findings, Broad has failed to
17 demonstrate that a POSA would have lacked a reasonable expectation of success given Count 1 or
18 Proposed Count 2 as prior art.

19 **2. Broad Has Failed To Establish Any Objective Indicia Of Non-**
20 **Obviousness**

21 Broad argues that the successful attachment of two NLSs to Cas9 constitutes unexpected
22 results, Mot. 16:16–25, but that assertion is not supported by fact or law. Broad's evidence shows
23 only results different in degree, not in kind. That is not enough. *Galderma Labs., L.P. v. Tolmar,*
24 *Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Unexpected results that are probative of nonobviousness

1 are those that are 'different in kind and not merely in degree from the results of the prior art.'"
2 (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). That
3 cited evidence, Zhang 2012 and Cong 2013, does not show superior, unexpected results. Ex. 2001,
4 Fig. 1B; Ex. 2201, Fig. 1A. Before the priority date, given Count 1 or Proposed Count 2 as prior
5 art, a POSA would have expected that attaching multiple NLSs to a protein, including two or more
6 NLSs, would improve nuclear localization. Ex. 1420, ¶141; F62. Broad's cited evidence shows
7 that a POSA would have expected increased nuclear localization of the Cas9 protein with two
8 NLSs compared to when only one or no NLS is used. Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex.
9 1420, ¶141; F63. Broad's cited evidence also fails to show that a Cas9 protein with two NLSs was
10 "unexpectedly more efficient." Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420, ¶141; F64. It
11 provides no data on efficiency, *i.e.*, function of the Cas9 protein. Ex. 2001, Fig. 1B; Ex. 2201, Fig.
12 2A; Ex. 1420, ¶141; F65. The data only shows the expected nuclear localization of the Cas9
13 protein, which is not the same as its function. Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420,
14 ¶141; F66. Table M of Example 14 of the '445 patent, though not cited by Broad, also does not
15 show an unexpected or significant increase in efficiency with two or more NLSs. Ex. 2029,
16 124:27–125:21 (Example 14, Table M); Ex. 1420, ¶141; F67. Rather, it shows that the Cas9
17 protein with one NLS attached to its N-terminus, one NLS attached to its C-terminus, and an NLS
18 attached to both its N- and C-termini, had the following activity: 6.45% (± 0.63), 5.10% (± 0.33),
19 and 8.9% (± 0.60), respectively—results entirely in line with expectations. Ex. 2029, 124:27–
20 125:21 (Example 14, Table M); Ex. 1420, ¶141; F68. Accordingly, Broad's NLS claims would
21 have been obvious over Count 1 and Proposed Count 2, and Broad has failed to meet its burden to
22 show otherwise.

1 **E. Broad's Claims Limited To A Cas9 Fused To Specified Protein Domains Or**
2 **Including Heterologous Domains Correspond To Count 1 Or Proposed**
3 **Count 2 Under 37 C.F.R. § 41.207(b)(2)**

4 On page 18, lines 20–24 of Broad's Motion 3, Broad argues that certain of its involved
5 "claims require that the Cas9 be fused to specified protein domains or include heterologous
6 domains and are thus patentably distinct" from Count 1 or Proposed Count 2. Mot. 18:20–24; *see*
7 *id.* at 18:20–20:17. The response is that Broad has failed to meet its burden under § 41.207(b)(2)
8 to establish that Count 1 or Proposed Count 2 would not have anticipated or rendered obvious
9 fusing the Cas9 protein to specified protein domains. 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R.
10 §§ 41.121(b), 41.208(b); *Schaenzer*, 2003 WL 22521270, at *2. Here, given Count 1 or Proposed
11 Count 2 as prior art, a POSA would have been motivated to fuse the Cas9 protein to specified
12 protein domains in the eukaryotic CRISPR-Cas system of Count 1 or Proposed Count 2 with a
13 reasonable expectation of success, and Broad has not shown otherwise. In fact, as of the priority
14 date, the fusing of proteins to specified protein domains was well known and widely employed.

15 **1. Broad Waived Its Argument**

16 Even giving Broad's obviousness argument its most generous construction, it consist of
17 only six conclusory sentences, Mot. 20:1–17, none of which provides a developed argument that
18 addresses the merits of Broad's claim in any substantive fashion. Broad has waived its argument.
19 *Oracle Am., Inc.*, 750 F.3d at 1377 n.17.

20 **2. The Eukaryotic CRISPR-Cas Systems Of Count 1 And Proposed**
21 **Count 2 Anticipate Fusing The Cas9 Protein To Specified Protein**
22 **Domains**

23 The ToolGen half of Count 1 and Proposed Count 2 recites "wherein the Cas9 polypeptide
24 comprises a nuclear localization signal[.]" Declaration (Paper No. 1), 12; Broad Motion 1 (Paper
25 No. 72), 3. That is, Count 1 and Proposed Count 2 recite a Cas9 protein having at least one NLS
26 attached thereto. As of the priority date, a POSA would have understood that an NLS attached to

a Cas9 protein as a fusion. Ex. 1420, ¶150; F69. Broad admits this fact in its Motion 3. *See, e.g.*, Mot. 16:16–18, 17:4–9, 17:16–18. Accordingly, Count 1 and Proposed Count 2 anticipate fusing the Cas9 protein to a specified protein domain as well as rendering it obvious.

3. A POSA Would Have Been Motivated To Use Fused Proteins In The Eukaryotic CRISPR-Cas System Of Count 1 Or Proposed Count 2

On page 20, lines 1–3 of Broad's Motion 3, Broad argues that "there is no teaching or suggestion in Count 1, Proposed Count 2, or the prior art directing a POSA to modify the naturally occurring Cas9 protein sequences as set forth in the[] claims." Mot. 20:1–3. Broad's argument, however, fails to acknowledge, let alone address, the vast array of prior-art references disclosing the use and numerous benefits of fusing proteins. Contrary to Broad's assertion, as of the priority date—indeed *more than a decade before*, it was well known in the art to fuse proteins to specified protein domains. Ex. 1327 (Brizzard and Chubet 1997), Abstract; Ex. 1328 (Hollenbaugh and Aruffo 2002), Abstract; Ex. 1329, (Margolin 2000), Abstract; F70. In fact, generating protein fusions had been used for decades before the priority date as a method of purifying proteins, and fusing green fluorescent protein (GFP) to proteins was also used as method of detecting protein localization in prokaryotic and eukaryotic cells. Ex. 1329, Abstract; Ex. 1420, ¶151; F71. Jinek 2012 even describes expressing a purified Cas9 "as a fusion protein[.]" Ex. 2202, Fig. S2; *see id.* at "Supplementary Materials and Methods" (paragraphs describing "Protein purification"), Fig. S11 ("The heterologous crRNA sequence was engineered to contain *S. pyogenes* DNA-targeting sp2 sequence at the 5' end fused to *L. innocua* or *N. meningitidis* tracrRNA-binding repeat sequence at the 3' end."). Moreover, such a modification would have been routine for a POSA as of the priority date. Ex. 1420, ¶151; F72. Thus, a POSA would have had a motivation to fuse the Cas9 protein of Count 1 or Proposed Count 2 to a specified protein domain and would have had a

1 reasonable expectation of successfully doing so. Ex. 1420, ¶151. Accordingly, Broad has failed
2 to meet its burden under § 41.208(b).

3 **4. Broad Has Failed To Establish Any Objective Indicia Of Non-**
4 **Obviousness**

5 Broad's argument that "unexpected benefits" arise from "fusing functional domains to
6 Cas9" is based on an unsubstantiated assertion from its own patent. Mot. 20:10–17. Broad argues
7 that "fusing functional domains to Cas9" has "unexpected benefits" simply because its own patent
8 specification says so. Mot. 20:10–15 (citing Ex. 2024, 73:22–29). This argument has fatal legal
9 and factual gaps.

