Filed on behalf of: **Junior Party, Broad** Paper No. ____

By: Raymond N. Nimrod
Matthew D. Robson
Quinn Emanuel Urquhart & Sullivan,
51 Madison Avenue
New York, NY 10010
Telephone: 212-849-7000
raynimrod@quinnemanuel.com
matthewrobson@quinnemanuel.com

By: Steven R. Trybus
Locke Lord LLP
111 South Wacker Drive
Chicago, IL 60606
Telephone: 312-443-0699
Steven.Trybus@lockelord.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,

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

Junior Party,

v.

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

Senior Party.

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

BROAD MOTION 3
(to designate claims as not corresponding to Count 1 or Proposed Count 2)

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I. PRECISE RELIEF REQUESTED

Junior Party, The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College (collectively "Broad"), moves pursuant to 37 C.F.R. §§ 41.121(a)(1)(iii) and 41.208(a)(1) that the PTAB designate five categories of Broad's claims (Categories A-E) as not corresponding to the count (whether Count 1 or Proposed Count 2) and designating a sixth category of claims (Category F), as not corresponding to Count 1:

Category A: use of vectors for RNA expression;

Category B: *Staphylococcus aureus* Cas9 protein ("SaCas9");

Category C: Cas9 chimeric CRISPR enzyme;

Category D: Cas9 with two or more nuclear localization signals ("NLSs");

Category E: Cas9 fused to specified protein domains; and

Category F: Claims not limited to single-molecule RNA.

If this motion is granted and Broad Motion 1 is denied, the following claims would remain designated as corresponding to the count if the Interference proceeds with Count 1: claim 18 of U.S. Patent No. 8,697,359 ("359 patent") (Ex. 2011), claims 26-30 of U.S. Patent No. 8,795,965 ("965 patent") (Ex. 2012), claims 2 and 5 of U.S. Patent No. 8,906,616 ("616 patent") (Ex. 2014), and claim 16 and 27 of U.S. Patent No. 9,840,713 ("713 patent") (Ex. 2043).

If this motion is granted and Broad Motion 1 is granted, the following claims should be designated as corresponding to Proposed Count 2: claims 15-20 of the 359 patent (Ex. 2011), claims 26-29 of U.S. Patent No. 8,771,945 ("945 patent") (Ex. 2015), claims 26-30 of the 965 patent (Ex. 2012), claims 24-30 of U.S. Patent No. 8,889,356 ("356 patent") (Ex. 2016), all claims of the 616 patent (Ex. 2014), claims 21-28 of U.S. Patent No. 8,945,839 ("839 patent") (Ex. 2022), and claims 15-17, 20-24, 26-28, 31-35, and 38-39 of the 713 patent (Ex. 2043). Upon the grant of Broad Contingent Motion 2, allowable claims 1, 40, and 41 of Application 15/160,710 ("710

application") (Ex. 2063) and allowable claims 74, 94, and 95 of Application 15/430,260 ("260 application") (Ex. 2065) should also be designated as corresponding to Proposed Count 2.

II. DESCRIPTION OF APPENDICES

Appendix A is a List of Exhibits Cited, Appendix B is the Statement of Material Facts, Appendix C is a Summary Chart of grounds and claims, and Appendix D is a Claim Differentiation Chart.

III. BACKGROUND

A. Count 1 And Proposed Count 2

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). MF 1. Unlike Count 1, the Broad half of Proposed Count 2 is Broad 710 Application claim 1 and so is generic with regard to the RNA configuration and encompasses both the single-molecule RNA ("sgRNA") and dual-molecule RNA ("dualRNA") configurations. MF 2.

B. The Currently Designated Claims Cover Many Different Inventions Separately Patentable From Count 1 and Proposed Count 2

The claims currently designated as corresponding to Count 1 include many drawn to inventions that are patentably distinct from the subject matter of Count 1 and Proposed Count 2. These separately patentable inventions include five categories: (a) vector delivery of the RNA, (b) use of SaCas9, (c) chimeric Cas9 formed of two fragments, each from a different Cas9 ortholog, (d) Cas9 having two or more NLSs, and (e) Cas9 with fused and heterologous protein domains. None of the claims directed to those improvements and selections are anticipated by, or obvious

1 in view of, Count 1 or Proposed Count 2 if considered as prior art alone or in proper combination

2 with the prior art.

3 **C. Non-Limited/Generic RNA vs. Single-Molecule RNA Claims**

4 In addition to those categories, Broad's claims that are not limited to single-molecule RNA

5 should also be designated as not corresponding to Count 1, which is so limited. Broad's generic

6 claims include its claims that do not limit the RNA configuration and also do not use the term

7 "guide RNA" in the claims. These claims are indisputably not limited to sgRNA.

8 In addition, Broad submits that its claims using the term "guide RNA," without a fused or

9 chimeric RNA limitation, are also not limited to the sgRNA configuration. Broad recognizes that

10 in Interference No. 106,115 ("115 Interference"), the PTAB construed "guide RNA" to be limited

11 to a "single-molecule RNA configuration." Ex. 2121, Paper No. 877, at 44. Broad respectfully

12 disagrees with that construction, especially given the accompanying evidence of how persons

13 having ordinary skill in the art ("POSAs") would have understood the plain meaning of the term

14 "guide RNA," in particular after publication of Jinek 2012. Ex. 2202, Jinek 2012.

15 Such additional evidence includes the involved ToolGen Application 14/685,510 ("510

16 application"), which exemplifies how POSAs understood the term "guide RNA" in the context of

17 single- and dual-molecule RNA for CRISPR-Cas9 systems after publication of Jinek 2012.

18 ToolGen's specification states that "guide RNA" can refer to either "single-chain RNA" or "two

19 RNA":

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

23 MFs 35-36; Ex. 2068, ¶¶ [168]-[0170]; Ex. 2067, ToolGen PCT, ¶¶ [0168]-[0169]; Ex. 2062 ¶¶

24 168-70. Likewise, ToolGen's 510 application original claim 1 used the generic term "guide RNA."

25 MF 37. Then, in original dependent claims 3 and 4 the ToolGen application narrowed the RNA to

1 either the dual-molecule (claim 3) or single-molecule (claim 4) RNA species within the generic
2 "guide RNA" genus. MF 38. Ex. 2067, 2062, Claims 3 and 4; Ex. 2068, WO 2014/065596 ("WO
3 596"), Claims 3 and 4.
4 ToolGen did not coin the term "guide RNA" or define it in a manner inconsistent with its
5 plain meaning. To the contrary, ToolGen used the term "guide RNA" consistent Jinek 2012's use
6 of the term to include both sgRNA and dualRNA. MF 39. For example, Jinek 2012 states: "In this
7 ternary complex, the ***dual tracrRNA:crRNA*** structure acts as ***guide RNA*** that directs the
8 endonuclease Cas9 to the cognate target DNA."[1] MF 40; Ex. 2202, Jinek 2012, at Figure S1
9 description. Certainly, a POSA's understanding of the term "guide RNA" in the context of
10 dualRNA and single-molecule RNA CRISPR-Cas9 systems after June 2012 would be guided by
11 the disclosure of Jinek 2012, which proposed the use of single-molecule RNA in CRISPR-Cas9
12 systems. Thus, the disclosures from ToolGen, along with references available at the time
13 (including as detailed by Dr. Seeger (Ex. 2454, Seeger Decl. ¶¶ 146-83), show that a POSA in
14 2012 understood "guide RNA" broadly as a generic term that included both single- and dual-
15 molecule RNA systems.
16 Broad's specification did not redefine "guide RNA" in a manner contrary to its plain
17 meaning. Indeed, the first half of Count 1 uses 359 patent dependent claim 18 that requires "a
18 guide sequence fused to a tracr sequence," rather than independent claim 15, which recites "guide
19 RNA." The presumption raised by claim differentiation of the dependent claims directed to single-
20 molecule RNA shows that Broad did not intend to redefine the ordinary meaning of the term "guide
21 RNA." The broadest reasonable interpretation of the term "guide RNA" should not be limited to
22 single-molecule RNA; thus, claims that use "guide RNA" (along with those claims that neither

[1] All emphases in this brief are supplied unless otherwise noted.

specify the RNA configuration nor use the term "guide RNA") should be designated as not corresponding to Count 1, which is limited to the single-molecule configuration of the RNA.

IV. ARGUMENT

"A claim corresponds to a count if the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim." 37 C.F.R. § 41.207(b)(2). Thus, Broad now takes up each of the categories A-F set forth above in turn and shows for each category why the claims in the category are separately patentable over the count because the claims are not anticipated or rendered obvious by the subject matter of the count.

A. Broad's Claims Requiring The Use Of Vectors For RNA Expression Should Be Designated As Not Corresponding To Count 1 Or Proposed Count 2

Many of Broad's involved claims are limited to use of vectors for delivery and expression of the RNA components. As one example (*see* Appendix C for a full list of claims that should be designated as not corresponding to the count on this basis), claim 1 of the 359 patent recites:

> A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)--CRISPR associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising:
>
> **a)** a first regulatory element operable in a eukaryotic cell operably linked to **at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA** that hybridizes with the target sequence, and
>
> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II Cas9 protein,
>
> **wherein components (a) and (b) are located on same or different vectors** of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

1 Ex. 2011, 359 patent, claim 1. Thus, these claims are directed to the improvement/selection in
2 which both the Cas9 and the RNA are introduced into the eukaryotic cell by one or more vectors.

3 In order to show that these claims are patentably distinct from the count, the issue presented
4 is whether these claims are anticipated by or obvious in view of the count. They are not.

5 With respect to anticipation, a genus (with regard to delivery), such as set forth in Count 1
6 and Proposed Count 2, neither of which set forth a requirement for how the RNA is delivered, does
7 not anticipate species such as Broad's claims that are restricted to delivery of the RNA via a vector.
8 Under Count 1 or Proposed Count 2, one may deliver the system, including the RNA, via non-
9 vector means such as microinjection of the system as a mature RNP or a RNA and mRNA. MF 3.
10 Because neither count recites that the RNA must be delivered via vector (Paper 1 at 12-13; Broad
11 Motion 1 at 4), neither count anticipates Broad's claims that specify vector delivery of the RNA
12 components. *See generally* Ex. 2454, Seeger Decl. ¶¶ 212-27.

