

Filed on behalf of: ILLUMINA

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.

Petitioner,

v.

Patent of THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF

NEW YORK

Patent Owner.

Case No. IPR2012-00007
U.S. Patent No. 7,790,869

PETITIONER ILLUMINA'S REPLY TO
PATENT OWNER COLUMBIA'S RESPONSE TO PETITION

Illumina Ex. 1128 Illumina v. Columbia IPR2018-00291, -00318, -00322, -00385, and -00797

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Columbia does not defend the validity of the original claims, essentially admitting unpatentability of the original challenged claims. Proposed claims 34-54 are unpatentable for the reasons in Illumina’s Petition, and for the reasons below.

I. COLUMBIA'S “STARTING POINT” ANALYSIS IS IRRELEVANT AND IMPROPER

Instead of addressing Illumina’s invalidity analysis, Columbia inappropriately tries to shoehorn the proposed claims into a pharmaceutical “lead compound” analysis for rebuttal. However, unlike the “starting point” case Columbia cited, the claims here are directed to sequencing methods, not pharmaceutical compounds. Columbia’s “starting point” analysis is thus inapplicable to the claims at issue. Moreover, Illumina has not asserted a “structural similarity” obviousness-type analysis, so the lead compound cases would not be relevant even if the Columbia claims were considered to be pharmaceutical compounds. Finally, even if a “starting point” analysis were appropriate, Columbia’s emphasis on a *single* starting point (3’-OH labeled dNTPs) is not. USPTO guidelines at 75 F.R. 53643, at 53652, col. 3 (“[i]t should be noted that the lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound.”) Instead, a “starting point” is any compound that would be “a natural choice for further development efforts.” *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). Tsien’s base-

labeled dNTPs are a natural choice for further development efforts in view of Tsien's teachings about label positioning and enzymatic competence, and Dr. Trainor himself agreed that a labeled base was a preferred embodiment of Tsien. Ex. 2094 at 237:19-239:9; Ex. 1002 at 27:35-30:36.

Nor are the straw man changes proposed by Dr. Trainor realistic. For example, Dr. Trainor posits that one of skill in the art would need to convert a ddNTP to a dNTP. *See, e.g.*, Ex. 2033 ¶¶ 65, 80. Not only is this wrong (both Tsien and Prober I/Hobbs disclose dNTPs), but no one of skill in the art would "convert" a ddNTP to a corresponding dNTP. Ex. 1053 ¶ 73. Rather, they would synthesize the dNTP from an appropriate starting material. *Id.* Also, contrary to Dr. Trainor's declaration (*see, e.g.*, Ex. 2033.¶¶ 61-63), the prior art as of 1999 provided express reasons to adopt the base-labeled approach for 3'-blocked nucleotides. Ex. 1045 at 956; Ex. 2094 at 349:20-350:21, 352:11-25; Ex. 1053 ¶¶ 60 & 98-109.

Thus, a lead compound analysis is not appropriate to analyze these claims, and, even if it were, Tsien's base labeled nucleotides would be a proper starting point. Tsien and other prior art expressly teach that base labeled nucleotides were a natural choice for further development at the time the '869 patent was filed.

II. CLAIMS 34-54 DO NOT REQUIRE INCORPORATION BY A POLYMERASE

Dr. Trainor's opinions are based on the incorrect premise that the *claims* require that the nucleotide analogue can be incorporated by a polymerase. *See, e.g.*,

Ex. 2033, ¶¶ 33, 39, 68(8), 108(4). No such requirement exists in claim 34, and no separate argument is present with respect to any dependent claim. Ex. 1053 ¶ 85. Claim 43 requires that the nucleotide is “incorporated onto a primer,” but does not specify that incorporation is performed by a polymerase. *Id.* Claim 49 requires only that the “cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.” *Id.* Dr. Trainor admitted that this property is met by any 3' blocking group that allows incorporation by a polymerase. Ex. 2094 at 154:10-156:22. For example, Tsien discloses an allyl 3' blocking group, which would not interfere. Ex. 1002 at 24:29-30; Ex. 2094 at 106:14-108:21.

III. CLAIMS 34-54 ARE OBVIOUS OVER TSIENT AND PROBER I

Illumina’s Petition demonstrated that Tsien in view of Prober I disclosed all limitations of Claims 35-54. Petition at 21-29. Columbia does not dispute this, instead raising motivation to combine, expectation of success, and secondary considerations.