10 *First*, as noted above, it is well settled that "conclusory statements in a patent's
11 specification cannot constitute evidence of unexpected results in the absence of factual support,"
12 *Sud-Chemie, Inc.*, 554 F.3d at 1009. U.S. Patent No. 8,993,233 ("the '233 patent") does not
13 provide *any* data or testing results that support Broad's argument, Ex. 2024, 73:22–29; F73. Broad
14 cites none.

15 *Second*, unexpected results must show "that the claimed invention exhibits some superior
16 property or advantage that a [POSA] would find surprising or unexpected." *In re Mayne*, 104 F.3d
17 at 1343. Here, Broad offers no surprising or unexpected results. Rather, it relies on benefits that
18 a POSA would have expected to achieve. Ex. 1420, ¶152. Dr. Seeger's testimony fails to fill the
19 gaps in Broad's argument. He, like Broad, cites only to the '233 patent's unsubstantiated
20 statements for support. Ex. 2454, ¶283. That is wholly inadequate. Broad has failed to meet its
21 burden under § 41.208(b).

22 **F. Broad's "Non-Limited RNA Claims" Correspond To Count 1 Under**
23 **37 C.F.R. § 41.207(b)(2)**

24 On page 20, lines 18–24 of Motion 3, Broad argues that because "Count 1 is directed to
25 eukaryotic CRISPR-Cas9 systems that require single molecule or chimeric RNA," those of

1 "Broad's involved claims . . . not limited to such a single molecule RNA" should be designated as
2 not corresponding to Count 1. Mot. 20:18–24; *see id.* at 20:18–31:21. Broad makes this argument
3 as to three subsets of claims (collectively, "the non-limited RNA claims"): (1) those "that do not
4 require an RNA component at all"; (2) those "that are generic as to the RNA component and do
5 not use the term 'guide RNA'"; and (3) those "that are generic as to the RNA component and that
6 use the term 'guide RNA,'" *id.* at 21:1–3. The response is that all of Broad's involved claims,
7 when properly construed, are single-guide claims, Ex. 1420, ¶¶51–54, and Broad, in attempting to
8 de-designate the non-limited RNA claims from Count 1, has failed to meet its burden under
9 § 41.207(b)(2) to prove otherwise, 37 C.F.R. § 41.207(b)(2); *see* 37 C.F.R. §§ 41.121(b),
10 41.208(b); *Schaenzer*, 2003 WL 22521270, at *2.

11 **1. Broad's Claims Reciting The Term "Guide RNA" Are Single-Guide**
12 **Claims**

13 On page 22, line 21 through page 28, line 21 of Broad's Motion 3, Broad argues that
14 Broad's claims reciting "guide RNA" are generic-guide claims. Mot. 22:21–28:21. The response
15 is that, irrespective of whether the term "guide RNA" had a plain and ordinary meaning in the art,
16 which it did not, each of Broad's patent specifications clearly and unequivocally define "guide
17 RNA" as a single-molecule guide. Ex. 1420, ¶53-54; F74. For example, U.S. Patent No. 8.697,359
18 ("the '359 patent") provides:

> 19 In aspects of the invention the terms "*chimeric RNA*", "*chimeric guide RNA*",
> 20 "*guide RNA*", "*single guide RNA*" and "synthetic guide RNA" are *used*
> 21 *interchangeably* and *refer to the polynucleotide sequence* comprising the guide
> 22 sequence, the tracr sequence and the tracr mate sequence.

23 Ex. 2011, 12:6–10 (emphases added); F75. Each of Broad's remaining specifications include this
24 same limiting definition. F76. As the Board previously held in the 115 interference, this disclosure
25 defines a "guide RNA" as a singular "polynucleotide sequence" comprising the "guide sequence,

1 the tracr sequence[,] and the tracr mate sequence." Ex. 1101, 29:22–30:5; Ex. 1420, ¶54; F77; *see*
2 *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998) (holding that
3 where "a patent applicant has elected to be a lexicographer by providing an explicit definition in
4 the specification for a claim term, . . . the definition selected by the patent applicant controls"). A
5 POSA as of the priority date would have understood that "guide sequence" and "tracr mate
6 sequence" refer to the crRNA component of the CRISPR-Cas system and "tracr sequence" refers
7 to the tracrRNA component of the CRISPR-Cas system. *See, e.g.*, Ex. 2011, 12:10–15, 21:18–25,
8 21:41–45; Ex. 2202, Fig. 5(A) (depicting a schematic diagram of the components of a CRISPR-
9 Cas9 system); Ex. 2214, Fig. 4; Ex. 1420, ¶55; F78. Thus, a "guide RNA," as defined by Broad,
10 comprises both RNA components of the CRISPR-Cas system—crRNA (by including guide
11 sequence and tracr mate sequence) and tracrRNA (by including tracr sequence)—in a singular
12 polynucleotide sequence, *i.e.*, a single-molecule guide. Ex. 1420, ¶55; F79. Moreover, the term
13 "guide RNA" is used interchangeably with "chimeric RNA" and "single guide RNA," which
14 indisputably are single-molecule guides. Ex. 1420, ¶56; F80. The above definition is not limited
15 to certain embodiments, contrary to Broad's current argument. Mot. 27:23–26. In fact, while the
16 specification uses the qualifying phrase "*several* aspects" or "*some* aspects" in other instances, *see,*
17 *e.g.*, Ex. 2011, 14:21–22, 23:18–27 (emphasis added), the above definition contains no such
18 qualifier. *Id.* at 12:6–10; Ex. 1420, ¶¶57–58; F81.

19 As this Board found in the 115 interference, Broad's claim differentiation arguments are
20 unavailing as a matter of fact and law. Mot. 24:1–25:16; *see* Ex. 1101, 32:16–18 ("Although some
21 dependent claims, such as claim 18 of the '359 patent, might indicate by claim differentiation that
22 the term "guide RNA" is generic, that presumption is overcome by Broad's specification.").
23 Indeed, in light of the disclosure that explicitly defines "guide RNA," claim differentiation, which

1 is merely a rebuttable inference based on the rules of ordinary word usage, has no place in this
2 case. That is why claim differentiation is "a guide, not a rigid rule"—it is "a rebuttable
3 presumption that may be overcome by a contrary construction dictated by the written
4 description[.]" *Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1323 (Fed. Cir.
5 2016); *see GPNE Corp. v. Apple Inc.*, 830 F.3d 1365, 1371 (Fed. Cir. 2016) ("Claim differentiation
6 is 'not a hard and fast rule,' but rather a presumption that will be overcome when the
7 specification . . . dictates a contrary construction." (quoting *Seachange Int'l, Inc. v. C-Cor, Inc.*,
8 413 F.3d 1361, 1369 (Fed. Cir. 2005)).
9 Such is the case here. The explicit, clear, and unambiguous definition provided in the
10 specification makes it unnecessary to resort to weak inferences from cherry-picked claims. *See*
11 Mot. 24:17–25:16. Broad *chose* to include that definition in *each* of its specifications, and that
12 definition controls over any inferences it might try to cobble together from other aspects of its
13 specification. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1379–82 (Fed. Cir.
14 2009) (five-judge panel) (holding that where a patentee "explicitly defines" a term in specification,
15 "[t]hat definition controls" over other references in specification, "preferred embodiments," and
16 extrinsic evidence); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1321 (Fed. Cir. 2005) ("[T]he
17 specification acts as a dictionary when it expressly defines terms used in the claims or when it
18 defines terms by implication." (internal quotation marks and citation omitted)).
19 Broad's remaining argument is equally unavailing. It contends that "[t]he Broad patents
20 disclose preferred embodiments that are dual-molecule RNA systems" and thus, "[i]f 'guide RNA'
21 were limited to single-molecule RNA systems, . . . such preferred embodiments would not be
22 covered by the patent claims." Mot. 25:18–21. As with claim differentiation, however, preferred
23 embodiments cannot overcome a clear and unambiguous definition. *Martek*, 579 F.3d at 1380–

1 81. Rather, the rule's application "is a question specific to the content of the specification," *Wang*
2 *Labs., Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1383 (Fed. Cir. 1999), and the Federal Circuit "ha[s]
3 previously interpreted claims to exclude embodiments where"—as here—"those embodiments are
4 inconsistent with unambiguous language in the patent's specification[,]" *Sinorgchem Co.,*
5 *Shandong v. Int'l Trade Comm'n*, 511 F.3d 1132, 1138 (Fed. Cir. 2007). Here, that "unambiguous
6 language" is found in the patent's express definition.