13 With respect to obviousness, there is no teaching or suggestion in either count, or in the
14 prior art, directing a POSA to vector-delivered RNA for use in eukaryotic cells, nor would a 2012
15 POSA have had a reasonable expectation of success in so doing. MF 4; *id*. There is no prior art
16 that delivered CRISPR-Cas9 systems to eukaryotic cells at all and so, of course, there is none
17 directed to vector delivery of the RNA. As noted above, neither count includes anything regarding
18 delivering the RNA components via vector. Delivery of the RNA components of a CRISPR-Cas9
19 system can be accomplished in multiple ways. Delivery of the CRISPR-Cas9 system has even been
20 called the "most difficult barrier" to *in vivo* use. Ex. 2648, Lino 2018, at Abstract. Indeed, during
21 the prosecution of a related case, ToolGen's expert Dr. Cullen made the point that delivery can be
22 key indicating that "the order of providing elements may be an important feature to getting the

1 CRISPR/Cas9 system to work in eukaryotic cells." Ex. 2069, 28 October 2016 Interview Summary
2 in 14/685,568.

3 Substantial evidence submitted herewith establishes the many ways that the RNA
4 components of the system can be delivered to a eukaryotic cell, many of which performed poorly
5 or failed outright. MF 5. For example, ToolGen's priority application (Kim P1) discloses delivery
6 to the eukaryotic cell only by a sequential process that includes adding extraordinarily high
7 amounts of already-translated single-molecule RNA to cells that have been previously transfected
8 with Cas9. MF6; Ex. 2062 at 9. Moreover, as set forth in the Seeger declaration, ToolGen's
9 delivery system triggered immune responses, causing cell death. Ex. 2454, Seeger Decl. ¶¶ 219-
10 22; Ex. 2647, Kim 2014; Ex. 2642, Kim 2018. Thus, the method of delivery of the CRISPR-Cas9
11 components to the eukaryotic cell is important.

12 As indicated in Kim P1, RNA could be delivered in an already-translated form. Such a
13 delivery could take place at the same time as delivery of the Cas9 (such as by introducing a pre-
14 formed RNP) or, as ToolGen attempted, delivery of the RNA may be done only long after the Cas9
15 was delivered. Other examples of potential methods for delivering the RNA components of the
16 CRISPR-Cas9 system include various transfection techniques, use of particles, as well as methods
17 such as microinjection and electroporation. The prior art does not teach or suggest the use of, or
18 providing reasons to select from that list, a vector for delivery of the RNA. Where, as here, the
19 prior art provides a number of choices, without any reason to make a particular selection, the
20 selection is not obvious. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F. 3d 1358, 1364
21 (Fed. Cir. 2008). Moreover, even if a POSA contemplated use of a vector for RNA delivery, there
22 would have been no reasonable expectation of success that such was appropriate for delivery to a
23 eukaryotic cell for all of the reasons set forth in the Seeger Declaration and the Decisions on

Motions in the 048 and 115 Interferences. Ex. 2454, Seeger Decl. ¶¶ 212-27; Ex. 2110, Paper 893, 048 Decision on Motions; Ex. 2121, Paper 877, 115 Decision on Motions. For that additional reason, the use of vector-delivery would not have been obvious. *See Novartis Pharm. Corp., v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019) (affirming that claims were not obvious even where the POSA would be motivated to pursue the claimed species if there was not a reasonable expectation of success given the uncertainty in the art).

In addition, vector-delivered RNA was shown by Broad to have unexpectedly positive results, supporting a finding of non-obviousness. MF 7-8; Ex. 2454, Seeger Decl. ¶¶ 225-26. This is demonstrated by the fact that the eukaryotic vector-based CRISPR-Cas9 system developed by Dr. Zhang is one of the most requested CRISPR vectors of all time from Addgene. MF 7; Exs. 2502-2505. The fact that vector delivery of the RNA components works, let alone works so robustly, was neither expected nor predictable based on the state of the art. As such, it is not obvious over the subject matter of the count treated as prior art to the claims. *See Appl. Of Albrecht*, 514 F.2d 1389, 1396 (C.C.P.A. 1975); *see also* MPEP § 2145.

Finally, CRISPR-Cas9 systems with vector-delivered RNA have shown commercial success. As set forth in the Seeger declaration, Broad licensee Editas Medicine is conducting a clinical trial using CRISPR-Cas9 systems that include vector delivery of the RNA and the Cas9 to human patients. MF 8; Ex. 2687, MacLeod 2021; Exs. 2517, 2686-87; Ex. 2454, Seeger Decl. ¶¶ 225-26. Commercial success is a powerful secondary indicia of non-obviousness that must be considered in an obviousness inquiry. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.,* 752 F.3d 967, 977 (Fed. Cir. 2014) ("Secondary considerations of nonobviousness 'must always when present be considered,' and can serve as an important check against hindsight bias."); *Power Integrations, Inc. v. Fairchild Semiconductor Intern., Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013)

("[O]bjective considerations, which [are] sometimes refer[red] to as 'secondary considerations,' [are] essential components of [an] obviousness analysis. Objective evidence of nonobviousness can include [] commercial success.") (internal citations omitted).

For the reasons set forth above, claims limited to vector-delivered RNA are patentably distinct from the subject matter of Count 1 and Proposed Count 2 and should be designated as not corresponding to either count.

B. Broad's Claims Limited To SaCas9 Should Be Designated As Not Corresponding To Count 1 Or Proposed Count 2

All of the Involved Claims of the U.S. Patent No. 8,865,406 ("406 patent") (Ex. 2017) and the U.S. Patent No. 8,895,308 ("308 patent") (Ex. 2013) and the 876 application are limited to using the *Staphylococcus aureus* Cas9 protein or a nucleotide sequence encoding such a protein. As one example, claim 1 of the 406 patent recites:

> A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) system comprising one or more vectors comprising:
>
> a) a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and
>
> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding **a *Staphylococcus aureus* Cas9 protein**,
>
> wherein components (a) and (b) are located on same or different vectors of the system,
>
> whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

1 Ex. 2017, 406 patent, claim 1. Thus, these claims are directed to the selection of SaCas9 as the
2 Cas9 component of the CRISPR-Cas9 system.

3 With respect to anticipation, neither count recites that the Cas9 be SaCas9 (or any particular
4 Cas9 protein). MF 9; Paper 1 at 12-13; Broad Motion 1 at 4. Thus, neither count anticipates claims
5 that require SaCas9. Ex. 2454, Seeger Decl. ¶¶ 228-48.

6 With respect to obviousness, there is no teaching or suggestion in either count or the prior
7 art to use SaCas9 in CRISPR-Cas9 systems in eukaryotic cells. MF 10; *id*. Moreover, CRISPR-
8 Cas9 systems using SaCas9 possess a surprising combination of small size and high efficacy in
9 eukaryotes. MF11; Ex. 2017, 406 patent at 83:1-25-84:1-23. These features render CRISPR-
10 SaCas9 systems advantageous for use in eukaryotic cell-based applications where vector delivery
11 using the highly versatile adeno-associated virus (AAV) is favored because AAV vectors are
12 notoriously space-constrained. MF 12; Ex. 2454, Seeger Decl. ¶¶ 237, 245; Ex. 2017, 406 patent
13 at 83:1-25-84:1-23.

14 As of 2012, there were more than 600 bacterial Cas9 orthologs that had been identified.
15 MF 13; Ex. 2226, Ran 2015; Ex. 2454, Seeger Decl. ¶ 234. Although SaCas9 was known as one
16 of those orthologs, that would not have suggested the use of, or provided a POSA any reasons for
17 the selection of, SaCas9 for use in eukaryotes over any of the other orthologs. MF 15; *Id*. Where,
18 as here, the prior art choices are vast, the prior art must provide some reason to make the selection
19 in order to find obviousness. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc*., 520 F.3d 1358, at
20 1364 (Fed. Cir. 2008). Here, the prior art failed to provide, or even suggest, a reason to select
21 SaCas9. Ex. 2454, Seeger Decl. ¶¶ 228-48. In the 115 Interference, the PTAB did not find a
22 teaching away; however, a lack of a teaching away does not equate to obviousness. *Rembrandt*
23 *Wireless Tech., LP v. Samsung Elecs. Co. Ltd.*, 853 F.3d 1370, 1379-80 (Fed. Cir. 2017) ("[T]he

1 absence of a formal teaching away in one reference does not automatically establish a motivation
2 to combine it with another reference in the same field."). Rather, even without a teaching away,
3 an affirmative showing of motivation for the selection of SaCas9 is required for a determination
4 that the selection would have been obvious. There is no such proof here.

5 The small size of SaCas9 alone did not provide motivation to select that ortholog. Ex. 2454,
6 Seeger Decl. ¶¶ 238-44. At the relevant time, the most commonly studied Cas9 ortholog in
7 prokaryotes was from *Streptococcus pyogenes* ("SpCas9") (MF 13), which achieved high
8 efficiencies in eukaryotic cells, as shown by later disclosed indel formation tests. Ex. 2454, Seeger
9 Decl. ¶ 230; Ex. 2201, Cong 2013; *see also* Ex. 2202, Jinek 2012, at p. 816. At 1368 amino acids
10 in length, SpCas9 is substantially larger than SaCas9 (1053 amino acids in length). MF 14; *See*
11 Ex. 2454, Seeger Decl. ¶¶ 235, 242-43, 245.

12 Additionally, the later study of Cas9 proteins smaller than SpCas9 has not shown
13 improvement in efficiency with smaller size. At least one group of researchers studied *S.*
14 *thermophilus* (StCas9), a smaller ortholog of 1121 amino acids. Ex. 2454, Seeger Decl. ¶¶ 238,
15 242-43; *see also* Ex. 2239, Gasiunas 2012, at E2579. No benefit was demonstrated with the smaller
16 StCas9 ortholog and so it would not have taught a POSA to choose SaCas9.