A. Motivations Existed to Make the Single Change to Tsien (in view of Prober I) to Meet All Limitations of the Challenged Claims

Columbia asserts that a skilled artisan would have had to make “7 [sic] changes” to the “starting point” in Tsien to arrive at the proposed claims. Paper 78 at 18; Ex. 2033 at ¶ 92. But Dr. Trainor admitted that all but two (#1 & #2) of the 8 “changes” are not changes at all – they are expressly disclosed in Tsien.

Specifically, Dr. Trainor agreed that Tsien teaches: (#3-5) chemically

cleavable linkers for nucleobases (Ex. 1002 at 28:1-4 & 28:19-36; Ex. 2094 at 113:19-115:14; 220:4-221:6 & 227:2-228:4); (#6-#7) a chemically removable 3-OH capping group (Ex. 1002 at 27:35-28:10; Ex. 2094 at 105:20-106:13, 217:11-218:10, & 219:14-220:3); and (#8) incorporation by polymerase (Ex. 1002 at 28:10-18; Ex. 2094 at 449:3-20 & 213:8-217:10). Dr. Trainor agreed that Tsien described its base-labeled approach as a preferred way to carry out its Fig. 2 process, and that features #3-8 were either required by or preferred in that Fig. 2 process. Ex. 1002 at 10:4-15, 12:14-18, & 14:22-26; Ex. 2094 at 213:8-217:10, 228:5-230:15, & 238:21-24; *see also* Ex. 1053 at ¶¶ 31-40. Also, “changes” #1 and #8 are not limitations of claim 34. Thus, none of Dr. Trainor’s changes #1 and #3-8 are actually changes to Tsien.

“Change” #2 is using a deazapurine, which is the only type of purine taught by Prober I. Ex. 1003 at 337, Fig. 2A. Thus, the issue of invalidity is the same one identified by the Board – whether a person of skill in the art would use deazapurines as in Prober I in the sequencing method of Tsien. Paper 38 at 25-27. A skilled artisan would have been motivated to make this “change” based on the express suggestion in Tsien to use the analogues in Prober I. Accordingly, claims 34-54 would have been obvious in view of Tsien and Prober I.

1. Tsien Expressly Teaches to Use Prober I’s 7-Deazapurine

Tsien cites to Prober I for guidance on the creation of nucleotide analogues

for use in SBS methods (Ex. 1002, at 28:5-18 & 29:3-16; *see also* Ex. 1021 ¶¶ 45-49, 53, 57, & 63-67), thus suggesting to modify the nucleotide analogues of Tsien using Prober I. Paper 38 at 25-27. Prober I only discloses labeling purines at the 7 position, and Dr. Trainor agrees that attaching labels there requires the use of 7-deazapurines. Petition at 27; Ex. 1021 at ¶ 49; Ex. 2094 at 309:16-19).

Columbia asserts that a skilled artisan could not have combined Tsien and Prober I to arrive at the proposed claims. Paper 78 at 19-21. But Tsien expressly teaches to combine Prober I's 7-deazapurines with the nucleotide analogues of Tsien. Ex. 1002 at 28:5-18 & 29:3-16; *see also* Ex. 1021 at 45-49, 53, 57, & 63-67; Paper 38 at 25-27. Indeed, 7-deazapurines are the only label option disclosed by Prober I for purine analogues. Ex. 1003; Ex. 1053 at ¶¶ 41-48.

Columbia wrongly asserts that Prober I's *dd*NTPs would have deterred a skilled artisan from combining the 7-deazapurine feature of Prober I with the *d*NTPs of Tsien. Paper 78 at 19-20. But Tsien itself expressly relied on Prober I for how to make and use *d*NTPs in SBS reactions. Ex. 1002 at 29:12-16; Ex. 2094 at 261:2-20; *see also* Ex. 1011 at 5:38-43 & Fig. 3 (showing similar reliance); Ex. 2033 at ¶ 32. The same is true of Columbia's argument regarding Prober I's synthesis disclosure (Ex. 2033 ¶ 72); Hobbs disclosed the method of making Prober I's nucleotides. Ex. 1021 at ¶ 46; Ex. 2094 at 239:20-240:10 & 264:19-265:9; Ex. 1050 at 2473-2474; *see also* Ex. 1053 at ¶ 55. Even the '869 patent

relied on Prober I's "well-established procedures" to make 7-deazapurine dNTPs. Ex. 1001 at 26: 32-34. The Board thus correctly determined that Tsien's express citation to Prober I constitutes a suggestion to use the teachings of Prober I to modify Tsien's nucleotide analogues for SBS methods.¹ Paper 38 at 25-27.