7 Most notably though, Broad fails to support its argument by explaining the import of even
8 a *single* embodiment. F82. This is not surprising, as the term "guide RNA" is used throughout
9 the specifications to refer to single-molecule guide RNA, while different terminology is used to
10 refer to dual-molecule guide RNA. *See, e.g.*, Ex. 2016, 105:1–106:16 (Example 6); Ex. 2013,
11 38:33–43; Ex. 2011, 21:41–45, 43:49–53, 43:56–50:5 (Example 1); Ex. 1420, ¶¶63–64; F83.
12 Example 6 of U.S. Patent No. 8,889,356 uses the term "guide RNA" to refer to only to single-
13 molecule guides. Ex. 2016, 105:1–106:16; Ex. 1420, ¶64; F84. It uses "tracrRNA" and "direct
14 repeat sequence" to refer to a dual-molecule guide, but uses "chimeric guide RNA" or "guide
15 RNA" to refer to a single-molecule guide. Ex. 2016, 105:1–106:16; Ex. 1420, ¶64; F85.
16 Moreover, it only reports the results of the single-molecule guides, concluding that the "optimized
17 chimeric guide RNA works better as indicated in Fig. 3." Ex. 2016, 106:9–10; Ex. 1420, ¶64; F86.
18 The referenced Fig. 3 also only shows the results of guide sequences 1, 2, and 3, which the
19 specification describes as single-molecule guides. Ex. 2016, 105:1–106:16, Fig. 3; Ex. 1420, ¶64;
20 F87. Example 6 is therefore titled "[o]ptimization of the Guide RNA," referring to only the single-
21 molecule guides that were tested. Ex. 2016, 105:4–5; Ex. 1420, ¶64; F88.

22 Dr. Seeger mischaracterizes certain disclosures in Broad's specifications as purportedly
23 using "guide RNA" for dual-molecule guides. Ex. 2454, ¶¶179–81. However, as Dr. Stoddard

1 explains, when these disclosures are read in proper context, none of them uses the term "guide
2 RNA" to refer to a dual-molecule guide. Ex. 1420, ¶¶65–70; F89. Similarly, column 38, lines 33
3 through 43 of U.S. Patent No. ("the '308 patent") fails to support Broad's construction. Ex. 2454,
4 ¶180. This section relates to single-guide molecules and uses the phrase "or combination of
5 tracrRNA and crRNA" to describe the term "chimeric guide RNA." Ex. 2013, 38:33–43; Ex.
6 1420, ¶65; F90. Likewise, those portions of the '359 patent to which Dr. Seeger cites, Ex. 2454,
7 ¶181 (citing Ex. 2011, 21:41–45, 43:57–50:5 (Example 1)), fail to even recite the term "guide
8 RNA," let alone use it in reference to a dual-molecule guide, Ex. 1420, ¶67; F91.

9 In sum, the intrinsic evidence, in particular the clear definition provided in the
10 specification, *compels* construing "guide RNA" in Broad's claims as a single-molecule guide, and
11 Broad has failed to justify de-designation. Ex. 1420, ¶74–75; F74–91.

12 **2. The Term "Guide RNA" Used In Broad's Claims Did Not Have A**
13 **Plain And Ordinary Meaning In The Art**

14 Broad argues that "a POSA would understand the plain meaning of 'guide RNA' to be a
15 generic term." Mot. 26:3–4. In an interference, "the patent claim shall be given its broadest
16 reasonable construction *consistent with the specification*." *Bamberger v. Cheruvu*, 55 U.S.P.Q.2d
17 1523, at *2 (B.P.A.I. 1998) (emphasis added). Further, extrinsic evidence purportedly
18 demonstrating the plain and ordinary meaning of a term is "entitled to no weight" where, as here,
19 the intrinsic evidence clearly sets forth, indeed explicitly dictates, the meaning of a term. *Vitronics*
20 *Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996); *see also Martek*, 579 F.3d at
21 1380–81.

22 Here, the patent contains an express definition, which is conclusive. *See Martek*, 579 F.3d
23 at 1380–81. Moreover, the other intrinsic evidence clearly and consistently shows that "guide
24 RNA" is a single-molecule guide, F74–91. Under those circumstances, there is no basis to look to

1 "plain meaning" to vary what the specification defines and teaches. Even so, the term "guide
2 RNA" did not have a plain and ordinary meaning in the art as of the priority date. Ex. 1420, ¶76;
3 F92. Both Broad and Dr. Seeger improperly rely on a slew of statements made *after* the priority
4 date, including statements made: (1) during prosecution of the '510 application; (2) in Ex. 2061,
5 U.S. Patent Application 13/842,859 ("the '859 application"), filed March 15, 2013; (3) during the
6 '048 interference; and (4) in "patent applications filed in . . . 2013," and "after 2012," including in
7 a "2014 paper," among others. Mot. 26:13–27:3; Ex. 2454, ¶¶166–68. These arguments carry no
8 weight.

9 Broad's two cited references published *before* the priority date, *i.e.*, Jinek 2012 (Ex. 2202),
10 and U.S. Patent Application 61/652,086 ("the '086 application") (Ex. 2002), demonstrate that there
11 was no plain and ordinary meaning at the time for "guide RNA," Mot. 27:4–6; Ex. 2454, ¶¶164–
12 65, 167; Ex. 1420, ¶77; F93, which is undoubtedly why the inventors included an explicit
13 definition. Notably, while Broad and Dr. Seeger argue that these references are representative of
14 the state of the art generally, both references actually emanate from a *single* source, *i.e.*, the CVC
15 inventors, Ex. 2202, 816, Ex. 2002, 169–70 ("Inventor Information"); and, though Jinek 2012 uses
16 the term "guide RNA," *e.g.*, Ex. 2202, 820, the '086 application does not, Ex. 2002; F94. Rather,
17 Broad and Dr. Seeger attempt to paste together an argument through a series of conclusory
18 assertions based on the '086 application's definition of an entirely different term, *i.e.*, "DNA-
19 targeting RNA." Ex. 2454, ¶167 (citing Ex. 2002, ¶[00045]). For example, Dr. Seeger asserts that
20 "'DNA-targeting RNA' is also referred to as 'guide RNA'" while citing to the '086 application,
21 Ex. 2454, ¶167; but, as noted above, the '086 application *never uses* the term "guide RNA." The
22 true source of Dr. Seeger's information is the 048 interference, which Dr. Seeger notes only with
23 a "*see also*" cite. *Id.* Such tactics taint the entirety of Broad's Motion 3 and Dr. Seeger's

1 declaration and should not be overlooked or rewarded. This leaves only Jinek 2012, which the
2 Board in the 115 interference, faced with similar evidence, found to be insufficient. Ex. 1101,
3 26:13–27:17. Accordingly, the ambiguity in the art regarding the meaning of "guide RNA" as of
4 the priority date further underscores why a POSA would have viewed the intrinsic evidence—
5 particularly Broad's explicit definition—as the controlling definition of "guide RNA" in the
6 context of Broad's patents. The intrinsic evidence here makes it clear that the terms "guide RNA,"
7 "chimeric guide RNA," and "single guide RNA" all defined as "the polynucleotide sequence
8 comprising the guide sequence, the tracr sequence and the tracr mate sequence," *i.e.*, a single-
9 molecule guide, and are used interchangeably. Ex. 1420, ¶¶80–81.