17 In any event, even if a POSA would have been focused on reduced size (and there is no
18 contemporaneous evidence suggesting that was the case), there is nothing pointing the POSA to
19 SaCas9 out of the many known "small" Cas9 orthologs that are similar in size to, or smaller than,
20 SaCas9. MF 15; Ex. 2454, Seeger Decl. ¶¶ 230-44. Even if there was a motivation to use a smaller
21 Cas9, that is not motivation to select SaCas9.

22 A POSA also would not have been motivated to investigate SaCas9 because its amino acid
23 sequence could be compared to previously characterized Cas9 proteins. Ex. 2454, Seeger Decl. ¶

242. As noted above, the most commonly studied Cas9 ortholog in the prior art was SpCas9. Ex. 2454, Seeger Decl. ¶ 230. Another Cas9 ortholog studied in the prior art, StCas9, shares about 60% sequence identity with SpCas9. Ex. 2454, Seeger Decl. ¶ 242; Ex. 2229, Nishimasu 2014, at 939. The sequence identity between SaCas9 and SpCas9 is at 17%, particularly low for orthologous proteins. Ex. 2454, Seeger Decl. ¶ 242; Ex. 2227, Nishimasu 2015, at 1114. Even if a POSA were somehow motivated to consider sequence identity, he or she would have steered away from selecting SaCas9 based on its lack of sequence homology with the most efficient and most frequently used Cas9 ortholog, SpCas9. Ex. 2454, Seeger Decl. ¶ 242.

In the 115 Interference, the PTAB noted that a SaCas9 system was one of a number of "model systems" established to study CRISPR/Cas functionality, citing Ex. 2215, Sapranauskas 2011. Sapranauskas, however, cites for this proposition to other scientists who had never reported any success in using SaCas9 systems in eukaryotes. Additionally, research from Sapranauskas and others establishes that there was little to no predictability as to which Cas9 orthologs could be used in systems that would be effective in eukaryotes. Sapranauskas does not provide motivation to try the SaCas9 ortholog in eukaryotic cells. Under such circumstances, the development of a eukaryotic CRISPR-SaCas9 system would not have been obvious. *See* Ex. 2454, Seeger Decl. ¶ 231.

In addition, the use of a CRISPR-SaCas9 system in eukaryotic cells has unexpected attributes demonstrating the non-obviousness of Broad's claims requiring SaCas9. Ex. 2454, Seeger Decl. ¶ 245. For example, the Broad scientists demonstrated that CRISPR-Cas9 systems using SaCas9 produced indels *in vivo* with efficiencies comparable to those achieved using SpCas9 ortholog, in stark contrast to the poorer performance of other Cas9 orthologs, such as StCas9. MF 16; *id.* The robust *in vivo* activity specific to SaCas9 was neither expected nor predictable based

on the state of the art. *Id.* These surprising advantages would not have been expected from Count 1 or Proposed Count 2, alone or in combination with the prior art, thus, rendering the involved SaCas9 claims non-obvious. Ex. 2454, Seeger Decl. ¶ 245; *In re Chupp*, 816 F. 2d 643, 646 (Fed. Cir. 1987) (superior, unexpected properties in one of a spectrum of common properties can be sufficient to show nonobviousness); *In re Albrecht*, 514 F. 2d 1389, 1396 (C.C.P.A. 1975); *see also* MPEP § 2145.

Finally, the commercial success of systems using SaCas9 is powerful objective evidence. SaCas9 has become an in-demand research tool for CRISPR-Cas9 systems and is used for more therapeutic applications than any other Cas9 ortholog. MF 17; Ex. 2454, Seeger Decl. ¶ 246. Commercial success is a powerful secondary indicia of non-obviousness that must be considered in an obviousness inquiry. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.,* 752 F.3d 967, 977 (Fed. Cir. 2014) ("Secondary considerations of nonobviousness 'must always when present be considered,' and can serve as an important check against hindsight bias."); *Power Integrations, Inc. v. Fairchild Semiconductor Intern., Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013) ("[O]bjective considerations, which [are] sometimes refer[red] to as 'secondary considerations,' [are] essential components of [an] obviousness analysis. Objective evidence of nonobviousness can include [] commercial success.") (internal citations omitted).

C. Broad's Claims That Require A Chimeric Cas9 Should Be Designated As Not Corresponding to Count 1 Or Proposed Count 2

All of the involved claims of Broad's U.S. Patent No. 8,889,418 ("418 patent") (Ex. 2060) are limited to a Cas9 that is a chimeric enzyme comprising a first fragment and a second fragment, wherein each of the first and second fragments are from a different Cas9 protein. As one example, claim 1 of the 418 patent recites:

> A modified Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) enzyme wherein the enzyme is a **Cas9 protein that is a chimeric CRISPR enzyme**

1 in that it **comprises a first fragment and a second fragment,** wherein **each of the**
2 **first and second fragments is from a different Cas9 protein** from a bacteria
3 belonging to the group consisting of Corynebacter, Sutterella, Legionella,
4 Treponema, Filifactor, Eubacterium, Streptococcus, Lactobacillus, Mycoplasma,
5 Bacteroides, Flaviivola, Flavobacterium, Sphaerochaeta, Azospirillum,
6 Gluconacetobacter, Neisseria, Roseburia, Parvibaculum, Staphylococcus,
7 Nitratifractor, and Campylobacter.

8 Ex. 2060, 418 patent, claim 1. Thus, these claims are directed to the improvement in which the
9 Cas9 is not taken from a single organism, but rather is a chimeric Cas9 that includes fragments
10 from different Cas9. NF 18. Claims 1-22 of the 418 patent are to the Cas9, a nucleic acid encoding
11 the Cas9 or a vector comprising such a nucleic acid and claims 23-28 are to eukaryotic CRISPR-
12 Cas9 systems or methods using a chimeric Cas9 with RNA. Such chimeric Cas9s can lead to
13 enhanced or new functions. *See* Ex. 2060, 418 patent, col. 82.

14 With respect to anticipation, neither Count 1 nor Proposed Count 2 recite that the Cas9 has
15 any chimeric aspect. Paper 1 at 12-13; Broad Motion 1 at 4. Thus, neither count anticipates claims
16 that require that the Cas9 be a chimeric Cas9.

17 With respect to obviousness, nothing in either count or in the prior art teaches, suggests, or
18 provides motivation to a POSA to design a chimeric Cas9 that is comprised of two fragments from
19 different organisms. MF 19; Ex. 2454, Seeger Decl. ¶¶ 249-57. As set forth in the Ex. 2060 418
20 patent, 4:21-25 ("These chimeric Cas9 proteins may have a higher specificity or a higher efficiency
21 than the original specificity or efficiency of either of the individual Cas9 enzymes from which the
22 chimeric protein was generated.") MF 20. The 418 patent also outlines unexpected benefits of a
23 chimeric Cas9:

24 The benefit of making chimeric Cas9 include:
25 a. reduce toxicity
26 b. improve expression in eukaryotic cells
27 c. enhance specificity
28 d. reduce molecular weight of protein, make protein smaller by combining the
29 smallest domains from different Cas9 homologs.
30 e. Altering the PAM sequence requirement

MF 21; Ex. 2060, 418 patent at 83:45-52.

For these reasons, and as set forth in the Seeger Declaration, there is nothing in Count 1 or Proposed Count 2 alone or in combination with the prior art that would have taught, suggested, or motivated a POSA to use a chimeric Cas9, and certainly not in a eukaryotic cell. Ex. 2454, Seeger Decl. ¶¶ 249-57.

D. Broad's Claims To The Use Of A Cas9 With Two Or More NLSs Should be Designated As Not Corresponding To Count 1 Or Proposed Count 2

The next set of the Broad involved claims that should be removed from the Interference are those claims requiring the use of "two or more" nuclear localization signals ("NLSs"). Ex. 2454, Seeger Decl. ¶¶ 258-78. These claims include all of the claims of the U.S. Patent No. 8,871,445 ("445 patent") (Ex. 2029) and U.S. Patent No. 8,932,814 ("814 patent") (Ex. 2037) as well as claim 7 of the 233 patent (Ex. 2024), claims 9-11 of the U.S. Patent Application Nos. 14/704,551 ("551 application") (Ex. 2051), and claim 34 of U.S. Application 15/330,876 ("876 application) (Ex. 2064). One example of these claims is claim 1 of the 445 patent:

> A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) system comprising one or more vectors comprising:
>
> a) a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and
>
> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II Cas9 protein,
>
> wherein components (a) and (b) are located on same or different vectors of the system,
>
> wherein the CRISPR-Cas system **comprises two or more nuclear localization signals (NLSs)**,

1 whereby the guide RNA targets the target sequence and the Cas9 protein cleaves
2 the DNA molecule, whereby expression of the at least one gene product is
3 altered; and, wherein the Cas9 protein and the guide RNA do not naturally
4 occur together.

5 Ex. 2029, 445 patent, claim 1. Thus, these claims are directed to the improvement in which the
6 Cas9 has two or more NLSs. This invention provides for significantly greater nuclear localization
7 and, unexpectedly, without the potential negative consequences that can arise from the engineering
8 of a protein that must fold and undergo multiple configuration changes in order to perform its
9 function.

10 With respect to anticipation, neither Count 1 nor Proposed Count 2 recite that the Cas9 has
11 any NLSs, let alone two or more. MF 22; Paper 1 at 12-13; Broad Motion 1 at 4. Thus, neither
12 count anticipates these claims that require two or more NLSs.

13 With respect to obviousness, the prior art did not provide any teaching or suggestion to use
14 two or more NLSs in a CRISPR-Cas system in a eukaryotic cell nor was there a reasonable
15 expectation of success in using two or more NLSs. MF 23; Ex. 2454, Seeger Decl. ¶¶ 258-78.
16 Moreover, even if some teaching or suggestion had been present, the Broad inventors demonstrated
17 that using two NLSs fused to Cas9 resulted in significantly greater co-localization of CRISPR-
18 Cas9 components in the nucleus of a eukaryotic cell than could be expected. MF 24; *id.* In a
19 eukaryotic cell, expression of a protein such as Cas9 is completed in the cytoplasm—outside of
20 the nucleus. Ex. 2454, Seeger Decl. ¶ 261. The Cas9 protein must then be localized to the nucleus
21 in order to form a complex with its RNA counterparts if the desire is to act on a genomic DNA
22 target, also contained within nucleus. *Id.* Two or more NLSs unexpectedly aided in the localization
23 of the CRISPR-Cas9 system to the nucleus of a eukaryotic cell ***without*** inhibiting functionality of
24 the Cas9. Ex. 2454, Seeger Decl. ¶¶ 258-78; Ex. 2001, Zhang B1, Figure 1B; Ex. 2201, Cong
25 2013, Figure 1A); Ex. 2793.

