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UNIVERSITY OF VIENNA, AND EMMANUELLE CHARPENTIER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

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

v.

TOOLGEN, INC.,
Senior Party

Application 14/685,510.

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

REPLY IN SUPPORT OF CVC MOTION 3

(to add the claims of ToolGen patent 10,851,380)

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I. INTRODUCTION

CVC's Motion 3 (Paper 363; hereinafter, "Motion") demonstrated that the claims of U.S. Patent No. 10,851,380 ("the '380 patent") are obvious variants of Count 1 in view of Jinek 2012. In particular, it would have been obvious to use a single guide RNA ("sgRNA") comprising a 5'-GG in Count 1's CRISPR-Cas9 systems for cleaving DNA in eukaryotic cells, as taught by Jinek 2012. The '380 patent's claims therefore correspond to Count 1 and should be added to the interference. In response, ToolGen's Opposition to CVC's Motion 3 (Paper 715; hereinafter, "Opposition") presents legally and factually incorrect nonobviousness arguments.[1]

ToolGen's arguments that "a POSA would not have had an expectation of success in implementing CRISPR/Cas9 in eukaryotic cells" do not apply the correct legal framework for claim correspondence. Opposition, 12:2-3. As the PTAB correctly noted in Interference No. 106,115, the count is treated as prior art in the obviousness analysis required to determine claim correspondence. *Regents of the Univ. of Cal. v. The Broad Inst., Inc.*, Interference No. 106,115, Paper 877, 66 (P.T.A.B. Sept. 10, 2020); 37 C.F.R. § 41.207(b)(2). Just as in the '115 Interference, Count 1 encompasses use of a CRISPR-Cas9 system in eukaryotic cells. Therefore, just as in the '115 Interference, an expectation of success in using a CRISPR-Cas9 system in eukaryotic cells is "assumed." *Id.* at 66. ToolGen offers no credible basis to disregard such an assumption. Moreover, when analyzing expectation of success for systems with the 5'-GG variant while assuming the functionality of Count 1, which is the proper perspective, the record contains an abundance of evidence that a POSA would have reasonably expected success. As explained in CVC's Motion,

[1] As authorized in the August 18, 2021, email from Maria King, Deputy Chief Clerk for Trials, CVC has 12 pages for this Reply to ToolGen's Opposition.

1 using that variant would require no more than using established and reliable methods for preparing
2 and introducing *in vitro* transcribed RNA according to Jinek 2012's teachings, as part of Count 1's
3 system. Motion, pp. 8-9; MF 25, 27, 67-69.

4 ToolGen's Opposition does not respond to CVC's analysis of how Count 1 and Jinek 2012
5 teach all elements of the '380 patent's claims. In fact, ToolGen admits that *in vitro*-transcribed
6 sgRNA prepared by the methods disclosed in Jinek can result in sgRNA having two guanines at
7 the 5' end. MF 5-7, 9-10, 28, 43. Instead, ToolGen argues that using sgRNA with a 5' GG is
8 nonobvious because expressing sgRNA from plasmids is preferred over directly introducing
9 sgRNA. ToolGen's argument is legally and factually meritless. Obviousness need not be
10 predicated on the "preferred, or the most desirable" feature in the art. *Apple Inc. v. Samsung*
11 *Electronics Co., Ltd.*, 816 F.3d 788, 801-802 (Fed. Cir. 2016). And, even if a POSA's preference
12 were significant, ToolGen's Opposition fails because it simply ignores and does not rebut CVC's
13 evidence that those of ordinary skill in the art *actually had chosen* to directly introduce RNA into
14 eukaryotic cells via methods such as RNA transfection and microinjection, in preference to
15 introducing plasmids. MF 11.

16 ToolGen's remaining arguments also are meritless. ToolGen's unexpected results
17 arguments fail because simply reporting a property of the claimed variant of Count 1 does not
18 render that variant nonobvious. *In re Kao*, 639 F.3d 1057, 1071-1072 (Fed. Cir. 2011). Moreover,
19 the purported unexpected increase in specificity lacks nexus with the 5'-GG aspect of the claims
20 in view of ToolGen's prior arguments that CRISPR systems without a 5'-GG offer the same
21 specificity. *Id.* at 1068. Finally, the novel procedural requirement that ToolGen advocates for
22 motions to add a patent is contradicted by previous cases.

23 **II. ARGUMENT**

24 **A. ToolGen's arguments regarding expectation of success in eukaryotic cells fail**

1 **because those arguments are irrelevant under the law**

2 Rather than analyze expectation of success under the appropriate legal framework for
3 correspondence to Count 1, ToolGen's Opposition (page 11, line 21, to page 15, line 3) relies on
4 statements regarding expectation of success from the '048 Interference, made in a different
5 context, as if they were dispositive here. The response is that these are vastly different proceedings,
6 both procedurally and factually. Here, unlike in the '048 Interference, Count 1 is prior art under
7 37 C.F.R. § 41.207(b)(2) and *already recites* eukaryotic use of CRISPR-Cas9, and thus arguments
8 pertaining to an alleged lack of expectation of success in eukaryotes are legally irrelevant and
9 baseless. The PTAB expressly stated this in response to a similar argument by Broad in the '115
10 Interference:

> 11 Broad refutes CVC's evidence, arguing that none of the publications
> 12 it cites show success in eukaryotic cells, which we held in the prior
> 13 '048 interference was necessary for a reasonable expectation of
> 14 success. (*See* Broad Reply 3, Paper 822, 19:9–23.) We are not
> 15 persuaded by Broad's argument because *the issue in the prior*
> 16 *interference was whether a CRISPR-Cas9 system would have been*
> 17 *expected to work in a eukaryotic cell. That issue is assumed under*
> 18 *the framework of 37 C.F.R. § 41.207(b)(2), wherein Count 1 is*
> 19 *presumed to be prior art to the Broad claims*. The issue for Broad's
> 20 request is whether adding two or more NLSs to the functional
> 21 eukaryotic system of Count 1 would have been obvious. Broad does
> 22 not direct us to evidence it would not have been obvious.

23 *Regents of the Univ. of Cal.*, Interference No. 106,115, slip op. at 66 (emphasis added); MF 57.
24 This statement squarely contradicts ToolGen's expectation of success arguments.

25 At page 12, line 20, to page 14, line 14, of the Opposition, ToolGen attempts to dismiss the
26 relevance of the PTAB's statement in the '115 Interference as "incorrect as a matter of fact and
27 law" in view of the '048 Interference's holding and "the earlier priority date and recitation of
28 additional limitations" in the claims. The response is that PTAB should reject ToolGen's argument
29 because it is fundamentally no different than Broad's failed argument in the '115 Interference.