1. The Emergence of 7-Deazapurines as the Preferred Label Site Elevated Motivation to Combine Tsien with Prober I

Columbia asserts that C8-labeled bases were "ideal" such that a skilled artisan would not have used C7-labeled bases. Paper 78 at 19. However, this argument ignored the emergence of C7-labeled 7-deazapurines as the dominant, preferred location for label attachment between Tsien's 1991 publication and 1999. Ex. 1053 ¶ 54. Applied Biosystems, the near-monopoly producer of reagents for Sanger sequencing (*i.e.*, "first generation" sequencing) used 7-deazapurines. Petition at 14; Ex. 1021 at ¶¶ 37, 43, & 59 (point 3); Ex. 1034 at 338:6-18 & 347:15-348:1; Ex. 2094 178:16-179:6 & 262:25-264:18; Ex. 1030; Ex. 1053 ¶ 44.

The literature recognized that the 7-deaza position was preferred over the C-8 position because 7-deazanucleotides were more readily incorporated by

¹ Another panel found that Tsien incorporated Prober I's deazapurines. IPR2013-00128, Paper 23, at 9-11. Incorporation by reference is a legal question. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1283 (Fed. Cir. 2000). The same facts support Illumina, that there is an express reason to combine here.

polymerase, and C-8 substitutions destabilize the double helix. Petition at 57-58; Ex. 1021 at ¶ 47; Ex. 2094 at 267:21-268:16, 276:22-333:21 (discussing Exs. 1041-1044), 333:22-334:7, 335:2-336:25, & 339:3-25; Ex. 1034 at 350:20-351:23; Ex. 1032 at 6:48-55 & 7:54-65; Ex. 1053 at ¶¶ 48, 50 & 51; *see also, e.g.*, Ex. 1043 at 1087; Ex. 1044 at 965. While Dr. Trainor argued that a person of skill in the art would not be concerned with more efficient incorporation (Ex. 2094 at 292:16-293:2), the prior art clearly contradicts him. Ex. 1002 at 19:30-32 & 26:6-12; Ex. 1013 at 8:41-60; Ex. 1001 at 2:43-49; Ex. 1053 at ¶ 51. Dr. Trainor further asserts that stabilization of the double helix would not matter because only a single nucleotide is required to be incorporated. Ex. 2094 at 297:11-298:5. But Tsien is not limited to a single incorporation, so a person of skill in the art seeking to implement the SBS method of Tsien would have been motivated to use the 7-deazapurines taught by Prober I and the subsequent literature because of their stabilizing effect on the double helix during sequencing. Ex. 1002 at 6:34-7:14, 11:5-12, 13:28-35, & 17:33-18:2; Ex. 1053 at ¶ 49-51. It is undisputed that this combination would meet the claims of the '869 patent.

Dr. Trainor asserted in his deposition that he had not heard of anyone applying the teachings of Prober I to SBS. Ex. 2094 at 311:14-312:13. However, his own testimony and declaration contradict this assertion. Ex. 2094 at 566:14-567:25; Ex. 2033 at ¶ 33 (citing Anazawa's discussion of using Prober I's

teachings to create base-labeled deaza dNTPs). Neither Columbia, nor Dr. Trainor addressed the fact that deazapurines were a known, interchangeable analogue of purines in next generation sequencing. Petition at 14-16; Ex. 1021 at ¶ 66; Ex. 1053 at 163:4-164:10. *See also, e.g., Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007).

In sum, combining Prober I's deazapurines with Tsien's nucleotide analogues would have been obvious to one of ordinary skill in the art because deazapurines were widely used and preferred. Thus, developments in the art between Tsien and the '869 patent, which Columbia failed to consider, elevated the desirability of combining Tsien with the 7-labeled deazapurines of Prober I.

B. One Would Reasonably Expect Success in Modifying Tsien's Nucleotides to Attach a Label at C7 of a Deazapurine

In addition to being motivated, one skilled in the art would have had a reasonable expectation of successfully attaching Tsien's label to the 7-position of a 7-deaza deoxypurine. The nucleotides of Tsien could have been modified by knowledge of the methods taught by Prober I, with only routine adaptations – use of a dNTP instead of a ddNTP, and use of a cleavable linker in place of (or in addition to) a non-cleavable linker. Ex. 1053 at ¶ ; Ex. 2033 at ¶ 104; Ex. 2094 at 170:7-171:5; 191:23-192:5. Prober I taught this method was highly general, and, as such, one would have expected to successfully incorporate these routine changes. Ex. 1003 at 337, col. 1; Ex. 1053 at ¶¶ 64-70.