1 In the work detailed in their first provisional patent application, US Application No. 61/736,527 ("Zhang B1") (Ex. 2001), filed December 12, 2012, the Broad inventors tested systems with a single NLS and systems with two NLSs for nuclear localization of both SpRNase III and SpCas9. Ex. 2454, Seeger Decl. ¶¶ 267-69. While a single NLS on the C-terminal end of SpRNase III (but not the N-terminus) was sufficient to target that protein to the nucleus (Ex. 2454, Seeger Decl. ¶¶ 267-69; Ex. 2001, Zhang Bl, ¶ 170), a version of SpCas9 with a NLS fused to each end of the protein exhibited a significantly higher degree of nuclear localization, and was unexpectedly more efficient over and above what a POSA may have expected from the prior art disclosures that in other systems use of more than one NLS could increase nuclear localization. MF 24; *Id*. For example, in an August 2012 update of key data (Ex. 2793, Email from Le Cong RE: CRISPR Update - Mammalian System 20120829, dated Aug. 29, 2012), one experiment showed a synergistic effect by using two NLSs resulting in nearly four times the cleavage vs the best achieved with one NLS. Ex. 2454, Seeger Decl. ¶ 270.

14 Additionally, a POSA would have understood that adding amino acids to a protein such as Cas9 could alter its folding affecting its structure and function in ways that were not predictable. MF 25; Ex. 2454, Seeger Decl. ¶¶ 271-76. The POSA, thus, had no foreknowledge of whether fusing two or more NLSs to the Cas9 protein of Count 1 would disrupt its structure or function in a eukaryotic cell. *Id*. This was so, even though the prior art contained publications that showed the use of multiple NLSs with other proteins. There is no evidence nor was there a reasonable expectation that the use and arrangement of any functional domain (*e.g.*, two or more NLSs), in the CRISPR-Cas system, *e.g.*, as a fusion to a Cas9, would be operative because functional domains may be buried or shielded during Cas9 protein folding, affecting the activity of the functional domains and the Cas9 protein itself. *Id.*; Ex. 2264, Turner 1996 (abstract evidences that

significant effects as to function, including loss of function, can result from converting a protein into a fusion protein); *see also* Ex. 2263, Brothers 2003 (abstract: "tags do have a significant effect on protein localization and function"). Also, tagging a protein with two NLSs could interfere with function; for instance, by interfering with a binding site or catalytic domain. Ex. 2454, Seeger Decl. ¶¶ 272-74; Ex. 2258, Fieck 1992, at 1785.

That use of any NLSs, let alone two or more NLSs with the CRISPR-Cas9 system was not a matter of routine skill in 2012 is demonstrated by the experience of the Doudna Lab. In the 115 Interference, the contemporaneous evidence showed that Dr. Doudna and her team of highly skilled collaborators spent months experimenting with various NLS configurations, and clearly were not able to predict which if any NLS configuration would succeed in eukaryotic cells. *See* Ex. 2704 ("[T]ry to move the NLS around [the Cas9 protein] to see if things improve." (May 8, 2012 email)). Indeed, Dr. Doudna also wondered at one point during the experimentation, whether using NLSs on the Cas9 was counter-productive. Ex. 2705 ("I wonder if having a too-efficient NLS on Cas9 is actually counterproductive, if it means that Cas9 is transported before it has a chance to find and bind the guide RNA… Thoughts?").

There is no teaching, suggestion, motivation, or reason in the counts treated as prior art or in other prior art that would have caused a POSA to use two or more NLSs for eukaryotic CRISPR-Cas9 systems, nor is there a showing that a POSA would have had a reasonable expectation that such a Cas9 would have significantly enhanced nuclear localization without loss of function.

E. Broad's Claims That Are Limited To A Cas9 Fused To Specified Protein Domains Or Including Heterologous Domains Should Be Designated As Not Corresponding To Count 1 or Proposed Count 2

These claims require that the Cas9 be fused to specified protein domains or include heterologous domains and are thus patentably distinct. All of the claims (1-43) of Broad's 233 patent (Ex. 2024), all claims (1-28) of U.S. Patent No. 8,999,641 ("641 patent") (Ex. 2047), claims

18-19, 25, 29-30 and 36 of the 713 Patent (Ex. 2043), and claim 21 of the 876 application (Ex. 2064) are in this category. As one example, claim 1 of the 641 patent recites that the Cas9 part of the system comprises:

> b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding **a fusion of a Type-II Cas9 protein and one or more protein domains,**
>
> wherein:
>
> components (a) and (b) are located on same or different vectors of the system, **the Cas9 protein comprises one or more mutations in a catalytic domain,** the guide RNA comprises a tracr sequence which is 30 or more nucleotides in length, the Cas9 protein and the guide RNA do not naturally occur together,
>
> whereby expression of the at least one gene product is altered through the CRISPR-Cas system acting as to the DNA molecule comprising the guide RNA directing sequence-specific binding of the CRISPR-Cas system and PAM recognition, and wherein
>
> the **one or more protein domains comprises** an epitope tag, a reporter, or a domain having transcription activation activity, transcription repression activity, transcription release factor activity, histone modification activity, RNA cleavage activity, nucleic acid or cellular molecule binding activity, activity as a light-responsive cytochrome heterodimer, transposase activity, integrase activity, recombinase activity, resolvase activity, invertase activity, protease activity, nuclease activity, transcription-protein recruiting activity, cellular uptake activity or antibody presentation activity.

Ex. 2047, 641 patent, claim 1. Thus, these claims are directed to the improvement in which the binding function of the Cas9 is used and the Cas9 is fused to one or more of a set of enumerated functional protein domains. This allows for a number of different mechanisms of action by the Cas9 and not just the DSBs that occur with the use of wild type Cas9.

With respect to anticipation, neither Count 1 nor Proposed Count 2 recites that the Cas9 is fused to specified protein domains. MF 26; Paper 1 at 12-13; Broad Motion 1 at 4. Thus, neither count anticipates these claims.

With respect to obviousness, 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 these claims. MF 27; Ex. 2454, Seeger Decl. ¶¶ 279-84. Both counts cover the use of Cas9 as part of the CRISPR-Cas9 system and do not teach, suggest, or motivate a POSA to make any modifications to the Cas9, let alone these specific modifications and for use in eukaryotic cells as the prior art did not even address functional eukaryotic CRISPR-Cas9 systems. And, the POSA would have been hesitant to both blindly modify the Cas9 and fuse it to protein domains, as it would have been expected that such engineering of the Cas9 could cause a lack of function in a eukaryotic cell. Ex. 2454, Seeger Decl. ¶¶ 279-84

As noted in the 233 patent, there is a benefit to fusing functional domains to Cas9 as doing so can "turn the Cas9/gRNA CRISPR system into a generalized DNA binding system [which] can execute functions beyond DNA cleavage." MF 28: Ex. 2024, 233 patent at 73:22-29. The 233 patent notes, for example, that "fusing functional domains onto a catalytically inactive Cas9, dCas9, … can impart novel functions, such as transcriptional activation/repression, methylation/demethylation, or chromatin modifications." *Id.* These unexpected benefits demonstrate the non-obviousness of Broad's claims directed to fusing functional domains to Cas9. *See generally*, Ex. 2454, Seeger Decl. ¶¶ 279-84.

F. Broad's Non-Limited RNA Claims Should Be Designated As Not Corresponding To Count 1

De-designation of the last category of claims (Category F) is relevant only if Motion 1 is denied and the Interference proceeds on Count 1.

As formulated, Count 1 is directed to eukaryotic CRISPR-Cas9 systems that require single-molecule or chimeric RNA. Many of Broad's involved claims are not limited to such a single-molecule RNA. Ex. 2454, Seeger Decl. ¶¶ 147-83. These claims fall into one of three groups: 1)

claims that do not require an RNA component at all; 2) claims that are generic as to the RNA component and do not use the term "guide RNA"; and 3) claims that are generic as to the RNA component and that use the term "guide RNA". The term "guide RNA" was construed in the 115 Interference as limited to the single-molecule RNA configuration. Ex. 2121, 115 Interference, Paper 877 at 33. However, in light of the evidence presented herewith, it is submitted that the broadest reasonable interpretation of "guide RNA" does not limit that term to single molecule RNA. *See also* Ex. 2454, Seeger Decl. ¶¶ 285-87.

If Motion 1 is denied, Broad respectfully requests that its generic RNA claims all be de-designated from Count 1.

1. Claims 15, 17-26, 28-41 Of The 713 Patent And Claims 1-24 Of The 418 Patent Do Not Use The Term "Guide RNA" And Are Indisputably Not Limited To Single-Molecule RNA

In Broad's 713 patent, independent Claims 15 and 26 (as well as many of the claims that depend from 15 or 26) are directed to methods of genome editing using a CRISPR-Cas system and the claims do not specify any particular configuration of the RNA components of the system; moreover, these claims do not use the term "guide RNA." MF 29; Ex. 2043, 713 patent. In addition, independent claim 1 of the 418 patent (as well as dependent claims 2-24) does not recite an RNA component at all, let alone a single-molecule RNA. *See* Ex. 2454, Seeger Decl. ¶¶ 150-54.

Claim 15 of the 713 patent is illustrative. In that claim, the method comprises delivering to target sequences in the cell of a plant or animal a Cas9 protein and RNA that is simply described as "a guide sequence linked to a tracr mate sequence; and a tracr sequence":

> A CRISPR-Cas complex-mediated method for the production of a multicellular genetically modified non-human animal or multicellular genetically modified plant, the method comprising delivery to one or more target sequences in a cell of the multicellular non-human animal or plant of:
>
> a Cas9 protein;

1 a guide sequence linked to a tracr mate sequence; and

2 a tracr sequence;

3 wherein the guide sequence directs sequence-specific binding of a CRISPR
4 complex to the target sequence in the cell, whereby the multicellular genetically
5 modified non-human animal or multicellular genetically modified plant is
6 produced, and displays a phenotype or carries DNA to display a phenotype of the
7 genetic modification.