1 Both ToolGen and Broad failed to recognize that the issue of whether a CRISPR-Cas9 system
2 would have been expected to work in eukaryotic cells is assumed under the framework of Rule
3 207(b)(2) when, as here, the count is treated as prior art and recites use of CRISPR-Cas9 in
4 eukaryotes. The priority date and recitation of other claimed features have no bearing on this aspect
5 of expectation of success. Contrary to ToolGen's assertion, assuming success with eukaryotic cells
6 would not "nullify the requisite obviousness analysis." *See* Opposition, pp 13-14. Rather, it means
7 applying Rule 207(b)(2) as it is expressly written, with Count 1 "treated as prior art to the claim."

8 The only element of the '380 patent's claim 1 not recited in Count 1 is that the guide RNA
9 comprises two guanines at its 5' end. Motion, pp. 6-7; MF 15. Therefore, the issue here is "whether
10 adding [a 5'-GG] to the functional eukaryotic system" of Count 1 would have been obvious.
11 *Regents of the Univ. of Cal.*, Interference No. 106,115, slip op. at 66. ToolGen has not even
12 attempted to rebut CVC's showing of a reasonable expectation of success in making that addition.

13 **B. ToolGen's arguments regarding motivation fail because they are contrary to**
14 **law and mischaracterize the art**

15 CVC's Motion showed that a POSA would have had reason to use a guide RNA comprising
16 a 5'-GG as part of the eukaryotic system of Count 1, specifically by applying Jinek 2012's method
17 of RNA preparation.[2] Motion, pp. 6-7. ToolGen's Opposition arguments regarding motivation are
18 both contrary to the law and are contradicted by the evidence.

19 ***1. ToolGen's motivation arguments are contrary to law***

[2] The discussion of Jinek 2012 during prosecution of the '380 patent does not detract from CVC's arguments because the Examiner considered Jinek 2012 in a completely different context: one in which Count 1 was not prior art. Thus, the cases ToolGen cites regarding prior consideration have no bearing here. Opposition, p. 4.

1 From page 4, line 13, to page 11, line 20 of its Opposition, ToolGen argues that "a POSA
2 would not have been motivated to modify Count 1 in view of Jinek 2012, because Jinek 2012
3 requires RNA transfection," and that the art provided plasmid expression as a "more
4 advantageous" method of RNA introduction than RNA transfection. The response is that the
5 Federal Circuit has repeatedly emphasized that "a motivation to use the teachings of a particular
6 prior art reference need not be supported by a finding that that feature be the 'preferred, or the
7 most desirable.'" *Apple Inc.*, 816 F.3d at 801-802 (quoting *Fulton,* 391 F.3d at 1200). Similarly,
8 "[a] known or obvious composition does not become patentable simply because it has been
9 described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551,
10 553 (Fed. Cir. 1994). ToolGen invites the PTAB to ignore this clear authority, and focuses instead
11 on the legally meaningless argument about whether CVC established "the desirability of using
12 RNA transfection *over* plasmid transfection." *See* Opposition, pp. 4-11 (emphasis added). This
13 legal flaw alone is sufficient reason to disregard ToolGen's arguments surrounding motivation.

14 15 16 ***2. ToolGen's plasmid-focused motivation arguments are contradicted by evidence regarding RNA transfection and microinjection, which ToolGen conceded were routine in the art***

17 CVC's Motion showed that the production and introduction of *in vitro*-transcribed RNA
18 as described in Jinek 2012 was well-established, quick, cost-effective, and accurate. Motion, pp.
19 7-8; MF 1-8. In addition, CVC's motion showed that the prior art disclosed introducing a variety
20 of *in vitro*-transcribed RNAs into eukaryotic cells using RNA transfection or microinjection, with
21 Dr. Bailey identifying exemplary publications describing such methods. Motion, pp. 7-8; Ex. 2015,
22 ¶¶77-80; MF 11, 65, 77. Collectively, this shows that a POSA would have been motivated to
23 prepare sgRNA using Jinek 2012's method and introduce it into eukaryotic cells. ToolGen's
24 Opposition neither challenges nor discredits this evidence.

25 Instead, on page 4, line 13, to page 11, line 20, ToolGen advances a series of arguments

1 relating to the purported benefits of plasmid transfection over RNA transfection. The response is
2 that ToolGen's arguments lack scientific merit. For example, CVC's motion provides evidence of
3 motivation to perform *either* RNA transfection *or* RNA microinjection of RNA into eukaryotic
4 cells. Motion, p. 8; Ex. 2015, ¶¶58, 79, 111; Ex. 2028, 9; Ex. 2067, 487; Ex. 2071, 1, Abstract; Ex.
5 2434, 1, Abstract; MF 17, 66. ToolGen's expert Dr. Cullen agreed that microinjection was used to
6 introduce reagents for "manipulating gene expression" such as the "tools for turning off genes
7 called RNA interference…[and] introducing new genes" into eukaryotic cells. Ex. 2538, 42:16-
8 48:13; MF 66. Dr. Cullen further specified that microinjection was "a fairly common technique"
9 that a POSA "would generally use" for introduction of such tools into *Drosophila* larvae, for
10 introduction "into individual mouse embryos," for introduction into "frog oocytes…because they
11 are really, really big and…easy to microinject," and for introduction into zebrafish. Ex. 2538, 40:1-
12 11, 42:16-48:13; MF 66. ToolGen does not respond to the RNA microinjection aspect of CVC's
13 motivation evidence, but instead focuses solely on RNA transfection. Therefore, regardless of the
14 merits of ToolGen's arguments regarding RNA transfection, CVC's motion presented strong,
15 unrebutted evidence of motivation.

16 In addition, the evidentiary record shows that ToolGen's Opposition is premised on
17 mischaracterizations regarding the use of RNA transfection in the art. For example, ToolGen
18 incorrectly argues, "a POSA would have understood the T7 promoter as being used exclusively in
19 *in vitro*, non-cellular experiments." Opposition p. 9. But Dr. Bailey provided four exemplary
20 references that describe the field's practice of introducing RNA made with a T7 promoter and T7
21 RNA Polymerase into eukaryotic cells, and ToolGen has not disputed the accuracy of this
22 evidence. Bailey Dec., ¶¶77-80; Ex. 2027, 951-953; Ex. 2065, 1229-1230; Ex. 2067, 487; Ex.
23 2068, 763; MF 11, 65.