10 **3. Claims 15, 17–26, 28–41 Of The '713 Patent And Claims 1–24 Of The**
11 **'418 Patent Are Single-Guide Claims**

12 On page 21, lines 10–12 of its Motion 3, Broad argues that "claims 15, 17–26, 28–41 of
13 the '713 patent and claims 1–24 of the '418 patent do not use the term 'guide RNA' and are
14 indisputably not limited to single-molecule RNA[.]" Mot. 21:10–12 (capitalization normalized);
15 *see id.* at 21:10–22:20. The response is that, as in the 115 interference, "Broad does not set forth
16 a clear argument that the subject matter of [these] generic claims, . . . would not be anticipated or
17 rendered obvious by the single-molecule RNA configuration CRISPR-Cas9 system recited in
18 Count 1[.]" Ex. 1101, 52:18–22; *see* 37 C.F.R. § 41.207(b)(2). In fact, Broad makes no such
19 argument in its Motion 3, and accordingly, it is waived. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*,
20 582 F.3d 1288, 1296 (Fed. Cir. 2009) ("If a party fails to raise an argument . . . , or presents only
21 a skeletal or undeveloped argument . . . , we may deem that argument waived[.]"). It is well
22 settled, however, that a species, here, Count 1, anticipates "generic" claims, here, claims 15, 17–
23 26, 28–41 of the '713 patent and claims 1–24 of the '418 patent. *In re Slayter*, 276 F.2d 408, 411
24 (C.C.P.A. 1960) ("It is well settled that a generic claim cannot be allowed to an applicant if the

prior art discloses a species falling within the claimed genus[.]"). Such is the case here. Accordingly, as in the 115 interference, "Broad has failed to meet its burden of showing that these claims were not properly designated as corresponding to Count 1." Ex. 1101, 52:21–23.

4. Broad's Argument That Its "Generic Claims . . . Should Be Designated As Not Corresponding To Count 1" Is Just As Unavailing Here As It Was In The 115 Interference

On page 29, lines 1 to 3 of its Motion 3, Broad argues that its "generic claims encompassing both single and dual-molecule RNA systems should be designated as not corresponding to Count 1[.]" Mot. 29:1–3 (capitalization normalized); *see id.* at 29:1–31:21. The response is that Broad's argument fails here, just as it did in the 115 interference, as matter of law. Ex. 1101, 47:12–52:23. In fact, Broad does nothing to address the Board's prior determinations as to its argument; instead, choosing simply to reuse its unavailing arguments from the 115 interference. Specifically, repeating comment 186 of the Final Rulemaking, Broad contends that the rule of 37 C.F.R. § 41.207(b)(2) "is not . . . a *per se* rule that must rigidly be applied, even if doing so would work an inequitable outcome." Mot. 29:7–9. As the Board previously held, however, comment 186 does not relate to § 41.207(b)(2); rather, it "relates to 37 C.F.R. § 41.207(b)(1), which provides the rebuttable presumption that all claims designated as corresponding to a count stand or fall together." Ex. 1101, 48:7–9; *see* Ex. 2305, 69 Fed. Reg. 49960-01, 49994 (Aug. 12, 2004). Moreover, as in the 115 interference, Broad's argument, that fairness and equity are (or should be) considerations in determining claim correspondence, finds no support in § 41.207(b)(2) or any other law, and Broad cites none. Ex. 1101, 48:16–49:14. Broad's citation to *Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington*, 334 F.3d 1264 (Fed. Cir. 2003), is misplaced. As the Board previously held, "[t]hat case does not discuss or hold issues of claim correspondence, as determined by a one-way test, but instead is about determination of interference-in-fact by a two-way test." Ex. 1101, 49:18–20. Finally, Broad argues that by failing to de-designate Broad's

1 "generic claims," the Board would cause Broad to "lose" its claims. Mot. 31:10–12. This
2 argument presumes, without proving, that Broad was first to invent the subject matter of its generic
3 claims. In a circular fashion, Broad assumes that it was first to invent, but there is no basis for
4 such an assumption, especially as to Junior Party Broad, or for the contention that de-designation
5 is somehow required. In fact, Broad has identified no legal principle that mandates de-designation
6 here. Accordingly, Broad has failed to meet its burden.

7 **III. CONCLUSION**

8 For the foregoing reasons, ToolGen respectfully requests that Broad's Motion 3 be denied.

9 Respectfully submitted,

10 Dated: August 6, 2021 /Timothy J. Heverin/
11 Timothy J. Heverin
12 Reg. No. 77,386
13 JONES DAY
14 Counsel for Senior Party ToolGen, Inc.
15

APPENDIX 1: LIST OF EXHIBITS CITED

Ex. No.	Description
1022	U.S. Application No. 12/565,589, as filed September 23, 2009.
1101	Paper 877, Decision on Motions 37 C.F.R. § 41.125(a), Interference 106,115, September 10, 2020.
1206	Jinek *et al.*, A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity, *Science*, 337, 816–21 (2012), with Supplemental Material.
1207	Makarova *et al.*, Evolution and Classification of the CRISPR-Cas Systems, *Nature Review Microbiology*, 9, 467–77 (2011).
1243	Molecular Cloning: A Laboratory Manual (3rd ed. Cold Spring Harbor Laboratory Press 2001), Chapter 16.
1248	Paul *et al.*, Effective expression of small interfering RNA in human cells, *Nature Biotech.*, 20, 505–508 (2002).
1309	Ichim *et al.*, RNA Interference: A Potent Tool for Gene-Specific Therapeutics, *American Journal of Transplantation*, 4, 1227–1236 (2004).
1310	Paddison *et al.*, Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells, *Genes & Development*, 16, 948–958 (2002).
1311	Sapranaukas et al., The *Streptococcus thermophiles* CRISPR/Cas system provides immunity in *Escherichia coli*, *Nucleic Acids Research*, 39(21), 9275–9282 (2011).
1312	Sequence of HE980540.1, ENA.
1313	Sequence of HE980450.1.
1314	Wu *et al.*, Effect of Genome Size on AAV Vector Packaging, *The American Society of Gene & Cell Therapy*, 18(1), 80–86 (2010).
1315	Her *et al.*, 435-bp Liver Regulatory Sequence in the Liver Fatty Acid Binding Protein (L-FABP) Gene Is Sufficient to Modulate Liver Regional Expression in Transgenic Zebrafish, *Developmental Dynamics*, 227, 347–356 (2003).
1316	Zon and Orkin, Sequence of the human GATA-1 promoter, Nucleic Acids Research, 20(7), 1812 (1992).
1317	Hamamoto *et al.*, Analysis of functional domains of endoglucanases from *Clostridium cellulovorans* by gene cloning, nucleotide sequencing and chimeric protein construction, *Mol. Gen. Genet.*, 231, 471–479 (1992).

Ex. No.	Description
1318	Matsui *et al.*, Production of chimeric protein coded by the fused viral H-*ras* and human N-*ras* genes in *Escherichia coli*, *Gene*, 52, 215–223 (1987).
1319	Rebar *et al.*, Induction of angiogenesis in a mouse model using engineered transcription factors, *Nature Medicine*, 8(12), 1427–1432 (2002).
1320	Cermak *et al.*, Efficient design and assembly of custom TALEN and other TAL effector-based constructs for DNA targeting, *Nucleic Acids Research*, 39(12), e82, 1–11 (2011).
1321	Reiss *et al.*, RecA protein stimulates homologous recombination in plants, *Proc. Natl. Acad. Sci. USA*, 94, 3094–3098 (1996).
1322	Los *et al.*, Halotag™ Technology: Cell Imagining and Protein Analysis, *Cell Notes*, 14, 1–11 (2006).
1323	Dai *et al.*, The Transcription Factors GATA4 and dHAND Physically Interact to Synergistically Activate Cardiac Gene Expression through a p300-dependent Mechanism, *J. Biol. Chem.*, 277(27), 24390–24398 (2002).
1324	Fischer-Fantuzzi and Vesco, Cell-dependent efficiency of reiterated nuclear signals in a mutant simian virus 40 oncoprotein targeted to the nucleus, *Mol. Cell. Biol.*, 8(12), 5495–5503 (1988).
1325	Planey *et al.*, Inhibition of Glucocorticoid-induced Apoptosis in 697 Pre-B Lymphocytes by the Mineralocorticoid Receptor N-terminal Domain, *J. Biol. Chem.*, 277(44), 42188–42196 (2002).
1327	Brizzard and Chubet, Epitope Tagging of Recombinant Proteins, *Current Protocols in Neuroscience*, 5.8.1–5.8.10 (1997).
1328	Hollenbaugh and Aruffo, Construction of Immunoglobulin Fusion Proteins, *Current Protocols in Immunology*, 10.19A.1–10.19A.11 (2002).
1329	Margolin, Green Fluorescent Protein as a Reporter for Macromolecular Localization in Bacterial Cells, *Methods*, 20, 62–72 (2000).
1420	August 6, 2021 Declaration of Dr. Barry Stoddard, Ph.D.
2001	U.S. Application 61/736,527, Zhang et al., December 12, 2012.
2002	U.S. Application 61/652,086, Jinek et al., May 25, 2012.
2011	U.S. Patent No. 8,697,359, issued on April 15, 2014, to Feng Zhang.
2013	U.S. Patent No. 8,895,308, issued on November 25, 2014, to Feng Zhang and Fei Ran.