8 Ex. 2043, 713 patent, claim 15; Paper No. 13 at 75-76. Thus, claim 15 (and likewise claim 26 with
9 similar language) does not specify whether the RNA sequences are in a dual-molecule format or
10 are linked as a single-molecule RNA and thus these claims are generic with respect to the
11 configuration of the RNA. Additionally, these claims do not use the term "guide RNA," but merely
12 set forth the three RNA sequences that are present. Dependent claims 17-25 and 28-41 of the 713
13 patent are similarly RNA construct-agnostic. *See* Ex. 2454, Seeger Decl. ¶¶ 150-51. Dependent
14 claims 16 and 27, in contrast, do specify that the RNA sequences are "within a chimeric RNA."

15 Claims 1-24 of the 418 patent (Ex. 2060) are directed to Cas9 and do not have any
16 limitation requiring RNA at all, let alone indicating the format of any RNA that may be used with
17 the claimed Cas9s. MF 30. Thus, these claims too are not limited to the use of single-molecule
18 RNA as in Count 1. *See* Ex. 2454, Seeger Decl. ¶¶ 152-54.

19 Claims 15, 17-26, 28-41 of the 713 patent (Ex. 2043) and claims 1-24 of the 418 patent
20 (Ex. 2060) are non-limited RNA claims that do not correspond to Count 1.

21 **2. Broad Claims To "Guide RNA" Also Cover Both Single- And Dual-**
22 **Molecule RNA Systems**

23 In addition to the claims in the 713 and 418 patents that do not specify the use of single-
24 molecule RNA/chimeric RNA and do not use the term "guide RNA," a number of Broad's other
25 claims are also generic as to the RNA but do include the term "guide RNA." In the 115 Interference
26 Decision on Motions, the PTAB construed the term "guide RNA" used in Broad's claims as limited

to the single molecule format. 115 Interference, Paper 877 at 33. Broad respectfully disagrees with that prior decision and asserts that the evidence provided herewith shows that broadest reasonable interpretation of "guide RNA" in Broad's claims is not so limited. *See also* Ex. 2454, Seeger Decl. ¶¶ 161-83.

In determining the meaning of "guide RNA" as set forth in the claims of Broad's patents for this Interference, the broadest reasonable interpretation ("BRI") standard applies. *See Bamberger v. Cheruvu*, 55 U.S.P.Q.2d 1523, at *2 (B.P.A.I. 1998) (BRI applies in interference proceedings). Respectfully, the BRI of "guide RNA" should be dictated by how the term was used generally in the art in 2012, including as it was used in Jinek 2012, by ToolGen in the involved 510 application, and how it is used in Broad's patents and applications (including that the doctrine of claim differentiation shows that "guide RNA" is being used generically in order to avoid a finding that several dependent claims are superfluous), rather than being limited based on a purported "definition" of "guide RNA" in a single sentence in the specification.

a. Intrinsic Evidence Supports Generic Understanding Of "Guide RNA"

The intrinsic record for the Broad patents at issue indicates that "guide RNA" includes both dual- and single-molecule RNA. Ex. 2454, Seeger Decl. ¶¶ 170-83. In reviewing Broad's Involved Claims, a clear pattern is established in several patents. An independent claim is directed to a "guide RNA." A dependent claim then narrows the guide RNA to a single-molecule RNA guide RNA (*i.e.*, by describing the guide RNA as a "fused" RNA or a "chimeric" RNA construct). *See* Ex. 2011, 359 patent at Claims 1, 4, 8, 11, 15, and 18; Ex. 2015, 945 patent at Claims 1 and 5; Ex. 2013, 308 patent at Claims 1, 6 and 10 and 25, 29, and 30; Ex. 2014, 616 patent at Claims 1, 2, and 5; and Ex. 2043, 713 patent at Claims 1, 8, and 9.

1 The doctrine of claim differentiation applies in this case: "The presence of a dependent
2 claim that adds a particular limitation gives rise to a presumption that the limitation in question is
3 not present in the independent claim." *Ex Parte Cresse*, Appeal No. 2008-4746, 2008 WL
4 5264251, at *4 (B.P.A.I. Dec. 16, 2008) (citing *Phillips v. AWH Corp*., 415 F.3d 1303, 1315 (Fed.
5 Cir. 2005)). While claim differentiation is a presumption, it is a strong presumption that is not to
6 be cast aside lightly. *InterDigital Communs., LLC v. ITC*, 690 F.3d 1318, 1324 (Fed. Cir. 2012)
7 ("The doctrine of claim differentiation is at its strongest in this type of case, 'where the limitation
8 is that sought to be 'read into' an independent claim already appears in a dependent claim.'" (citing
9 *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004)).

10 Ignoring the doctrine of claim differentiation also leads to constructions that render claims
11 superfluous in Broad's patents. In the hierarchy of claim construction tenets, "[i]t is highly
12 disfavored to construe terms in a way that renders them void, meaningless, or superfluous." *Wasica*
13 *Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017). Accordingly,
14 "claim differentiation . . . is clearly applicable" when the only meaningful difference between the
15 two claims is eliminated by reading in limitation of the dependent claim into the independent claim.
16 *Wenger Mfg., Inc. v. Coating Mach. Sys., Inc.*, 239 F.3d 1225, 1233 (Fed. Cir. 2001).

17 The below claim series indicate instances where claim differentiation is required otherwise
18 a dependent claim becomes superfluous:[2]

19-25
- U.S. Patent No. 8,895,308: Claim 1 describes a method using CRISPR-Cas system having "guide RNA" that hybridizes to the target sequence. Claim 6 covers the "method of claim 1, wherein the guide RNA comprises a guide sequence and a tracr sequence." Claim 10 requires the "method of claim 6, wherein the guide sequence and tracr sequence are chimeric." If the "guide RNA" of Claim 1 is already defined to be chimeric RNA (*i.e.*, a single-molecule RNA), Claim 10 is superfluous over Claim 6. Ex. 2013; MF 31.

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[2] The full text of each claim series is set forth in Appendix 4.

- U.S. Patent No. 8,906,616: Claim 1 describes a CRISPR-Cas system having a "guide RNA" polynucleotide sequence comprising a guide sequence, a tracr mate sequence, and a tracr sequence. Claim 2 covers the "composition of claim 1, wherein the modified guide RNA comprises a chimeric guide sequence and a tracr sequence." Claim 5 covers the "composition of claim 1, wherein the modification comprises fusing the tracr mate sequence and the tracr sequence through an artificial loop." If the "guide RNA" of Claim 1, which includes a guide sequence and a tracr sequence, is already defined to be chimeric or fused, Claims 2 and 5 are superfluous. Ex. 2014; MF 32.

Other Involved Claims also provide an indication that the term "guide RNA" should be interpreted generically. Whenever Broad intended the guide RNA to be chimeric, that requirement is expressly stated in the claim. For example, in the 965 patent, all of the claims explicitly require that the guide RNA be "composed of a chimeric RNA." Ex. 2012, 965 patent at independent claims 1, 10, 17, and 26. Notably, in the 965 patent (Ex. 2012), none of the dependent claims include limitations that the components of the guide RNA be fused or bound to one another in a chimeric manner (MF 33)—that characteristic is already taught by the explicit use of the term "chimeric" in the independent claims.

That "guide RNA" is a generic term is also supported by the examples in the specifications. The Broad patents disclose preferred embodiments that are dual-molecule RNA systems. MF 34; Ex. 2011, 359 patent at 43:49-53, 44:5-8; Ex. 2454, Seeger Decl. ¶¶ 179-81. If "guide RNA" were limited to single-molecule RNA systems, however, such preferred embodiments would not be covered by the patent claims. Such a result "is rarely, if ever, correct." *Ex Parte Andrew Graham, Ando Feyh, & Bernhard Gehl*, Appeal No. 2017-009616, 2018 WL 4356999, at *3 (P.T.A.B. Aug. 23, 2018); *MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir. 2007) ("[A] claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct.") (citation omitted).

b. Extrinsic Evidence Shows The Plain Meaning Of "Guide RNA" Encompassed Dual- And Single-Molecule RNA Constructs

1 A proper claim construction analysis should also evaluate evidence of how a POSA would
2 understand the plain meaning of the term "guide RNA." *See* Ex. 2454, Seeger Decl. ¶¶ 162-69.
3 Broad submits that even prior to publication of Jinek 2012, a POSA would understand the plain
4 meaning of "guide RNA" to be a generic term. However, certainly after publication of Jinek 2012,
5 a POSA would so conclude. Jinek 2012 proposed the use of single-molecule RNA systems for
6 CRISPR-Cas9 in June 2012 and also showed dual-RNA systems. Thus, after June 2012, a POSA
7 would be guided by Jinek's use of the term "guide RNA" in connection with single- and dual-
8 molecule RNA. Jinek 2012 very clearly states: "In this ternary complex, the ***dual***
9 ***tracrRNA:crRNA*** structure acts as ***guide RNA*** that directs the endonuclease Cas9 to the cognate
10 target DNA." MF 40; Ex. 2202, Jinek 2012, at Figure S1, description. Thus, Jinek 2012 taught that
11 "guide RNA" was a generic term covering both single- and dual-RNA systems. *See, e.g.,* Ex. 2202,
12 Jinek 2012, at Fig. S1, caption; Ex. 2454, Seeger Decl. ¶¶ 164-65.
13 Consistent with Jinek 2012, ToolGen's inventors understood that "guide RNA" was a
14 generic term. ToolGen's specification for its 510 application at issue provides that "guide RNA"
15 can refer to chimeric RNA ("single-chain RNA") or the use of two RNA components (referred to
16 as "dualRNA"):

17 In the present invention, the guide RNA may consist of two RNA, i.e., CRISPR
18 RNA (crRNA) and transactivating crRNA (tracrRNA) or be a single-chain RNA
19 (sgRNA) produced by fusion of an essential portion of crRNA and tracrRNA.