1 The record also contains abundant evidence directly contradicting ToolGen's assertions
2 regarding the purported infrequency of RNA transfection. While ToolGen asserts that "RNA
3 transfection was not routinely employed in the art for introducing RNA into eukaryotic cells"
4 (Opposition, p. 6), ToolGen's own expert Dr. Cullen characterized RNA transfection as a "routine
5 technique" for introducing "DNA or RNA" into mammalian cells. Ex. 2538, 37:14-39:8; MF 67.
6 Similarly, ToolGen's other expert Dr. Turchi stated during deposition that RNA transfection was
7 a "fairly standard" method for the introduction of "RNA into cells." Ex. 2537, 95:3-96:3; MF 67.
8 The standard and routine nature of RNA transfection is also demonstrated by Dr. Turchi's
9 admission that he identified "a few hundred" papers relating to RNA transfection in his own
10 searches of the literature. Ex. 2537, 36:20-37:10; MF 68. These admissions are consistent with Dr.
11 Bailey's testimony regarding the exemplary publications showing transfection of T7-transcribed
12 RNA into eukaryotic cells. Ex. 2015, ¶¶79, 107. The standard and routine nature of RNA
13 transfection is further demonstrated by the pre-2012 availability of various commercial
14 transfection reagents advertised as being appropriate for RNA transfection. Ex. 2517, 3615; Ex.
15 2518, 957, 960; Ex. 2519, 27.1.4; Ex. 2520, 1; Ex. 2521, 1; Ex. 2522, 8; Ex. 2523, 1; Ex. 2524, 1;
16 Ex. 2525, 2; Ex. 2537, 96:4-16; MF 69. Such an abundance of evidence establishes by more than
17 a preponderance of the evidence that a POSA would have known of methods of transfecting RNA
18 into eukaryotic cells, and been capable of applying such techniques. Moreover, the relative
19 frequency of publications using plasmids and RNA transfection is irrelevant because a POSA "is
20 presumed to be aware of *all* the pertinent prior art." *Standard Oil Co. v. American Cyanamid Co.*,
21 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis added); *see also*, *In re Sernaker*, 702 F.2d 989, 994
22 (Fed. Cir. 1983).

23 ToolGen also asserts that "POSAs understood RNA transfection to be especially

1 problematic," citing only passages in Ichim (Ex. 2065 at 1232) and Gao (Ex. 1559 at 1017) for
2 their discussions of RNA "delivery." Opposition, p. 6. But the cited passages have nothing to do
3 with RNA transfection into eukaryotic cells. Rather, they solely discuss the question of how to
4 deliver RNAs to the correct location within the body as part of therapeutic applications. MF 74.
5 For example, the cited passage in Ichim relates to the "[c]linical applicability" of viral vectors and
6 immunoliposomes for siRNA therapeutics, following previous successful use in eukaryotic cells
7 and animals. Ex. 2065, 1232-1233; MF 75. Similarly, the cited passage in Gao relates to how
8 "liposomes, nanoparticles and cationic polymer carriers may represent a promising strategy for
9 siRNA-based therapies." Ex. 1559, 1017; MF 76. The '380 patent's claims do not require a
10 therapeutic effect. Therefore, neither Ichim nor Gao would have diminished a POSA's motivation
11 to use *in vitro* transcription, coupled with RNA transfection or microinjection, to introduce RNA
12 into eukaryotic cells. MF 70.

13 **C. ToolGen's unexpected results arguments apply the wrong legal standard**

14 The proper comparison for an analysis of unexpectedly superior results is relative to the
15 closest prior art. *See, e.g.*, *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368 (Fed. Cir.
16 2017). This comparison is lacking in ToolGen's Opposition. In *Ritzberger v. Durchang*,
17 Interference No. 106,012, Paper 210, 25 (P.T.A.B. Sept. 29, 2016), this same PTAB panel noted
18 that because "the Count is taken as prior art in determining obviousness[, the patent owner] cannot
19 rely on evidence of unexpected results that are attributable to a feature in the prior art, i.e., a feature
20 of the Count." *Id.* (quotation omitted). Based on the proper comparison—between the '380 patent's
21 claims and Count 1—ToolGen's unexpected results argument lacks nexus with the '380 patent's
22 claims.

23 As CVC previously explained, ToolGen argued during prosecution of a related application
24 that a claim identical to ToolGen's half of Count 1 (*i.e.*, a cell comprising a CRISPR-Cas9 system

1 that need not have a 5'-GG on the guide RNA) displayed unexpectedly superior specificity relative
2 to other gene editing systems. Motion, pp. 10-12; Ex. 2120, 8210-8211; MF 16. On page 15, line
3 4, to page 17, line 23, of its Opposition, ToolGen now argues that the *same data* support separate
4 patentability of the ’380 patent’s claims based on the presence of the 5'-GG. The response is that
5 there can be no unexpectedly superior results because ToolGen has already argued that the same
6 “unexpectedly superior specificity” results from something other than the 5'-GG. “Where the
7 offered secondary consideration actually results from something other than what is both claimed
8 *and novel in the claim*, there is no nexus to the merits of the claimed invention.” *In re Kao*, 639
9 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis added). Put another way, there can be no unexpectedly
10 superior results for a claimed species when a previously-disclosed genus to which the species
11 belong demonstrates those same results. *AbbVie, Inc. v. Mathilda and Terence Kennedy Inst. of*
12 *Rheumatology Trust*, 764 F.3d 1366, 1380 (Fed. Cir. 2014) (dismissing an assertion of unexpected
13 results when “[a prior genus] patent relied on the results … that … [the patent owner] now contends
14 show that the method of the [later species] patent led to unexpected results”).

15 ToolGen asserts that the presence of a 5'-GG contributes “even greater specificity” to the
16 CRISPR-Cas9 system. Opposition, pp. 16-17. ToolGen has not substantiated such a distinction.
17 ToolGen relies upon data from the ’380 patent to support its argument. However, the ’380 patent
18 concludes that a 5'-GG “can affect mutation frequencies at [both] on-target and off-target sites”
19 because the sgRNAs with the 5'-GG were “less active at on-target sites…and off-target sites,”
20 relative to sgRNAs without a 5'-GG. Ex. 2011, 36:38-44; MF 71-72. Therefore, the ’380 patent
21 indicates that a 5'-GG’s may *decrease overall* cleavage rather than increase specificity at the target
22 site. Ex. 2011, 36:38-44; MF 71-72. But even taking as true ToolGen’s assertion of “even greater
23 specificity,” this cannot support an unexpected results argument because “[u]nexpected results that

1 are probative of nonobviousness are those that are 'different in kind and not merely in degree from
2 the results of the prior art.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir.
3 2013) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)).
4 At most, ToolGen alleges a mere difference in degree and its unexpected results argument fails for
5 this additional reason.