Ex. No.	Description
2016	U.S. Patent No. 8,889,356, issued on November 18, 2014, to Feng Zhang.
2017	U.S. Patent No. 8,865,406, issued on October 21, 2014, to Feng Zhang and Fei Ran.
2024	U.S. Patent No. 8,993,233, issued on March 31, 2015 to Feng Zhang et al.
2029	U.S. Patent No. 8,871,445, issued on October 28, 2014, to Le Cong and Feng Zhang.
2060	U.S. Patent No. 8,889,418 issued on November 18, 2014, to Feng Zhang, et al.
2061	U.S. Patent Application 13/842,859, to Doudna et al.
2201	Cong *et al.*, Multiplex Genome Engineering Using CRISPR/Cas Systems, *Science*, 339, 819–823 (2013) with Supplemental Material.
2202	Jinek *et al.*, A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity, *Science*, 337 816–821 (2012) with Supplemental Material.
2214	Deltcheva *et al.*, CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III, *Nature*, 471, 602–607 (2011) with Supplementary Materials.
2226	Ran *et al.*, In vivo genome editing using Staphylococcus aureus Cas9, *Nature*, 520,186–191 (2015).
2258	Fieck *et al.*, Modifications of the E. coli Lac repressor for expression in eukaryotic cells: effects of nuclear signal sequences on protein activity and nuclear accumulation, *Nucleic Acids Res.*, 20(7), 1785–1791 (1992).
2262	In-Hyun Park *et al.*, Regulation of Ribosomal S6 Kinase 2 by Mammalian Target of Rapamycin, *J. Biol. Chem*., 277(35), 31423–31429 (2002).
2263	Brothers, *et al.*, Unexpected Effects of Epitope and Chimeric Tags on Gonadotropin-Releasing Hormone Receptors: Implications for Understanding the Molecular Etiology of Hypogonadotropic Hypogonadism, *The Journal of Clinical Endocrinology & Metabolism*, 88(12), 6107–6112 (2003).
2264	Turner *et al.*, Carboxyl-terminal Vesicular Stomatitis Virus G Proteintagged Intestinal Na+-dependent Glucose Cotransporter (SGLT1*), J. Biol. Chem.*, 271(13), 7738–7744 (1996).
2265	Song and Markley, Cautionary Tail: The Presence of an NTerminal Tag on Dynein Light-Chain Roadblock/LC7 Affects Its Interaction with a Functional Partner, *Protein & Peptide Let.*, 14(3), 265–268 (2007).
2267	Lyssenko *et al.*, Cognate putative nuclear localization signal effects strong nuclear localization of a GFP reporter and facilitates gene expression studies in Caenorhabditis elegans, *BioTechniques*, 43(5), 596–600 (2007).

Ex. No.	Description
2268	Luo *et al.*, Multiple Nuclear Localization Sequences Allow Modulation of 5-Lipoxygenase Nuclear Import, *Traffic*, 5, 847–854 (2004).
2305	Rules of Practice Before the Board of Patent Appeals and Interferences, 69 Fed. Reg. 49960-01.
2454	Declaration of Christoph Seeger, executed May 28, 2021.
2504	Jennifer Tseng, https://blog.addgene.org/15-years-of-addgene-the-top-15-plasmids, (Jan. 8, 2019) (accessed on October 8, 2019).
2648	Lino *et al.*, Delivering CRISPR: a review of the challenges and approaches, *Drug Delivery*, 25(1), 1234–1257 (2018).
2654	Liu *et al.*, Synthetic chimeric nucleases function for efficient genome editing, *Nat Commun.*, 10, 5524 (2019).
2683	Ma *et al.*, Engineer chimeric Cas9 to expand PAM recognition based on evolutionary information, *Nat Commun.*, 10, 560 (2019).

APPENDIX 2: STATEMENT OF MATERIAL FACTS

Junior Party's Alleged Facts 1-40 and Senior Party's Answers

1. Count 1 is an "or" count drawn (first half) to a eukaryotic CRISPR-Cas9 system comprising Cas9 and RNA that comprises a guide sequence fused to a tracr sequence that targets and hybridizes to a DNA target sequence (Ex. 2011, '359 patent, claim 18), or (second half) a mammalian cell comprising a CRISPR-Cas9 system comprising Cas9 or a nucleic acid encoding Cas9 and a chimeric guide RNA (Ex. 2062, ToolGen, claim 85). Paper 1 at 12-13.

Response: Admitted.

2. Proposed Count 2 substitutes the Broad half of the current "or" count with allowed claim 1 of the 710 application that encompasses both dual-molecule and single-molecule RNA. Broad Motion 1 at 4.

Response: Admitted.

3. Under Count 1 or Proposed Count 2, one may deliver the system via non-vector means such as microinjection of the system as a mature RNP or a RNA and mRNA. Paper 1 at 12-13; Broad Motion 1 at 4.

Response: Admitted.

4. There is no teaching or suggestion in either Count 1 or Proposed Count 2, or in the prior art, directing a POSA to vector-delivered RNA for use in eukaryotic cells, nor would a 2012 POSA have had a reasonable expectation of success in so doing. *See generally* Ex. 2454, Seeger Decl. ¶¶ 212-27; Ex. 2110, Paper 893, 048 Decision on Motions; Ex. 2121, Paper 877, 115 Decision on Motions; Paper 1 at 12-13; Broad Motion 1 at 4.

Response: Denied.

5. There are many ways that the RNA components of the system can be delivered to a eukaryotic cell, many of which performed poorly or failed outright. *See* Ex. 2454, Seeger Decl. ¶¶

1 212-27.

2 **Response: The statement is too vague to be admitted or denied, therefore, ToolGen is**

3 **unable to admit or deny this fact.**

4 6. ToolGen's priority application (Kim P1) discloses for delivery to the eukaryotic cell only

5 a sequential process that includes adding extraordinarily high amounts of already- translated RNA

6 to cells previously transfected with Cas9. *Id*. ¶¶ 219-22; Ex. 2062 at 9.

7 **Response: Denied.**

8 7. Dr. Zhang's vector systems are among the most requested CRISPR vectors by researchers

9 in the field. Exs. 2502-2505; Ex. 2454, Seeger Decl. ¶¶ 225-27.

10 **Response: Denied.**

11 8. Broad licensee Editas Medicine is conducting a clinical trial using CRISPR-Cas9 systems

12 that include vector delivery to human patients. *Id*.; Ex. 2687, MacLeod 2021; Exs. 2517, 2686-87.

13 **Response: Admitted, but only to the extent the clinical trial involves two patients;**

14 **otherwise, denied.**

15 9. Neither Count 1 nor Proposed Count 2 recites any particular ortholog of Cas9 protein,

16 including SaCas9. Paper 1 at 12-13; Broad Motion 1 at 4.