20 MF 36; Ex. 2068, 418 patent, ¶¶ 168-70; Ex. 2067, ToolGen PCT, ¶¶ [0168]-[0169]. As originally
21 filed, the ToolGen application further included as Claim 1 a composition comprising a "guide
22 RNA." MF 37; Ex. 2067, ToolGen PCT; Ex. 2062, 510 application original claims. Original
23 Claims 3 and 4 respectively limited that "guide RNA" to a dualRNA (a dual molecule RNA) and
24 a "single-chain" guide RNA (a single molecule RNA). MF 38; *id*. Again, consistent with Jinek
25 2012, claim 3 recites that "guide RNA is a dualRNA comprising a crRNA and a tracrRNA." Ex.

2067, ToolGen PCT; Ex. 2062, 510 application original claims. The ToolGen 510 specification exemplifies that after Jinek 2012, skilled artisans working in the CRISPR-Cas9 field understood that "guide RNA" was a generic term that encompassed dualRNA and single-molecule RNA.

ToolGen's 510 application, when considered in view of Jinek 2012 and other multiple references available at the time, is substantial evidence that "guide RNA" was understood by POSAs to include both single and dual molecule RNA systems. Ex. 2454, Seeger ¶¶ 162-69.

c. Broad Did Not Act As Its Own Lexicographer Or Redefine The Term "Guide RNA"

In the 115 Interference, the PTAB limited the term "guide RNA" to single molecule RNA primarily because of one sentence within the voluminous specification for Broad's patents. While a patentee may act as their own "lexicographer" and redefine a term contrary to its plain and understood meaning, "a clear and unambiguous definition" limiting the term "contrary to its plain and ordinary meaning" is required. *Bradium Techs. LLC v. Iancu*, 923 F.3d 1032, 1044 (Fed. Cir. 2019). Here, the sentence at issue does not provide either a clear or unambiguous limiting definition at all.

In the detailed description of the invention, the Broad inventors state the following:

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

Ex. 2011, 359 patent at 12:6-16. This statement does not "clearly express an intent" to redefine "guide RNA." *See Ex Parte Charles John Berg, Jr. & John David Norcom*, Appeal No. 2010-004063, 2012 WL 1744485, at *2 (B.P.A.I. Apr. 25, 2012). Instead, it refers to the use of guide RNA only "in aspects of the invention," not in the context of the invention or the specification as a whole. As noted previously, multiple claims and the disclosures of preferred embodiments in the specification indicate that guide RNA may also include a dual molecule RNA system. Thus, any

interpretation of this sentence to limit "guide RNA" conflicts with other aspects of the specification, the claims and examples. Because there certainly is not an "unambiguous" definition provided as to guide RNA, the plain and ordinary meaning of the term should prevail.

Additionally, when definitions are presented in the Broad patents, those definitions do not use the "in aspects of the invention" language. Instead, as one example in the very next paragraph of the specification (and in multiple other paragraphs), when Broad defined terms, it used express and non-limiting definitional language, stating that "[A]s used herein the term" [ ] "means" [ ]." Ex. 2011, 359 patent at 12:17-20; *see also id.* at 12:21-23. This is a clear definition, unlike the qualified "aspects" statement used for "guide RNA." *See also* Ex. 2454, Seeger Decl. ¶¶ 170-75, 182.

Lastly, even if the specification language cited by the PTAB were definitional, the language does ***not*** limit "guide RNA" to any specific RNA configuration. Rather, it recites that the term guide RNA "***refers to***" "the polynucleotide sequence comprising the guide sequence, the tracr sequence and the tracr mate sequence." Ex. 2011, 359 patent at 12:6-10. That is, to the extent the sentence is seen as definitional, it indicates "guide RNA" refers to three RNA sequences (the guide sequence, the tracr sequence, and the tracr mate sequence). But the definition (assuming *arguendo* it is a definition) indicates "guide RNA" refers to the sequences but is silent on and does not require that the guide sequence and tracr mate sequence be fused to the tracr sequence or otherwise limit the configuration of these three sequences within the "guide RNA."

When the proper broadest reasonable interpretation of "guide RNA" is used, Broad's Involved Claims that refer to "guide RNA" include both single and dual-molecule RNA systems.

1 **3. Broad's Generic Claims Encompassing Both Single And Dual-**
2 **Molecule RNA Systems Should Be Designated As Not Corresponding**
3 **to Count 1**

4 If this Interference is continued with Count 1, Broad's "generic" non-limited RNA claims
5 should be designated as not corresponding to Count 1. It is presumed that a "claim corresponds to
6 a count if the subject matter of the count, treated as prior art to the claim, would have anticipated
7 or rendered obvious the subject matter of the claim." 37 C.F.R. § 41.207(b)(2). This is not,
8 however, a *per se* rule that must rigidly be applied, even if doing so would work an inequitable
9 outcome. Ex. 2305, Rules of Practice Before the Board of Patent Appeals and Interferences, 69
10 FR 49960-01, at *49994 (Comment 186/Answer). In these circumstances, Broad's generic claims
11 should be designated as not corresponding to Count 1.

12 *a. Failure To Grant This Motion Could Improperly Award Priority*
13 *To The Genus Based Only On The Single-Molecule Species*

14 With Count 1, the PTAB will make a priority determination only as to the single-molecule
15 RNA invention in eukaryotic cells. It will not make any determination as to who first invented the
16 generic, non-limited RNA invention in eukaryotic cells, even though Broad's currently designated
17 claims include that invention as well. In determining which party was the first to invent single-
18 molecule CRISPR, without designating the generic claims as not corresponding to Count 1, the
19 PTAB could give the prevailing party on single-molecule RNA rights to the generic CRISPR
20 system for eukaryotic cells.

21 The major advance was successful engineering of CRISPR-Cas9 systems for use in
22 eukaryotic cells, regardless of the particular variation of RNA design. It would be entirely
23 inequitable to award priority to that fundamental invention of eukaryotic CRISPR systems to a
24 party who made only one species of that invention, potentially long after the other party made the
25 broad, fundamental breakthrough. Broad's genus claims should be given to the earlier inventor of

1 the genus, not to the later inventor of the single-molecule guide RNA species. "[P]riority as to the
2 generic invention by applicant is not necessarily disproved by his not being the first inventor of
3 one species, which species is specifically claimed by the patentee, when it has been fully
4 established that applicant in fact was the first to possess the generic aspects of the invention." *Ex*
5 *Parte Hardman*, 142 U.S.P.Q. 329 (BNA), at *2 (July 28, 1964).

6 To be clear, Broad believes that even if this case proceeds to priority on Count 1, the
7 evidence will establish that the Broad invented the single-molecule RNA eukaryotic CRISPR
8 invention prior to ToolGen. Proceeding with the single-molecule RNA Count 1 in this case,
9 however, raises the specter of a potentially improper and inequitable result. Broad could be denied
10 generic claims, even though ToolGen was well behind Broad's invention of the genus, if ToolGen
11 establishes that it made the single-molecule RNA species first. If the generic subject matter is to
12 be awarded (or taken away) in this Interference, it should be decided based on the earliest invention
13 within the genus and not merely by picking the sgRNA variant to the prejudice of Broad.

14 De-designating Broad's generic RNA claims is consistent with the Federal Circuit's
15 decision in *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F. 3d 1264, 1268 (Fed. Cir.
16 2003). There, the Federal Circuit upheld the PTAB's decision to not apply a one-way test for
17 determining interference-in-fact, as that would be over-inclusive in determining whether
18 potentially interfering claims were to the "same patentable invention." *Id.* Specifically, the Federal
19 Circuit explained, affirming the PTAB's decision, that a "genus [that] was invented before" a
20 species is "separately patentable from, the species" for the purposes of determining an
21 interference-in-fact. *Id.* at 1270. The Federal Circuit found that the PTAB had the discretion to
22 adopt a two-way test to prevent "the proliferation of unnecessary, wasteful interference

proceedings concluding that both parties are entitled to patents in situations in which the claimed inventions do not define the same patentable invention, but merely overlap in scope." *Id.* at 1268.

The current case is critically similar to *Eli Lilly* in that, given the complexity and unpredictability of the CRISPR-Cas9 art, the development of one working species (the single molecule RNA system) should not grant rights to the genus where the other working species was invented first. The development of eukaryotic CRISPR technology was a breakthrough technological advance for which there was no reasonable expectation of success regardless of whether the RNA components were in one or two molecules. In unpredictable arts, multiple species can be separately patentable.

b. Unless This Motion Is Granted, Broad Could Lose Generic Claims Because It Cannot Rely On Its Dual-Molecule RNA Proofs To Establish Priority

Proceeding with Count 1 while simultaneously failing to designate generic RNA claims as not corresponding to Count 1 would also work an unfairness to Broad. If only Count 1 proceeds, ToolGen will likely argue that Broad cannot rely on its early dual-molecule RNA proofs to establish a reduction to practice for the narrow Count 1. Thus, Broad's generic and dual-molecule RNA claims will be at risk while at the same time Broad is prevented from relying on its dual-molecule proofs. This is patently unfair to Broad and the PTAB should not structure the interference in a manner so highly prejudicial.

For the foregoing reasons, if the Interference proceeds on Count 1, Broad requests that the PTAB designate its generic RNA eukaryotic CRISPR claims as not corresponding to Count 1.

V. CONCLUSION

For the foregoing reasons, Broad respectfully requests that the PTAB grant this motion.