6 **D. CVC's Motion Complied with 37 C.F.R. §§ 41.202 and 41.203**

7 On page 18, line 10, to page 19, line 8, ToolGen's Opposition alleges that CVC did not
8 "'[e]xplain in detail why the applicant will prevail on priority.'" The answer is that ToolGen has
9 not identified any cases requiring a party requesting adding patents to an existing interference to
10 also establish a priority case.

11 ToolGen's sole authority, *Australia v. Leiden*, Interference No. 106,007 (Paper 53), dealt
12 with declaring a *new* interference, where the PTAB was rightfully considering whether the
13 requesting party had a basis for believing it could prevail on priority in the requested interference.
14 The situation here is different. In declaring this interference with the Count 1, the PTAB has
15 already accepted that CVC has a basis for prevailing on priority against ToolGen for the subject
16 matter of the Count. *See, e.g.*, Paper 25, pp. 2-3 (granting CVC authorization to file a motion for
17 priority benefit); Paper 365 (Junior Party's Priority Statement). Thus, the only issue here is whether
18 the '380 patent's claims correspond to Count 1. Consistent with the absence of any requirement
19 for a priority analysis in the context of adding patents to an existing interference, members of this
20 PTAB panel have repeatedly granted motions to add patents or claims without a priority analysis
21 in the motion. *See, e.g.*, *Ritzberger v. Durchang*, Interference No. 106,012 before Lane, Moore,
22 and Katz, Paper 179 (presenting motion to add three patents without referencing priority) and
23 Paper 210 (pp. 16-25, granting motion to add three patents); *DeVaul v. Knoblach*, Interference No.
24 106,058 before Shafer, Lane, and Moore, Paper 25 (presenting motion to add claims without

1 referencing priority) and Paper 27 (granting motion to add claims).

2 Should the PTAB decide, however, that CVC should have provided a more detailed 3 showing regarding priority as part its Motion, the PTAB should use its discretion under Rule 4 41.104(b) to waive that requirement in this case. The '380 patent is a member of the same family 5 as ToolGen's involved application, and does not claim an earlier priority date than ToolGen's 6 involved application. MF 73. Accordingly, the priority case asserted as part of CVC's other 7 pleadings (*e.g.*, as part of CVC's Priority Statement, Motion to Be Accorded Benefit, and eventual 8 Motion for Judgment Based on Priority) is applicable here as well.

9 **III. CONCLUSION**

10 CVC's Motion 3 established that the '380 patent's claims correspond to Count 1 because 11 they are directed to obvious variants of Count 1, and those claims therefore should be added to this 12 proceeding. ToolGen's Opposition does not rebut CVC's showing.

13 Respectfully submitted,

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14

APPENDIX 1 – LIST OF EXHIBITS

Exhibit No.	Description
1245	Rosenberg et al., Vectors for selective expression of cloned DNAs by T7 RNA polymerase, Gene, 56, 125–135 (1987).
1247	Mellon et al., Identification of DNA Sequences Required for Transcription of the Human αl-Globin Gene in a New SV40 Host-Vector System, Cell, 27, 279–288 (1981).
1248	Paul et al., Effective expression of small interfering RNA in human cells, Nature Biotech., 20, 505–508 (2002).
1283	Dana Carroll, Issues in CRISPR-Cas Editing, YOUTUBE, 32:42–32:57 (Nov. 4, 2017), https://www.youtube.com/watch?v=5bHKz142FHs.
1412	July 15, 2021 Declaration of John J. Turchi, Ph.D.
1550	Deposition Transcript of Scott Bailey, Ph.D., The Regents of the University of California v. ToolGen, Inc., Interference No. 106, 127, June 25, 2021.
1559	Gao et al., Research Progress on siRNA Delivery with Nonviral Carriers, International Journal of Nanomedicine, 1017–1025 (2011).
2003	Prov. Appl. No. 61/757,640, filed January 28, 2013
2011	U.S. Patent No. 10,851,380
2012	File History for U.S. Appl. No. 14/685,510
2015	Declaration of Scott Bailey, Ph.D.
2027	Paddison, P.J., *et al*., “Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells,” *Genes & Development* 16:948–958 (2002)
2028	Hwang, W.Y., *et al*., “Efficient genome editing in zebrafish using a CRISPR-Cas system,” *Nature Biotechnology* 31(3):227-229, Supplementary Information (2013)
2029	Deltcheva, E., *et al*., “CRISPR RNA maturation by *trans*-encoded small RNA and host factor RNase III,” *Nature* 471:602-609, Supplementary Information (2011)
2031	Jinek, M., *et al*., “A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity,” *Science* 337(6096):816-821 (2012) with Supplementary Information
2064	Lu, C. and Li, P., “Chapter 5: Preparation of Short RNA by In Vitro Transcription,” Recombinant and In Vitro RNA Synthesis Methods and Protocols, pp. 59-68, Ed. Conn, G.L., Humana Press, Inc., United States (2012)
2065	Ichim, T.E., *et al*., “RNA Interference: A Potent Tool for Gene-Specific Therapeutics,” *American Journal of Transplantation* 4:1227–1236 (2004)
2067	Qu, X., *et al*., “ndrg4 is required for normal myocyte proliferation during early cardiac development in zebrafish,” *Developmental Biology* 317: 486–496 (2008)
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Exhibit No.	Description
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2071	Yuan, S. and Sun, Z., "Microinjection of mRNA and Morpholino Antisense Oligonucleotides in Zebrafish Embryos," *J. Vis. Exp*. 27:e1113 (2008)
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2118	Yan-Shan Dai, *et al*., The Transcription Factors GATA4 and dHAND Physically Interact to Synergistically Activate Cardiac Gene Expression through ap300-dependent Mechanism, *J. Biol. Chem*. 277(27): 4390 – 24398 (2002)
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2434	Rosen, J.N., *et al*., "Microinjection of Zebrafish Embryos to Analyze Gene Function," *Journal of Visualized Experiments* 25: 1-5 (2009)
2517	Corey, D.R., "Chemical modification: the key to clinical application of RNA interference?" *J. Clin. Invest*. 117(12): 3615-3622 (2007)
2518	Chang, K., *et al*., "RNAi in Cultured Mammalian Cells Using Synthetic siRNAs," *Cold Harbor Spring Protoc.* 2012(9):957-961 (2012)
2519	Sakurai, K., *et al*., "Silencing of Gene Expression in Cultured Cells Using Small Interfering RNAs," *Curr. Protoc. Cell Biol.* 47:27.1.1-27.1.28 (2010)
2520	PureFection™ Nanotechnology-based Transfection Reagent, SBI System Biosciences (2010)
2521	Lipofectamine 2000 Reagent, Invitrogen by Life Sciences (Rev. July 20, 2012)
2522	HiPerFect Transfection Reagent Handbook, Fifth Edition October 2012, Qiagen Sample & Assay Technologies
2523	Escort™ IV Transfection Reagent, Sigma (Oct. 2010)
2524	Mirus, The Transfection Experts, Fischer Scientific (2010)
2525	siPORT™ NeoFX™ Transfection Agent, Invitrogen by Life Sciences (Rev. Sept. 2011)