17 **Response: Admitted.**

18 10. There is no teaching or suggestion in Count 1, Proposed Count 2, or the prior art to use

19 SaCas9 in CRISPR-Cas9 systems in eukaryotic cells.

20 **Response: Denied.**

21 11. CRISPR-Cas9 systems using SaCas9 possess a combination of small size and high efficacy

22 in eukaryotes. Ex. 2017, '406 patent, 83:1-25-84:1-23; Ex. 2454, Seeger Decl. ¶¶ 228-48.

Response: This statement is too vague to be admitted or denied, therefore, ToolGen is unable to admit or deny this fact.

12. Small size and high efficacy in eukaryotes render CRISPR-SaCas9 systems advantageous for use in eukaryotic cell-based applications where vector delivery using the highly versatile adeno-associated virus (AAV) is favored because AAV vectors are space-constrained. Ex. 2454, Seeger Decl. ¶¶ 237, 245; Ex. 2017, '406 patent, 83:1-25-84:1-23.

Response: The statement is too vague to be admitted or denied, therefore, ToolGen is unable to admit or deny this fact.

13. As of 2012, the most commonly studied Cas9 ortholog in prokaryotes was from *Streptococcus pyogenes* ("SpCas9"), and more than 600 bacterial Cas9 orthologs that had been identified. Ex. 2226; Ex. 2454, Seeger Decl. ¶ 234.

Response: Denied.

14. SpCas9 is larger than SaCas9. Ex. 2454, Seeger Decl. ¶ ¶ 235, 242-43, 245.

Response: Admitted.

15. As of 2012, there was nothing in the art pointing the POSA to use SaCas9 in eukaryotic cells including nothing point to SaCAs9 out of the many known "small" Cas9 orthologs that are similar in size to, or smaller than, SaCas9. Ex. 2454, Seeger Decl. ¶¶ 230-44.

Response: Denied.

16. Broad determined that using Cas9 from *Streptococcus aureus* in a CRISPR-Cas9 system for DNA cleavage or editing or for modulating transcription in a eukaryotic cell provides a surprising combination of benefits not taught or suggested by the prior art, namely high efficiency and small size. *See* Ex. 2454, Seeger Decl. ¶¶ 228-48.

Response: Denied.

1 17. SaCas9 is used for more therapeutic applications than any other Cas9 ortholog. Ex. 2454,
2 Seeger Decl. ¶ 246; *See* Ex. 2017, 406 Patent at 83:25-84:23; Exs. 2687, 2517, 2686.
3 **Response: The statement is too vague to be admitted or denied, therefore, ToolGen is**
4 **unable to admit or deny this fact.**
5 18. All claims of Broad's 418 patent (Ex. 2060) are directed to the improvement in which the
6 Cas9 is not taken from a single organism but rather is a chimeric Cas9 that includes two fragments
7 from different Cas9, which has unexpected benefits. *Id*. at 83:45-52; Ex. 2454, Seeger Decl. ¶¶
8 249-57.
9 **Response: Admitted to the extent the Broad Ex. 2060 Claim 1 is directed to a chimeric**
10 **Cas9 that includes two fragments from different Cas9; otherwise, denied.**
11 19. Count 1, Proposed Count 2, and the prior art do not teach, suggest, or provide motivation
12 to a POSA to design a chimeric Cas9 that is comprised of two fragments from different organisms.
13 Ex. 2454, Seeger Decl. ¶¶ 249-57; Paper 1 at 12-13; Broad Motion 1 at 4.
14 **Response: Denied.**
15 20. Ex. 2060 418 patent, 4:21-25 recites "[t]hese chimeric Cas9 proteins may have a higher
16 specificity or a higher efficiency than the original specificity or efficiency of either of the
17 individual Cas9 enzymes from which the chimeric protein was generated."
18 **Response: Admitted.**
19 21. The 418 patent (Ex. 2060 at 83:45-52) also recites benefits of a chimeric Cas9.
20 **Response: Admitted to the extent Ex. 2060 recites benefits of a chimeric Cas9 without**
21 **providing any supporting data; otherwise, denied.**
22 22. Neither Count 1 nor Proposed Count 2 recite that the Cas9 has any NLSs at all nor do they
23 recite use of two or more NLSs. Paper 1 at 12-13; Broad Motion 1 at 4.

1 **Response: Denied.**

2 23. The prior art did not provide any teaching or suggestion to use two or more NLSs in a
3 CRISPR-Cas system in a eukaryotic cell nor was there a reasonable expectation of success in using
4 two or more NLSs. Ex. 2454, Seeger Decl. ¶¶ 258-78.

5 **Response: Denied.**

6 24. Broad determined that, unexpectedly, the use of two or more NLSs resulted in CRISPR-
7 Cas9 systems with significantly improved localization to the nucleus, as compared to systems
8 lacking two or more NLSs. *See generally* Ex. 2454, Seeger Decl. ¶¶ 258-78; Ex. 2001, Zhang B1,
9 Figure 1B; Ex. 2201, Cong 2013, Figure 1A; Ex. 2793.

10 **Response: Denied.**

11 25. A POSA would have understood that adding amino acids to a protein such as Cas9 could
12 alter its folding affecting its structure and function in ways that were not predictable. Ex. 2454,
13 Seeger Decl. ¶¶ 271-76; Ex. 2258 at 1785-1790; Exs. 2263-2265.

14 **Response: Admitted.**

15 26. Neither Count 1 nor Proposed Count 2 recites that the Cas9 is fused to specified protein
16 domains. Paper 1 at 12-13; Broad Motion 1 at 4.

17 **Response: Denied.**

18 27. There is no teaching or suggestion in Count 1, Proposed Count 2, or the prior art directing
19 a POSA to modify the naturally occurring Cas9 to include protein domains. Ex. 2454, Seeger Decl.
20 ¶¶ 279-84.

21 **Responsne: Denied.**

22 28. The 233 patent notes that there is a benefit to fusing functional domains to Cas9, as doing
23 so can "to turn the Cas9/gRNA CRISPR system into a generalized DNA binding system [which]

1 can execute functions beyond DNA cleavage." Ex. 2024 at 73:22-37.

2 **Response: Admitted to the extent the quoted language appears in Ex 2024; otherwise,**

3 **denied.**

4 29. Broad's 713 patent (Ex. 2043), includes claims, including claims 15-26 and 28-41, that are

5 not limited to single-molecule RNA and do not contain the term "guide RNA." *See* Ex. 2454,

6 Seeger Decl. ¶¶ 150-151.

7 **Response: Denied.**

8 30. Independent claim 1 and dependent claims 2-24 of Broad's 418 patent (Ex. 2060) do not

9 recite any RNA component. *See* Ex. 2454, Seeger Decl. ¶¶ 152-54.

10 **Response: Denied.**

11 31. In U.S. Patent No. 8,895,308, claim 1 describes a method using CRISPR-Cas system

12 having "guide RNA" that hybridizes to the target sequence and claim 6 covers the "method of

13 claim 1, wherein the guide RNA comprises a guide sequence and a tracr sequence." Ex. 2013.

14 **Response: Admitted to the extent the quoted language appears in Ex 2013; otherwise,**

15 **denied.**

16 32. In U.S. Patent No. 8,906,616, claim 1 describes a CRISPR-Cas system having a "guide

17 RNA" polynucleotide sequence comprising a guide sequence, a tracr mate sequence, and a tracr

18 sequence, claim 2 covers the "composition of claim 1, wherein the modified guide RNA comprises

19 a chimeric guide sequence and a tracr sequence" and claim 5 covers the "composition of claim 1,

20 wherein the modification comprises fusing the tracr mate sequence and the tracr sequence through

21 an artificial loop." Ex. 2014.

22 **Response: Admitted to the extent the quoted language appears in Ex 2014; otherwise,**

23 **denied.**

1 33. In the 965 patent (Ex. 2012), none of the dependent claims include limitations that the

2 components of the guide RNA be fused or bound to one another in a chimeric manner.

3 **Response: Denied.**

4 34. The Broad patents disclose preferred embodiments that are dual-molecule RNA systems.