1 Dated: May 28, 2021 Respectfully submitted,

2 */Raymond N. Nimrod/*
3 Raymond N. Nimrod
4 Reg. No. 31,987
5 Matthew D. Robson (*pro hac*)
6 Quinn Emanuel Urquhart & Sullivan, LLP
7 51 Madison Avenue
8 New York, NY 10010
9 Telephone: 212-849-7000
10 raynimrod@quinnemanuel.com
11 matthewrobson@quinnemanuel.com

12 Steven R. Trybus
13 Reg. No. 32,760
14 Locke Lord LLP
15 111 South Wacker Drive
16 Chicago, IL 60606
17 Telephone: (312) 443-0699
18 steven.trybus@lockelord.com

19 Counsel for Junior Party

APPENDIX A: LIST OF EXHIBITS CITED

Ex.	Description
2001	U.S. Application 61/736,527, Zhang et al., December 12, 2012.
2011	U.S. Patent No. 8,697,359, issued on April 15, 2014, to Feng Zhang ("the 359 Patent").
2012	U.S. Patent No. 8,795,965, issued on August 5, 2014, to Feng Zhang ("the 965 Patent").
2013	U.S. Patent No. 8,895,308, issued on November 25, 2014, to Feng Zhang and Fei Ran ("the 308 Patent")
2014	U.S. Patent No. 8,906,616, issued on December 9, 2014, to Feng Zhang et al. ("the 616 Patent")
2015	U.S. Patent No. 8,771,945, issued on July 8, 2014, to Feng Zhang ("the 945 Patent")
2016	U.S. Patent No. 8,889,356, issued on November 18, 2014, to Feng Zhang ("the 356 Patent")
2017	U.S. Patent No. 8,865,406, issued on October 21, 2014, to Feng Zhang and Fei Ran ("the 406 Patent")
2022	U.S. Patent No. 8,945,839, issued on February 3, 2015, to Feng Zhang ("the 839 Patent")
2024	U.S. Patent No. 8,993,233, issued on March 31, 2015 to Feng Zhang et al. ("the 233 Patent")
2029	U.S. Patent No. 8,871,445, issued on October 28, 2014, to Le Cong and Feng Zhang ("the 445 Patent")
2037	U.S. Patent No. 8,932,814, issued on January 13, 2015, to Le Cong and Feng Zhang ("the 814 Patent")
2043	U.S. Patent No. 9,840,713, issued on December 12, 2017 to Feng Zhang ("the 713 Patent")
2047	U.S. Patent No. 8,999,641, issued on April 7, 2015 to Feng Zhang et al. ("the '641 Patent")
2051	U.S. Patent Application No. 14/704,551, Ex. 22 to Sanjana Declaration ("NIH application") (Ex. 2411)
2060	U.S. Patent No. 8,889,418 issued on November 18, 2014, to Feng Zhang, et al. ("the 418 Patent")
2062	U.S. Patent Application 14/685,510, Kim et al., April 13, 2015 (the '510 Application)

Ex.	Description
2063	U.S. Patent Application 15/160,710, Zhang, May 20, 2016 (the ’710 Application)
2064	U.S. Application 15/330,876, Zhang, et al., November 7, 2016 (the ’876 Application)
2065	U.S. Patent Application 15/430,260, Zhang, February 10, 2017 (the ’260 Application)
2068	International PCT Publication WO 2014/065596 A1, filed on October 23, 2013
2069	Interview Summary in Application No. 14/685568, October 28, 2016
2110	Paper 893, Decision on Motions 37 C.F.R. § 41.125(a), Interference 106,048, February 15, 2017.
2121	Paper 877, Declaration of Interference, Interference 106,015, September 10, 2020.
2201	Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339(6121) SCIENCE 819-823 (2013) with Supplemental Material.
2202	Jinek et al., *A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity*, 337(6096) SCIENCE 816-821 (2012) with Supplemental Material.
2215	Sapranauskas et al., *The* Streptococcus thermophilus *CRISPR/Cas system provides immunity in* Escherichia coli, 39(21) NUCL. ACIDS RES. 9275-9282 (2011).
2226	Ran et al., *In vivo genome editing using* Staphylococcus aureus *Cas9*, 520 Nature 186-191 (2015).
2227	Nishimasu et al., *Crystal Structure of* Staphylococcus aureus *Cas9*, 162 Cell 1113-1126 (2015).
2229	Nishimasu et al., *Crystal structure of Cas9 in complex with guide RNA and target DNA*, 156 Cell 935-949 (2014).
2239	Gasiunas et al., Cas9-crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria, 109(39) PNAS e2579-86 (2012).
2258	Fieck, A., 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) (Ex. 1235)
2263	Brothers, S.H., 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) (Ex. 2203)

Ex.	Description
2264	Turner, J.R., et al., Carboxyl-terminal Vesicular Stomatitis Virus G Protein-tagged Intestinal Na^+-dependent Glucose Cotransporter (SGLT1), J. Biol. Chem., 271(13): 7738–7744 (1996) (Ex. 2239)
2305	Rules of Practice Before the Board of Patent Appeals and Interferences, 69 Fed. Reg. 49960-01.
2454	Declaration of Christoph Seeger, executed May 27, 2021
2502	pX330-U6-Chimeric_BB-CBh-hSpCas9, https://www.addgene.org/42230/ (accessed on October 8, 2019).
2503	https://www.broadinstitute.org/research-highlights-crispr (accessed on October 8, 2019).
2504	Jennifer Tseng, https://blog.addgene.org/15-years-of-addgene-the-top-15-plasmids, (Jan. 8, 2019) (accessed on October 8, 2019).
2505	https://www.addgene.org/search/advanced/?q=PX330, (accessed on October 8, 2019).
2642	Kim et al., *CRISPR RNAs trigger innate immune responses in human cells*, Genome Research, 28: 367-73 (March 2018)
2647	Kim et al., *Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins*, 14: 1012-19 (June 2014)
2648	Lino, et al. Delivering CRISPR: a review of the challenges and approaches, Drug Delivery, VOL. 25, NO. 1, 1234–1257 (2018). https://doi.org/10.1080/10717544.2018.1474964
2704	Email from Martin Jinek to Jennifer Doudna, dated May 8, 2012, 1 page
2705	Email from Aaron Cheng to Jennifer Doudna, dated September 14, 2012, 4 pages
2793	Email from Le Cong to Feng Zhang, Shuailiang Lin, David Cox, and Michael Yim, dated August 29, 2012, with 20 page attachment, 21 pages total

APPENDIX B: STATEMENT OF MATERIAL FACTS

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.

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.

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.

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.

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. ¶¶ 212-27.

6. ToolGen's priority application (Kim P1) discloses for delivery to the eukaryotic cell only a sequential process that includes adding extraordinarily high amounts of already-translated RNA to cells previously transfected with Cas9. *Id*. ¶¶ 219-22; Ex. 2062 at 9

1 **7.** Dr. Zhang's vector systems are among the most requested CRISPR vectors by
2 researchers in the field. Exs. 2502-2505; Ex. 2454, Seeger Decl. ¶¶ 225-27.
3 **8.** Broad licensee Editas Medicine is conducting a clinical trial using CRISPR-Cas9
4 systems that include vector delivery to human patients. *Id*.; Ex. 2687, MacLeod 2021; Exs. 2517,
5 2686-87.
6 **9.** Neither Count 1 nor Proposed Count 2 recites any particular ortholog of Cas9
7 protein, including SaCas9. Paper 1 at 12-13; Broad Motion 1 at 4.
8 **10.** There is no teaching or suggestion in Count 1, Proposed Count 2, or the prior art
9 to use SaCas9 in CRISPR-Cas9 systems in eukaryotic cells.
10 **11.** CRISPR-Cas9 systems using SaCas9 possess a combination of small size and
11 high efficacy in eukaryotes. Ex. 2017, '406 patent, 83:1-25-84:1-23; Ex. 2454, Seeger Decl. ¶¶
12 228-48.
13 **12.** Small size and high efficacy in eukaryotes render CRISPR-SaCas9 systems
14 advantageous for use in eukaryotic cell-based applications where vector delivery using the highly
15 versatile adeno-associated virus (AAV) is favored because AAV vectors are space-constrained.
16 Ex. 2454, Seeger Decl. ¶¶ 237, 245; Ex. 2017, '406 patent, 83:1-25-84:1-23.
17 **13.** As of 2012, the most commonly studied Cas9 ortholog in prokaryotes was from
18 *Streptococcus pyogenes* ("SpCas9"), and more than 600 bacterial Cas9 orthologs that had been
19 identified. Ex. 2226; Ex. 2454, Seeger Decl. ¶ 234.
20 **14.** SpCas9 is larger than SaCas9. Ex. 2454, Seeger Decl. ¶ ¶ 235, 242-43, 245.
21 **15.** As of 2012, there was nothing in the art pointing the POSA to use SaCas9 in
22 eukaryotic cells including nothing point to SaCAs9 out of the many known "small" Cas9
23 orthologs that are similar in size to, or smaller than, SaCas9. Ex. 2454, Seeger Decl. ¶¶ 230-44.

1 **16.** Broad determined that using Cas9 from *Streptococcus aureus* in a CRISPR-Cas9 2 system for DNA cleavage or editing or for modulating transcription in a eukaryotic cell provides 3 a surprising combination of benefits not taught or suggested by the prior art, namely high 4 efficiency and small size. *See* Ex. 2454, Seeger Decl. ¶¶ 228-48.

5 **17.** SaCas9 is used for more therapeutic applications than any other Cas9 ortholog. 6 Ex. 2454, Seeger Decl. ¶ 246; *See* Ex. 2017, 406 Patent at 83:25-84:23; Exs. 2687, 2517, 2686.

7 **18.** All claims of Broad's 418 patent (Ex. 2060) are directed to the improvement in 8 which the Cas9 is not taken from a single organism but rather is a chimeric Cas9 that includes 9 two fragments from different Cas9, which has unexpected benefits. *Id*. at 83:45-52; Ex. 2454, 10 Seeger Decl. ¶¶ 249-57

11 **19.** Count 1, Proposed Count 2, and the prior art do not teach, suggest, or provide 12 motivation to a POSA to design a chimeric Cas9 that is comprised of two fragments from 13 different organisms. Ex. 2454, Seeger Decl. ¶¶ 249-57; Paper 1 at 12-13; Broad Motion 1 at 4.

14 **20.** Ex. 2060 418 patent, 4:21-25 recites "[t]hese chimeric Cas9 proteins may have a 15 higher specificity or a higher efficiency than the original specificity or efficiency of either of the 16 individual Cas9 enzymes from which the chimeric protein was generated."

17 **21.** The 418 patent (Ex. 2060 at 83:45-52) also recites benefits of a chimeric Cas9.

18 **22.** Neither Count 1 nor Proposed Count 2 recite that the Cas9 has any NLSs at all nor 19 do they recite use of two or more NLSs. Paper 1 at 12-13; Broad Motion 1 at 4.