Exhibit No.	Description
2537	Deposition Transcript of John Turchi, Ph.D., with errata, Patent Interference No. 106,127 (August 11, 2021)
2538	Deposition Transcript of Bryan Cullen, Ph.D., with errata, Patent Interference No. 106,127 (August 12, 2021)

1 # APPENDIX 2 – STATEMENT OF MATERIAL FACTS

2 TOOLGEN'S RESPONSES TO CVC'S STATEMENTS OF FACT

3 **1.** By Oct. 23, 2012, methods of preparing RNA using *in vitro* transcription ("IVT") with T7
4 RNA polymerase were known in the art. Ex. 2064, 59; Ex. 2065, 1229.

5 **Response: Admitted that, by October 23, 2012, IVT with T7 RNA polymerase was a**
6 **known method of preparing some RNA. Otherwise, denied.**

7 **2.** By Oct. 23, 2012, a POSA would have known that the consensus promoter for T7 RNA
8 polymerase ("T7 RNAP") is TAATACGACTCACTATAGG. Ex. 2069, 180; Ex. 2064, 59-60.

9 **Response: Denied.**

10 **3.** Using T7 RNAP and the T7 RNAP promoter TAATACGACTCACTATAGG to transcribe
11 RNA results in a 5'-GG on the transcribed RNA. Ex. 2069, 180; Ex. 2064, 59-60.

12 **Response: Admitted that using T7 RNAP and the T7 RNAP promoter**
13 **TAATACGACTCACTATAGG to transcribe RNA may result in a GG at the 5' end.**
14 **Otherwise, denied.**

15 **4.** By Oct. 23, 2012, a POSA would have known that including the terminal GG sequence in the
16 T7 RNA polymerase promoter is critical for transcriptional yield with T7 RNAP. Ex. 2070, 30
17 Ex. 2064, 60; Ex. 2027, 952

18 **Response: Denied.**

19 **5.** Jinek 2012 discloses making sgRNA and crRNA with IVT using T7 RNA polymerase. Ex.
20 2031, Fig. 5 and Suppl. Methods.

21 **Response: Admitted.**

22 **6.** Jinek 2012 discloses using TAATACGACTCACTATAGG as the promoter for making RNA
23 with IVT using T7 RNAP. Ex. 2031, Table S3.

1 **Response: Admitted that Jinek discloses using TAATACGACTCACTATAGG as a**
2 **promoter for making RNA in some instances. Otherwise, denied.**
3 **7.** Jinek 2012 discloses making crRNA with primers that, when used for IVT with T7 RNAP,
4 would have resulted in a 5'-GG directly adjacent to the targeting region of the crRNA. Ex.
5 2031, Table S3; Ex. 2069, 180; Ex. 2064, 59-60.
6 **Response: Admitted that Jinek discloses instances of making crRNA with primers that,**
7 **when used for IVT with T7 RNAP may have resulted in a GG at the 5' end. Otherwise,**
8 **denied.**
9 **8.** Jinek 2012 demonstrated that RNA made with IVT using T7 RNAP and the consensus T7
10 RNAP promoter was functional in a CRISPR-Cas9 system, including in cleaving eukaryotic
11 DNA sequences. Ex. 2031, Figs. 1-5.
12 **Response: Denied.**
13 **9.** Deltcheva (Ex. 2029) discloses making crRNA and tracrRNA with IVT using T7 RNA
14 polymerase. Ex. 2029, Suppl. Methods.
15 **Response: Admitted.**
16 **10.** Deltcheva discloses making crRNA and tracrRNA with promoters that, when used for IVT
17 with T7 RNAP, would have resulted in a 5'-GG on the transcribed RNAs. Ex. 2029, Suppl.
18 Table 10; Ex. 2069, 180; Ex. 2064, 59-60.
19 **Response: Admitted that Deltcheva discloses making RNA with promoters that, when**
20 **used for IVT with T7 RNAP, may have resulted in a GG at the 5' end. Otherwise, denied.**
21 **11.** By Oct. 23, 2012, a POSA would have known that IVT of RNA with T7 RNAP had been used
22 to make RNA that was subsequently introduced into eukaryotic cells. Ex. 2027, 952; Ex. 2065,
23 1228-1229; Ex. 2067, 487; Ex. 2068, 763.

1 **Response: Admitted only as to mRNA, shRNA, and siRNA. Otherwise, denied.**

2 **12.** By Oct. 23, 2012, NLS tags were commonly placed at the C-terminus of proteins to obtain
3 nuclear localization. Ex. 2117, 42189; Ex. 2118, 24391.

4 **Response: Admitted that Ex. 2117 and Ex. 2118 disclose the use of multiple NLSs.**
5 **Otherwise, denied.**

6 **13.** By Oct. 23, 2012, human cells were used for genome editing experiments with ZFN and
7 TALEN systems. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4.

8 **Response: Admitted that, by October 23, 2012, some genome editing experiments in**
9 **human cells used ZFN and TALEN systems. Otherwise, denied.**

10 **14.** By Oct. 23, 2012, using vectors was a known method for expressing exogenous proteins within
11 eukaryotic cells. Ex. 2111, 9284-9285, 9291; Ex. 2110, 3-4.

12 **Response: Admitted that, by October 23, 2012, using vectors was a known method for**
13 **expressing some exogenous proteins within eukaryotic cells. Otherwise, denied.**

14 **15.** The only difference between the CRISPR-Cas9 system in ’380 patent’s claims and Count 1 is
15 the presence of a 5'-GG on the guide RNA. Ex. 2011, 179:18-38.