5 Ex. 2011, 359 patent at 43:49-53, 44:5-8; Ex. 2454, Seeger Decl. ¶¶ 179-81.

6 **Response: Denied.**

7 35. On April 13, 2015, ToolGen filed the 510 application as a continuation of PCT application

8 PCT/KR2013/009488 (the "ToolGen PCT application") (Ex. 2067), which had been filed on

9 October 23, 2013, and claiming priority to provisional patent applications dating back to October

10 23, 2012. Ex. 2062, 510 application; Ex. 2067, ToolGen PCT.

11 **Response: Admitted.**

12 36. ToolGen's patent applicatons explicitly define "guide RNA" to encompass both dual- and

13 single-molecule RNA configurations:

14 In the present invention, ***the guide RNA may consists of two RNA***, i.e., CRISPR RNA
15 (crRNA) and transactivating crRNA (tracrRNA) ***or be a single-chain RNA*** (sgRNA)
16 produced by fusion of an essential portion of crRNA and tracrRNA.

17 Ex 2068, ¶¶ [168]-[0170]; Ex. 2067, ToolGen PCT, ¶¶ [0168]-[0169]; Ex. 2062, 510

18 application, ¶¶ [0094]-[0095] (emphasis added).

19 **Response: Admitted to the extent the quoted language appears in Ex 2068, Ex 2067,**

20 **and Ex 2062; otherwise, denied.**

21 37. In the original claims of the ToolGen PCT application and the 510 application, the

22 inventors included claims reciting "guide RNA," without any restriction as to RNA configuration.

23 Ex. 2067, ToolGen PCT; Ex. 2062, 510 application original claims.

24 **Response: Denied.**

25 38. In the original claims of the ToolGen PCT application and the 510 application, the

1 inventors included claims 3 and 4, which respectively limited that "guide RNA" to a dualRNA (a
2 dual molecule RNA) and a "single-chain" guide RNA (a single molecule RNA). Ex. 2067,
3 ToolGen PCT; Ex. 2062, 510 application original claims.

4 **Response: Denied.**

5 39. In the disclosures from Ex. 2067 and 2063 referenced in MFs 4 and 5, ToolGen used the
6 term "guide RNA" consistent Jinek 2012's use of the term to include both sgRNA and dualRNA.

7 **Response: Denied.**

8 40. Jinek 2012 states: "In this ternary complex, the dual tracrRNA:crRNA structure acts as
9 guide RNA that directs the endonuclease Cas9 to the cognate target DNA." Ex. 2202, Jinek 2012,
10 at Figure S1 description.

11 **Response: Admitted.**

ToolGen's Additional Material Facts

41. As of the priority date, the use of vectors, *e.g.*, plasmid vectors, was well known and widely employed for introducing DNA sequences encoding RNA molecules into eukaryotic cells. Ex. 1420, ¶¶143–45.

42. Vectors are molecules that are delivered into a cell for RNA expression. Ex. 1420, ¶143.

43. In 2012, the prior art was replete with descriptions of the use and benefits of vectors in eukaryotic cells. *See, e.g.*, Ex. 1309, 1229; Ex. 1310, 956; Ex. 1420, ¶143.

44. In 2012, a POSA would have understood that vectors provided the advantage of continuous and sustained RNA expression and chemical stability within eukaryotic cells. Ex. 1420, ¶144.

45. sgRNA, with its single-stranded structure, is significantly more susceptible to degradation compared to double-stranded RNA structures. Ex. 1420, ¶144.

46. In 2012, a POSA would have known about vectors, as well as their numerous benefits. Ex. 1248, 505 (Abstract); Ex. 1243, 28, 30, 64; Ex. 1309, 1229; Ex. 1310, 956; Ex. 1420, ¶145.

47. Dr. Seeger in paragraph 239 of his declaration articulates the number of "Cas9 orthologues smaller than SpCas9," not SaCas9; and the cited Figs. 4A–D do not identify the proteins that were as small or smaller than SaCas9 or SpCas9. Ex. 2017, Figs. 4A–D; Ex. 1420, ¶97.

48. As of the priority date, it was well known in the art to design chimeric proteins in both prokaryotic and eukaryotic cells. Ex. 1317, Abstract; Ex. 1318, Abstract.

49. As of the priority date, several naturally occurring chimeric variants of Cas proteins were well known in the art. Ex. 1207, Abstract; Ex. 1420, ¶148.

50. As of the priority date, a chimeric Cas9 protein was known for the ability to alter the functions of the wild-type Cas9 protein. Ex. 1420, ¶148.

51. As of the priority date, PAM sequences were known to differ between Cas proteins. Ex.

1 1207, 467; Ex. 1420, ¶148.

2 52. Designing a chimeric Cas protein to modify target PAM sequences would have been

3 routine for a POSA as of the priority date. Ex. 1420, ¶148.

4 53. U.S. Patent No. 8,889,418 ("the '418 patent") provides no data or testing results to support

5 Broad's argument that chimeric Cas9 has unexpected benefits. Ex. 2060, 83:45–52.

6 54. Before the priority date, a POSA knew to attach, and had attached, NLSs to Cas proteins

7 of Type I and III CRISPR systems, and to proteins of Zinc Finger Nucleases, TALENs, Rec A,

8 Lac, and HaloTag^{TM} proteins. Ex. 1022, ¶¶0054, 0058; Ex. 1319, Abstract; Ex. 1320 , Fig. 1(b);

9 Ex. 1321, 3095; Ex. 2258, 1785 (last paragraph); Ex. 1322, 11; Ex. 1420, ¶115.

10 55. Park (Ex. 2262) notes that the degree of nuclear localization corresponded to the number

11 of NLSs present. Ex. 2262, 31427; Ex. 1420, ¶122.

12 56. Before the priority date, several well-known and readily available commercial eukaryotic

13 expression vectors attached two or more NLSs to proteins expressed from the vector. Ex. 1323,

14 24391; Ex. 1325, 42189 ; Ex. 1420, ¶127.

15 57. Before the priority date, POSAs routinely used NLSs to localize prokaryotic and eukaryotic

16 proteins, with different sequence and three-dimensional structure, to the nucleus. Ex. 1420, ¶130.

17 58. Before the priority date, POSAs routinely attached two or more NLSs to proteins to

18 increase nuclear localization while maintaining protein function. Ex. 1420, ¶¶130–31.

19 59. Jinek 2012 attached a four-amino-acid tag to a Cas9 while retaining function. Ex. 2202;

20 Ex. 1420, ¶¶130–31.

21 60. In the 115 interference, the Board found that "Fieck teaches that one NLS position

22 produced 'efficient nuclear accumulation, strong repressor activity and greater sensitivity to IPTG

23 induction.'" Ex. 1101, 64:2–4 (quoting Ex. 2258, Abstract).

1 61. Broad's exhibits 2258, 2263, 2264, and 2265 each shows successful attachment of peptide
2 tags to proteins after routine experimentation. Ex. 2258, 1785; Ex. 2263, Abstract, 6111; Ex. 2264,
3 7738, 7744; Ex. 2265, 265, 268; Ex. 1420, ¶¶137–39.
4 62. Before the priority date, given Count 1 or Proposed Count 2 as prior art, a POSA would
5 have expected that attaching multiple NLSs to a protein, including two or more NLSs, would
6 improve nuclear localization. Ex. 1420, ¶141.
7 63. Zhang 2012 and Cong 2013 show that a POSA would have expected increased nuclear
8 localization of the Cas9 protein with two NLSs compared to when only one or no NLS is used.
9 Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420, ¶141.
10 64. Zhang 2012 and Cong 2013 fail to show that a Cas9 protein with two NLSs was
11 "unexpectedly more efficient." Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420, ¶141.
12 65. Neither Zhang 2012 nor Cong 2013 provide data on efficiency, *i.e.*, function of the Cas9
13 protein. Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420, ¶141.
14 66. Zhang 2012 and Cong 2013's data only shows the expected nuclear localization of the Cas9
15 protein. Ex. 2001, Fig. 1B; Ex. 2201, Fig. 2A; Ex. 1420, ¶141.
16 67. Table M of Example 14 of the '445 patent does not show an unexpected or significant
17 increase in efficiency with two or more NLSs. Ex. 2029, 124:27–125:21; Ex. 1420, ¶141.
18 68. Table M of Example 14 of the '445 patent shows that the Cas9 protein with one NLS
19 attached to its N-terminus, one NLS attached to its C-terminus, and an NLS attached to both its N-
20 and C-termini, had the following activity: 6.45% (± 0.63), 5.10% (± 0.33), and 8.9% (± 0.60),
21 respectively. Ex. 2029, 124:27–125:21; Ex. 1420, ¶141.
22 69. As of the priority date, a POSA would have understood that an NLS attached to a Cas9
23 protein as a fusion. Ex. 1420, ¶150.