20 **23.** The prior art did not provide any teaching or suggestion to use two or more NLSs 21 in a CRISPR-Cas system in a eukaryotic cell nor was there a reasonable expectation of success in 22 using two or more NLSs. Ex. 2454, Seeger Decl. ¶¶ 258-78.

23 **24.** Broad determined that, unexpectedly, the use of two or more NLSs resulted in

1 CRISPR-Cas9 systems with significantly improved localization to the nucleus, as compared to
2 systems lacking two or more NLSs. *See generally* Ex. 2454, Seeger Decl. ¶¶ 258-78; Ex. 2001,
3 Zhang B1, Figure 1B; Ex. 2201, Cong 2013, Figure 1A; Ex. 2793.

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

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

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

12 **28.** The 233 patent notes that there is a benefit to fusing functional domains to Cas9,
13 as doing so can "to turn the Cas9/gRNA CRISPR system into a generalized DNA binding system
14 [which] can execute functions beyond DNA cleavage." Ex. 2024 at 73:22-37.

15 **29.** Broad's 713 patent (Ex. 2043), includes claims, including claims 15-26 and 28-
16 41, that are not limited to single-molecule RNA and do not contain the term "guide RNA." *See*
17 Ex. 2454, Seeger Decl. ¶¶ 150-151.

18 **30.** Independent claim 1 and dependent claims 2-24 of Broad's 418 patent (Ex. 2060)
19 do not recite any RNA component. *See* Ex. 2454, Seeger Decl. ¶¶ 152-54.

20 **31.** In U.S. Patent No. 8,895,308, claim 1 describes a method using CRISPR-Cas
21 system having "guide RNA" that hybridizes to the target sequence and claim 6 covers the
22 "method of claim 1, wherein the guide RNA comprises a guide sequence and a tracr sequence."
23 Ex. 2013.

1 **32.** In U.S. Patent No. 8,906,616, claim 1 describes a CRISPR-Cas system having a
2 "guide RNA" polynucleotide sequence comprising a guide sequence, a tracr mate sequence, and
3 a tracr sequence, claim 2 covers the "composition of claim 1, wherein the modified guide RNA
4 comprises a chimeric guide sequence and a tracr sequence" and claim 5 covers the "composition
5 of claim 1, wherein the modification comprises fusing the tracr mate sequence and the tracr
6 sequence through an artificial loop." Ex. 2014.

7 **33.** In the 965 patent (Ex. 2012), none of the dependent claims include limitations that
8 the components of the guide RNA be fused or bound to one another in a chimeric manner

9 **34.** The Broad patents disclose preferred embodiments that are dual-molecule RNA
10 systems. Ex. 2011, 359 patent at 43:49-53, 44:5-8; Ex. 2454, Seeger Decl. ¶¶ 179-81.

11 **35.** On April 13, 2015, ToolGen filed the 510 application as a continuation of PCT
12 application PCT/KR2013/009488 (the "ToolGen PCT application") (Ex. 2067), which had been
13 filed on October 23, 2013, and claiming priority to provisional patent applications dating back to
14 October 23, 2012. Ex. 2062, 510 application; Ex. 2067, ToolGen PCT.

15 **36.** ToolGen's patent applications explicitly define "guide RNA" to encompass both
16 dual- and single-molecule RNA configurations:

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

20 Ex. 2068, ¶¶ [168]-[0170]; Ex. 2067, ToolGen PCT, ¶¶ [0168]-[0169]; Ex. 2062, 510
21 application, ¶¶ [0094]-[0095] (emphasis added).

22 **37.** In the original claims of the ToolGen PCT application and the 510 application, the
23 inventors included claims reciting "guide RNA," without any restriction as to RNA

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

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

3 inventors included claims 3 and 4, which respectively limited that "guide RNA" to a dualRNA (a

4 dual molecule RNA) and a "single-chain" guide RNA (a single molecule RNA). *Id*.

5 **39.** In the disclosures from Ex. 2067 and 2063 referenced in MFs 4 and 5, ToolGen

6 used the term "guide RNA" consistent Jinek 2012's use of the term to include both sgRNA and

7 dualRNA.

8 **40.** Jinek 2012 states: "In this ternary complex, the dual tracrRNA:crRNA structure

9 acts as guide RNA that directs the endonuclease Cas9 to the cognate target DNA." Ex. 2202,

10 Jinek 2012, at Figure S1 description.

APPENDIX C: CHART OF GROUNDS AND CLAIMS

Patent	Claims Currently Designated to Count 1	RNA Vector	SaCas9	Chimeric Cas9	NLSs ≥ 2
8,867,359	1-20	1-14			
8,771,945	1-29	1-25			
8,795,965	1-30	1-25			
8,865,406	1-30	1-23	ALL		
8,871,445	1-30	1-25			ALL
8,889,356	1-30	1-23			
8,889,418	1-28	25-28		ALL	
8,895,308	1-30	1-24, 29	ALL		
8,906,616	1-30				
8,932,814	1-30	1-24			ALL
8,945,839	1-28	1-20			
8,993,233	1-43	ALL			7
8,999,641	1-28	1-21			
9,840,713	1-41	1-14, 37, 40-41			
14/704,551	2, 4-18	ALL			9-11
15/330,876	1, 16-21, 30-40	ALL	ALL		34

Patent	Claims Currently Designated to Count 1	Cas9 Domains	No RNA at all	Generic RNA[3]	Single-Molecule RNA [FOR INFO ONLY]
8,867,359	1-20			1-3, 5-10, 12-17, 19-20	4, 11, 18
8,771,945	1-29			1-4, 6-29	5
8,795,965	1-30				ALL
8,865,406	1-30			ALL	
8,871,445	1-30			ALL	
8,889,356	1-30			ALL	
8,889,418	1-28		1-24	25-28	
8,895,308	1-30			1-9, 11-28	10, 29-30
8,906,616	1-30			1, 3-4, 6-30	2, 5
8,932,814	1-30			ALL	

[3] Broad lists here all claims that it contends should be considered generic as to the RNA configuration, including those that recite a "guide RNA." For the reasons discussed in Motion 3, "guide RNA" is a generic term encompassing both single- and dual-molecule RNA systems. Claims reciting the term "guide RNA" with no limitation to only the single-molecule RNA species are as follows: 8,867,359 (Claims 1-3, 5-10, 12-17, 19-20); 8,771,945 (Claims 1-4, 6-29); 8,865,406 (All); 8,871,445 (All); 8,889,356 (All); 8,889,418 (Claims 25-28); 8,895,308 (Claims 1-9, 11-28); 8,906,616 (Claims 1, 3-4, 6-30); 8,932,814 (All); 8,945,839 (All); 8,993,233 (All); 8,999,641 (All); 9,840,713 (Claims 1-7, 10-14).

8,945,839	1-28			ALL	
8,993,233	1-43	ALL		ALL	
8,999,641	1-28	ALL		ALL	
9,840,713	1-41	18-19, 25, 29-30, 36		1-7, 10-15, 17-26, 28-41	8-9, 16, 27
14/704,551	2, 4-18			ALL	
15/330,876	1, 16-21, 30-40	21		1, 16-21, 30-39	40

APPENDIX D: CLAIM DIFFERENTIATION EXAMPLES

U.S. Patent 8,895,308	
<u>Claim 1</u>: Describes method using CRISPR-Cas system having "a CRISPR-Cas system guide RNA that hybridizes with the target sequence" 1. A method of altering expression of at least one gene product in a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding said gene product comprising introducing into said eukaryotic cell an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) system comprising one or more vectors comprising: a) a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Staphylococcus aureus Cas9 protein, wherein the CRISPR-Cas system further comprises one or more nuclear localization signal(s) (NLS(s)), and components (a) and (b) are located on same or different vectors of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule; the method further comprising inserting DNA into a cleaved strand of the DNA molecule; whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.	**<u>Claim 6</u>**: The method of claim 1, wherein the guide RNA comprises a guide sequence and a tracr sequence. **<u>Claim 10</u>**. The method of claim 6, wherein the guide sequence and tracr sequence are chimeric.

U.S. Patent 8,906,616	
Claim 1: Claim 1 describes a CRISPR-Cas system having a "guide RNA" polynucleotide sequence comprising a guide sequence, a tracr mate sequence, and a tracr sequence. 1. An engineered, non-naturally occurring composition comprising a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system having a guide RNA polynucleotide sequence, wherein the polynucleotide sequence comprises (a) a guide sequence capable of hybridizing to a target sequence in a eukaryotic cell, (b) a tracr mate sequence, and (c) a tracr sequence wherein (a), (b) and (c) are arranged in a 5' to 3' orientation, wherein when transcribed, the tracr mate sequence hybridizes to the tracr sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to the target sequence, wherein the to CRISPR complex comprises a Type II Cas9 protein complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracr sequence, wherein in the polynucleotide sequence, one or more of the guide, tracr and tracr mate sequences are modified.	**Claim 2**: The composition of claim 1, wherein the modified guide RNA comprises a chimeric guide sequence and a tracr sequence. **Claim 5:** The composition of claim 1, wherein the modification comprises fusing the tracr mate sequence and the tracr sequence through an artificial loop.

CERTIFICATE OF FILING AND SERVICE

I hereby certify that on May 28, 2021, a true and complete copy of the foregoing **BROAD MOTION 3** (to designate claims as not corresponding to Count 1 or Proposed Count 2) is being filed and served by 5:00 pm PT /8:00 pm ET via the Interference Web Portal and by agreement served by email on the Senior Party by 8:00 pm PT / 11:00 pm ET to:

aminsogna@jonesday.com
tjheverin@jonesday.com
ncgeorge@jonesday.com
rcrich@jonesday.com
cplatt@jonesday.com
ToolGenBroad126@jonesday.com

/*Raymond N. Nimrod*/

Raymond N. Nimrod
Reg. No. 31,987
Matthew D. Robson (pro hac)
Quinn Emanuel Urquhart & Sullivan, LLP
51 Madison Avenue
New York, NY 10010
Telephone: 212-849-7000
raynimrod@quinnemanuel.com
matthewrobson@quinnemanuel.com