16 **Response: Denied.**

17 **16.** During prosecution of the ’510 patent, ToolGen argued that the claims that would become
18 Count 1 were commensurate in scope with an unexpected increase in specificity. Ex. 2012,
19 6774-6775, 6910-6914, 6939-6940.

20 **Response: Denied.**

21 **17.** By Oct. 23, 2012, injection of *in vitro* transcribed RNA was known as an essential quick and
22 robust tool for exploring gene function in the zebrafish embryos. Ex. 2071, 1.

23 **Response: Denied.**

1 **18.** The ’380 patent’s method claims recite no active steps beyond a general instruction to
2 “introduce” a CRIPSR-Cas9 system into cells. Ex. 2011, 179:18-180:38.
3 **Response: Denied.**
4 **19.** By Oct. 23, 2012, a POSA would understand a chimeric guide RNA to comprise a crRNA and
5 a tracrRNA linked together with intervening nucleotides. Ex. 2031, Fig. 5.
6 **Response: Denied.**
7

1 CVC's RESPONSES TO TOOLGEN'S ADDITIONAL MATERIAL FACTS

2 **20.** Jinek describes only the use of a prokaryotic CRISPR/Cas9 system *in vitro*, that is, in a non-
3 cellular experimental environment. Ex. 2031.

4 **CVC Response: Denied**

5 **21.** Jinek does not report the results of any experiments using CRISPR/Cas9 in eukaryotic cells.
6 Ex. 2031.

7 **CVC Response: Admitted**

8 **22.** Jinek says nothing of cell introduction. Ex. 2031.

9 **CVC Response: Denied**

10 **23.** Jinek was addressed during prosecution of the '380 patent, and the examiner determined that
11 independent claim 1—and in particular, the 5'-GG limitation—was nonobvious in view of
12 Jinek. Ex. 2120, 8386.

13 **CVC Response: Admitted that the examiner noted that applicant's arguments were**
14 **sufficient to overcome the prior art references used against then-pending claim 84.**

15 **24.** Independent claim 1 of the '380 patent recites a method of "introducing into [a] eukaryotic
16 cell" a CRISPR/Cas9 system comprising an sgRNA having, among other things, "two guanines
17 at [the] 5' end[.]" Ex. 2011, 179:32–36.

18 **CVC Response: Admitted**

19 **25.** As of the priority date, a POSA would have understood that introducing RNA into eukaryotic
20 cells might be accomplished using various methods of transfection, among them plasmid
21 transfection and RNA transfection. Ex. 2065, 1228–30; Ex. 1412, ¶ 39.

22 **CVC Response: Admitted that a POSA was aware of methods of introducing RNA into**
23 **eukaryotic cells, including direct RNA transfection, transfection of plasmids encoding**

1 **RNA, and microinjection of RNA.**

2 **26.** Plasmid transfection is a mechanism of introducing plasmid DNA into a cell, where DNA
3 segments are then transcribed, within the cell, into RNA. Ex. 1247, 286; Ex. 1412, ¶ 39.

4 **CVC Response: Admitted that plasmid transfection is one of the known methods of**
5 **introducing plasmid DNA into a cell, and that plasmids may be designed such that DNA**
6 **is transcribed into RNA within the cell. Otherwise, denied.**

7 **27.** RNA transfection is a method of introducing RNA that is *in vitro* transcribed and purified,
8 directly into a cell. Ex. 1245, 132; Ex. 1246, 6077–78; Ex. 1412, ¶ 39.

9 **CVC Response: Admitted that RNA transfection is a method of introducing RNA directly**
10 **into a cell, and that RNA for transfection may be *in vitro* transcribed and purified.**
11 **Otherwise, denied.**

12 **28.** Jinek describes a method of preparing RNA, specifically, the method of "[i]n vitro transcription
13 [(or "IVT")] and purification of RNA . . . using [a] T7 Flash in vitro Transcription Kit . . . and
14 [polymerase chain reaction]-generated DNA templates carrying a T7 promoter sequence." Ex.
15 2031, "Supplementary Materials and Methods."

16 **CVC Response: Admitted**

17 **29.** As of the priority date, a POSA would have understood that *in vitro* transcribed RNA, such as
18 that prepared using the Jinek method, could only be effectively introduced into eukaryotic cells
19 using RNA transfection. Ex. 1412, ¶ 40.

20 **CVC Response: Denied.**

21 **30.** As of the priority date, RNA transfection was not routinely employed in the art for introducing
22 RNA into eukaryotic cells. Ex. 1412, ¶ 41.

23 **CVC Response: Denied**

31. Fewer than forty papers were published on lipid-based RNA transfection up to 2012 and less than fifty papers using other chemical means. Ex. 1412, ¶ 45.

CVC Response: Denied

32. As of the priority date, a POSA would have understood RNA transfection to be problematic, particularly in eukaryotic cells. Ex. 1412, ¶ 41.

CVC Response: Denied

33. Ichim discloses that RNA transfection was problematic, particularly in eukaryotic cells. Ex. 2065, 1232.

CVC Response: Denied

34. Gao discloses that RNA transfection was problematic, particularly in eukaryotic cells. Ex. 1559, 1017.

CVC Response: Denied

35. Jinek fails to acknowledge, let alone provide guidance as to how a POSA might address and overcome problems associated with direct RNA transfection in eukaryotic cells of bacterial RNA. Ex. 2031.

CVC Response: Denied.

36. Jinek is entirely silent concerning methods of RNA introduction in both prokaryotic cells and eukaryotic cells. Ex. 2031.

CVC Response: Denied

37. As of the priority date, plasmid transfection was widely employed in the art for introducing DNA sequences encoding RNA molecules into eukaryotic cells. Ex. 1248, 505 (Abstract); Ex. 1412, ¶ 42.