1 70. As of the priority date, it was well known in the art to fuse proteins to specified protein

2 domains. Ex. 1327, Abstract; Ex. 1328, Abstract; Ex. 1329, Abstract.

3 71. Before the priority date, generating protein fusions had been used as a method of purifying

4 proteins, and fusing green fluorescent protein (GFP) to proteins was also used as method of

5 detecting protein localization in prokaryotic and eukaryotic cells. Ex. 1329; Ex. 1420, ¶151.

6 72. Generating protein fusions would have been routine for a POSA as of the priority date. Ex.

7 1420, ¶151.

8 73. U.S. Patent No. 8,993,233 does not provide any data or testing results supporting

9 unexpected benefits from fusing functional domains to Cas9. Ex. 2024, 73:22–29.

10 74. Broad's patent specifications define "guide RNA" as a single-molecule guide. Ex. 2011,

11 12:6–10; Ex. 1420, ¶53–54.

12 75. U.S. Patent No. 8.697,359 ("the '359 patent") states: "In aspects of the invention the

13 terms "*chimeric RNA*", "*chimeric guide RNA*", "*guide RNA*", "*single guide RNA*" and "synthetic

14 guide RNA" are *used interchangeably* and *refer to the polynucleotide sequence* comprising the

15 guide sequence, the tracr sequence and the tracr mate sequence." Ex. 2011, 12:6–10

16 76. All of Broad's specifications include this limiting definition: "In aspects of the invention

17 the terms "*chimeric RNA*", "*chimeric guide RNA*", "*guide RNA*", "*single guide RNA*" and

18 "synthetic guide RNA" are *used interchangeably* and *refer to the polynucleotide sequence*

19 comprising the guide sequence, the tracr sequence and the tracr mate sequence." Ex. 2016; Ex.

20 2013; Ex. 2011.

21 77. The Board previously held in the 115 interference that Broad defines a "guide RNA" as a

22 singular "polynucleotide sequence" comprising the "guide sequence, the tracr sequence[,] and the

23 tracr mate sequence." Ex. 1101, 29:22–30:5; Ex. 1420, ¶54.

1 78. A POSA as of the priority date would have understood that "guide sequence" and "tracr
2 mate sequence" refer to the crRNA component of the CRISPR-Cas system and "tracr sequence"
3 refers to the tracrRNA component of the CRISPR-Cas system. *See, e.g.*, Ex. 2011, 12:10–15,
4 21:18–25, 21:41–45; Ex. 2202, Fig. 5(A); Ex. 2214, Fig. 4; Ex. 1420, ¶55.
5 79. A "guide RNA," as defined by Broad, comprises both RNA components of the CRISPR-
6 Cas system—crRNA and tracrRNA—in a singular polynucleotide sequence, *i.e.*, a single-
7 molecule guide. Ex. 1420, ¶55.
8 80. Broad's specifications use "guide RNA" interchangeably with "chimeric RNA" and
9 "single guide RNA," which are single-molecule guides. Ex. 1420, ¶56.
10 81. Broad's specifications use "guide RNA" interchangeably with "chimeric RNA" and
11 "single guide RNA" with no qualifying language. Ex. 2011, 12:6–10; Ex. 1420, ¶57–58.
12 82. Broad's specifications do not disclose a single embodiment that is a dual-molecule RNA
13 system. Ex. 2016; Ex. 2013; Ex. 2011.
14 83. The term "guide RNA" is used throughout Broad's specifications to refer to single-
15 molecule guide RNA; different terminology is used to refer to dual-molecule guide RNA. *See,*
16 *e.g.*, Ex. 2016, 105:1–106:16; Ex. 2013, 38:33–43; Ex. 2011, 21:41–45, 43:49–53, 43:56–50:5.
17 84. Example 6 of U.S. Patent No. 8,889,356 uses the term "guide RNA" to refer to only to
18 single-molecule guides. Ex. 2016, 105:1–106:16; Ex. 1420, ¶64.
19 85. Example 6 of U.S. Patent No. 8,889,356 uses "tracrRNA" and "direct repeat sequence" to
20 refer to a dual-molecule guide, but uses "chimeric guide RNA" or "guide RNA" to refer to a single-
21 molecule guide. Ex. 2016, 105:1–106:16; Ex. 1420, ¶64.
22 86. Example 6 of U.S. Patent No. 8,889,356 only reports the results of the single-molecule
23 guides, concluding that the "optimized chimeric guide RNA works better as indicated in Fig. 3."

1 Ex. 2016, 106:9–10; Ex. 1420, ¶64.

2 87. Example 6 of U.S. Patent No. 8,889,356 referenced Fig. 3 also only shows the results of
3 guide sequences 1, 2, and 3, which the specification describes as single-molecule guides. Ex.
4 2016, 105:1–106:16, Fig. 3; Ex. 1420, ¶67.

5 88. Example 6 of U.S. Patent No. 8,889,356 is titled "[o]ptimization of the Guide RNA,"
6 referring to only the single-molecule guides that were tested. Ex. 2016, 105:4–5; Ex. 1420, ¶64.

7 89. When the disclosures in Broad's specifications are read in proper context, none of them
8 uses the term "guide RNA" to refer to a dual-molecule guide. Ex. 1420, ¶¶65–70.

9 90. Column 38, lines 33 through 43 of U.S. Patent No. ("the '308 patent") section relates to
10 single-guide molecules and uses the phrase "or combination of tracrRNA and crRNA" to describe
11 the term "chimeric guide RNA." Ex. 2013, 38:33–43; Ex. 1420, ¶65.

12 91. The portions of the '359 patent to which Dr. Seeger cites, Ex. 2454, ¶181 (citing Ex. 2011,
13 21:41–45, 43:57–50:5 (Example 1)), fail to recite the term "guide RNA," and do not use it in
14 reference to a dual-molecule guide, Ex. 1420, ¶67.

15 92. The term "guide RNA" did not have a plain and ordinary meaning in the art as of the
16 priority date. Ex. 1420, ¶76.

17 93. Jinek 2012 (Ex. 2202), and U.S. Patent Application 61/652,086 ("the '086 application")
18 (Ex. 2002) demonstrate that there was no plain and ordinary meaning as of the priority date for
19 "guide RNA." Mot. 27:4–6; Ex. 2454, ¶¶164–65, 167; Ex. 1420, ¶77.

20 94. Jinek 2012 recites "guide RNA"; the '086 application does not. Ex. 2202, 830; Ex. 2002.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **TOOLGEN OPPOSITION 3 (as of August 6, 2021)** was filed via the Interference Web Portal on August 6, 2021 by 8:00 PM EDT, and thereby served on the attorneys of record for the Junior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to agreement of the parties, service copies are being sent by email to counsel for Junior Party as follows:

Steven Trybus
Steven.Trybus@lockelord.com

Ray Nimrod
raynimrod@quinnemanuel.com

Ian Ibarra
ianibarra@quinnemanuel.com

Matthew Robson
matthewrobson@quinnemanuel.com

Zach Summers
zachsummers@quinnemanuel.com

Interference106126@lockelord.com

/Timothy J. Heverin/
Timothy J. Heverin
Reg. No. 77,386
JONES DAY
Counsel for Senior Party ToolGen, Inc.