CVC Response: Admitted

1 **38.** As of the priority date, a POSA would have understood plasmid transfection to be the most
2 desirable and most common method of RNA introduction given its ease of use and numerous
3 benefits over other methods, particularly RNA transfection. Ex. 1248, 505 (Abstract); Ex.
4 1550, 61:3–7, 77:14; 1243; Ex. 1412, ¶ 42.
5 **CVC Response: Denied**
6 **39.** Dr. Bailey indicated on cross-examination that plasmid transfection was a well-known
7 technique to introduce RNA into eukaryotic cells. Ex. 1550, 61:3-7; *see also id.*, 77:14-18.
8 **CVC Response: Admitted**
9 **40.** Ichim discloses "several advantages" of using plasmid transfection in eukaryotic cells. Ex.
10 2065, 1229.
11 **CVC Response: Admitted that Ichim discloses several advantages of a particular**
12 **plasmid-based method of siRNA delivery using "a partially palindromic hairpin loop**
13 **mRNA." Otherwise, denied.**
14 **41.** Paddison recognizes several benefits of plasmid transfection. Ex. 2027, 952–53, 956.
15 **CVC Response: Admitted that Paddison discloses that plasmids may be used to stably**
16 **express RNA. Otherwise, denied.**
17 **42.** sgRNA is more susceptible to degradation compared to double-stranded RNA structures, e.g.
18 siRNA and shRNA. Ex. 1412, ¶ 48.
19 **CVC Response: Denied**
20 **43.** While *in vitro*-transcribed sgRNA prepared by the Jinek method may result in RNA having
21 two guanines at the 5' end, this is due to the fact that using T7 RNA polymerase in conjunction
22 with the T7 promoter requires one or more guanines at the 5' end of the RNA transcript. Ex.
23 1245, 132.

1 **CVC Response: Admitted that *in vitro*-transcribed sgRNA prepared by the Jinek method**
2 **results in RNA having two guanines at the 5' end. Otherwise, denied.**
3 **44.** It was ToolGen that first recognized the significance of using two guanines at the 5' end. Ex.
4 2011, 36:28–49.
5 **CVC Response: Denied**
6 **45.** During a 2017 presentation, Dr. Carroll, stated: "Another thing that Jin-Soo Kim found was
7 that if you . . . put a couple of extra Gs on the 5' end of the guide RNA . . . it actually improves
8 the specificity[.]" Ex. 1283, 32:42–32:57.
9 **CVC Response: Admitted that Dr. Carroll stated "Another thing that Jin-Soo Kim found**
10 **was that if you just put a couple of extra Gs on the 5' end of the guide RNA that don't**
11 **match the target, it actually improves the specificity a little bit," which he attributed to**
12 **"eliminating [the] excess affinity" for both on and off-target binding. Ex. 1283, 27:12-16,**
13 **32:4-10.**
14 **46.** During a 2017 presentation, Dr. Carroll referenced only "data from [Dr. Kim's] paper" in
15 discussing the use and significance of two guanines at the 5' end; he never referenced Jinek or
16 any other CVC disclosure as teaching or suggesting the use or significance of two guanines at
17 the 5' end. Ex. 1283, 32:58–33:04.
18 **CVC Response: Denied**
19 **47.** Eukaryotic promoters do not require one or more guanines at the 5' end. Ex. 1412, ¶ 47.
20 **CVC Response: Admitted that some eukaryotic promoters do not require one or more**
21 **guanines at the 5' end.**
22 **48.** As of the priority date, a POSA would have understood the T7 promoter as being used
23 exclusively in *in vitro*, non-cellular experiments. Ex. 1412, ¶ 47.

1 **CVC Response: Denied**

2 **49.** As of the priority date, the U6 promoter was being used in ZFN and TALEN systems. Ex.
3 1412, ¶ 47.

4 **CVC Response: Admitted**

5 **50.** In its Motion 1 (Paper 368), CVC admits that the U6 promoter "was commonly used" in ZFN
6 and TALEN systems. CVC Motion 1, 13:15.

7 **CVC Response: Admitted that CVC's Motion 1 states that Feng Zhang "expressed RNA**
8 **using a U6 promoter that was commonly used to express shRNAs."**

9 **51.** CVC, in its own experiments described in U.S. Provisional Application No. 61/757,640,
10 utilized DNA plasmids to introduce CRISPR RNA into eukaryotic cells. Ex. 2003, ¶¶ 408–23.

11 **CVC Response: Admitted**

12 **52.** As of the priority date, nothing in the prior art suggested the desirability of using RNA
13 transfection over plasmid transfection for the introduction of sgRNA in eukaryotic cells.

14 **CVC Response: Denied**

15 **53.** In its Motion 3, CVC offers no evidence of the desirability of using RNA transfection over
16 plasmid transfection.

17 **CVC Response: Denied**

18 **54.** Paddison provides that "[d]elivery of siRNAs can be accomplished by any of a number of
19 transient transfection methodologies," Ex. 2027, 952–53 (paragraph bridging pages 952 and
20 953), but offers no evidence that RNA transfection was a desirable method of introducing
21 sgRNA into eukaryotic cells.

22 **CVC Response: Admitted that Paddison states, "[d]elivery of siRNAs can be**
23 **accomplished by any of a number of transient transfection methodologies." Otherwise,**

1 **denied.**

2 **55.** The Board previously held, and the Federal Circuit affirmed, that as of December 2012, a
3 POSA "would not have reasonably expected success" in implementing CRISPR/Cas9 in
4 eukaryotic cells. *Broad Inst.*, 2017 WL 657415, at *12.

5 **CVC Response: Admitted that the Board stated, in the context of its decision on a motion**
6 **for no interference-in-fact for Interference 106,048, that "one of ordinary skill in the art**
7 **would not have reasonably expected success before experiments in eukaryotic cells were**
8 **done." Otherwise, denied.**

9 **56.** The senior party in the '115 interference "argu[ed] that none of the publications" cited by the
10 junior party—including Jinek—"show[ed] success in eukaryotic cells," which the Board held
11 in Interference No. 106,048 to be "necessary for a reasonable expectation of success." *Regents*
12 *of the Univ. of California*, Interference No. 106,115, slip op. at 66.

13 **CVC Response: Admitted that the PTAB stated "Broad refutes CVC's evidence, arguing**
14 **that none of the publications it cites show success in eukaryotic cells, which we held in**
15 **the prior '048 interference was necessary for a reasonable expectation of success," and**
16 **that CVC had previously cited Jinek 2012.**

17 **57.** In the '115 Interference, the Board explained that "the issue in the ['048] interference was
18 whether a CRISPR-Cas9 system would have been expected to work in a eukaryotic cell," but
19 in the '115 interference, "[t]hat issue [was] assumed under the framework of 37 C.F.R. §
20 41.207(b)(2)[.]" *Regents of the Univ. of California*, Interference No. 106,115, slip op. at 66.

21 **CVC Response: Admitted that the Board stated, "We are not persuaded by Broad's**
22 **argument because the issue in the prior interference was whether a CRISPR-Cas9 system**
23 **would have been expected to work in a eukaryotic cell. That issue is assumed under the**

1 **framework of 37 C.F.R. § 41.207(b)(2), wherein Count 1 is presumed to be prior art to**
2 **the Broad claims."**
3 **58.** Neither Jinek nor Deltcheva disclose use of CRISPR/Cas9 in eukaryotic cells, much less that
4 such use was made "regularly and successfully" as of the priority date. Ex. 2029; Ex. 2031.
5 **CVC Response: Denied**
6 **59.** The '380 patent discloses that ToolGen "tested whether the addition of two guanine nucleotides
7 at the 5' end of sgRNA could make [RNA-guided endonucleases] more specific by comparing
8 5'-GGX20; (or 5'-GGGX19) s[g]RNA with 5'-GX19 sgRNA." Ex. 2011, 36:28–31.
9 **CVC Response: Admitted that this text appears in the patent, but denied that this**
10 **statement has been proven.**
11 **60.** The '380 patent discloses that "GGX20 sgRNAs discriminated off-target sites effectively. In
12 fact, the T7E1E assay barely detected [RNA-guided endonuclease]-induced indels at six out
13 of the seven validated off-target sites when [ToolGen] used the four GGX20 sgRNAs[.]" Ex.
14 2011, 36:34–37.
15 **CVC Response: Admitted that this text appears in the patent, but denied that this**
16 **statement has been proven.**
17 **61.** The '380 patent discloses that "[t]hese results show that the extra nucleotides at the 5' end can
18 affect mutation frequencies at on-target and off-target sites, perhaps by altering guide RNA
19 stability, concentration, or secondary structure. These results suggest that three factors-the use
20 of synthetic guide RNA rather than guide RNA-encoding plasmids, dualRNA rather than
21 sgRNA, and GGX20 sgRNA rather than GX19 sgRNA-have cumulative effects on the
22 discrimination of off-target sites." Ex. 2011, 36:40–49.
23 **CVC Response: Admitted that this text appears in the patent, but denied that this**

statement has been proven.

62. Dr. Carroll, during a 2017 presentation, while addressing “off-target effects and delivery hurdles when using CRISPR-Cas technology for genome engineering,” referred to Dr. Kim’s use of two guanines at the 5' end not only as a “method[] to improve specificity,” but as a “high-fidelity modification[]” compared to “basic [CRISPR/Cas] systems.” Ex. 1283, 39:10–40:44.

CVC Response: Denied

63. Because CRISPR/Cas9 is a multi-component complex, wherein the Cas9 protein portion is most commonly expressed in a cell following plasmid transfection, it would be most convenient to use plasmid transfection for the RNA portion. Ex. 1412, ¶ 43.

CVC Response: Denied

64. As of the priority date, a POSA would have understood plasmid transfection to provide continuous and sustained RNA expression and chemical stability within eukaryotic cells. Ex. 1412, ¶¶ 42, 44.

CVC Response: Admitted

1 CVC'S ADDITIONAL STATEMENTS OF FACT

2 **65.** Multiple prior art references before October 2012 disclosed introducing RNA made using T7
3 RNA polymerase into eukaryotic cells. Ex. 2015, ¶¶77-80; Ex. 2027, 951-953; Ex. 2065, 1229-
4 1230; Ex. 2067, 487; Ex. 2068, 763.

5 **66.** Before October 2012, microinjection was a known method of introducing RNA that a POSA
6 would have used with a range of different eukaryotic model systems. Ex. 2538, 40:1-11, 43:16-
7 45:18; Ex. 2015, ¶¶58, 79, 111; Ex. 2028, 9; Ex. 2067, 487; Ex. 2071, 1, Abstract; Ex. 2434,
8 1, Abstract.

9 **67.** RNA transfection was a standard and routine method for the introduction of RNA into cells
10 prior to October 2012. Ex. 2537 95:3-96:3; Ex. 2538, 37:14-39:8.

11 **68.** Dr. Turchi performed searches that identified a few hundred papers published prior to October
12 2012 relating to RNA transfection. Ex. 2537, 36:20-37:10.

13 **69.** A range of different commercial transfection reagents advertised as being appropriate for RNA
14 transfection was available before October 2012. Ex. 2517, 3615; Ex. 2518, 957, 960; Ex. 2519,
15 27.1.4; Ex. 2520, 1; Ex. 2521, 1; Ex. 2522, 8; Ex. 2523, 1; Ex. 2524, 1; Ex. 2525, 2; Ex. 2537,
16 96:4-16.

17 **70.** Therapeutic delivery of RNA is not required by the claims of the '380 patent. Ex. 2011, 179:18-
18 180:39.

19 **71.** The '380 patent concludes that sgRNAs with the 5'-GG were "less active at on-target sites"
20 than sgRNAs without a 5'-GG. Ex. 2011, 36:38-44.

21 **72.** The '380 patent provides evidence that the 5'-GG decreases cleavage at both the desired target
22 and the potential off-target cleavage sites. Ex. 2011, 36:38-44.

23 **73.** The '380 patent is a member of the same patent family as ToolGen's involved U.S. Application

1 14/685,510, and does not claim an earlier priority date than the ’510 application. Ex. 2011,
2 Cover Page.
3 **74.** Ichim (Ex. 2065) and Gao (Ex. 1559) discuss “delivery” of RNA in the context of how to get
4 therapeutic RNAs to the correct location within the body. Ex. 2065, 1232; Ex. 1559, 1017.
5 **75.** Ichim’s statement that the “promise of siRNA-therapeutics is held back by the question of
6 delivery” is a reference to the immunogenicity observed when using a viral vector to deliver
7 an siRNA therapy. Ex. 2065, 1232-1233.
8 **76.** Gao’s statement regarding the “problems” with delivery is a reference to “some fatal
9 disadvantages of viral vectors” when delivering siRNA therapeutics. Ex. 1559, 1017.
10 **77.** The prior art disclosed transfecting chemically modified siRNA into eukaryotic cells. Ex. 2517,
11 3615.

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **CVC MOTION 3 (to add the claims of ToolGen patent 10,851,380)** was filed via the Interference Web Portal by 8:00 PM Eastern Time on August 27, 2021, pursuant to an agreement between the parties, and thereby served on the attorney of record for the Senior Party pursuant to ¶ 105.3 of the Standing Order. Pursuant to the agreement between the parties, the foregoing was also served via email by 11:00 PM Eastern Time on counsel for the Senior Party at:

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