Indeed, the '869 specification takes this modification as so well accepted that it does not even explain how 7-labeled 7-deazapurine nucleotides are made. Instead, citing to Prober I and Hobbs, it provides just two sentences stating that the synthesis begins with 7-deaza-substituted intermediates prepared according to “well-established procedures.” Ex. 1001 at 24:64-67 and Fig. 8 (showing 7-deaza dGTP); Ex. 2094 at 174:17-176:23; 179:7-23; Ex. 1053 at ¶ 78-79. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) (“Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.”).

Dr. Trainor suggested in his declaration that it would have been difficult to make 7-deaza dATP and 7-deaza dGTP based on the disclosure of ddNTPs in Prober I. Ex. 2033 at ¶ 80. As just noted, this is inconsistent with the '869 patent itself. Further, Dr. Trainor admitted at his deposition that his own patent (Hobbs) taught that 7-deaza dATP with C7 attached linkers could be readily made and incorporated. Ex. 2094 at 241:22-244:2 & 264:10-267:7 (discussing Ex. 1013 at 28:62-67 and 27:39-59); *see also* Ex. 1053 at ¶ 65. He also admitted that a skilled artisan would have reasonably expected to successfully make 7-deaza dGTP. Ex. 2094 at 179:7-23, 247:10-249:4, & 258:18-259:23; Ex. 1053 at ¶ 75. In addition, others had published precursors and methods that could be used to make 7-labeled 7-deaza dATPs and dGTPs usable in Tsien's method. Ex. 1044, at 963; Ex. 1043,

at 1084-85 and “*Scheme*”; Ex. 1042 at 1811; Ex. 1053 ¶ 45.

Regarding the use of a cleavable linker, Tsien describes Prober I’s synthetic route as having “great flexibility in that *the linker can be varied with respect to length or functionality.*” Ex. 1002 at 29:12-19 (emphasis added); Ex. 2094 449:3-450:9. Dr. Trainor did not disagree with Tsien; he addressed the linker used in Prober I, but he never suggested that a cleavable linker would not be expected to be usable in its place. Ex. 2033 ¶ 111. Then, at his deposition, he admitted that attaching a 7-deaza dNTP intermediate to a cleavable linker/label would be “a trivial reaction” (Ex. 2094 at 189:7-190:2), whether the nucleotide was a ddNTP or a dNTP. *Id.* at 190:3-193:2; *see also* Ex. 1053 at ¶ 72.

Accordingly, a person of ordinary skill would reasonably expect that the nucleotide analogues used in the ’869 claims could have been readily produced.

C. One Would Have Reasonably Expected Successful Polymerase Incorporation of Modified Nucleotides

In a single paragraph, but without explanation, Dr. Trainor asserted that a nucleotide with a 3’-OH block and a label attached to the base would not be expected to be incorporated by a polymerase. Ex. 2033 at ¶ 113. This unsupported opinion contradicts the teachings in the prior art and the ’869 patent. Tsien stated that a 3’-OH blocked, base-labeled nucleotide would be incorporated. Ex. 1002 at 26:1-12 & 28:5-12; Ex. 1053 at ¶ 87. The ’869 patent also states that base-labeled nucleotides and 3’-OH blocked nucleotides were known to be recognized by

polymerases. Ex. 1001 at 2:44-55, 3:12-16. The knowledge that C7-labeled deazapurines promote stable incorporation would have enhanced the expectation of successful incorporation. Ex. 1032 at 6:48-55 & 7:54-65; Ex. 2094 at 291:24-292:17; Ex. 1053 at ¶ 90.

IV. CLAIMS 34-54 ARE OBVIOUS OVER STEMPLE AND ANAZAWA

Columbia's minimal discussion in its Response (p. 21-25) does not set forth any argument related to features not present in Stemple in view of Anazawa.

A. Stemple III Discloses Every Element Except Attachment of a Label to a Deazapurine Base of a Nucleotide Analogue

Columbia asserts that a skilled artisan would have had to make four “changes” to the “starting point” in Stemple III to arrive at the proposed claims. Paper 68 at 23-24; Ex. 2033 at ¶ 108. Three of the four “changes” asserted by Dr. Trainor with respect to Fig. 1B are taught by Stemple III. Ex. 1053 at ¶ 116. Dr. Stemple III expressly teaches that “[i]n another preferred embodiment, the labeling group is attached to the base of each nucleotide with a detachable linker rather than to the detachable 3' blocking group. The labeling group and the 3' blocking group can be removed enzymatically, chemically, or photolytically.” Ex. 1008, at 3:31-35. Dr. Trainor's opinion that Stemple III discloses only photocleavable nucleotides (*see* Ex. 2033, ¶¶ 110-112) is without basis. Ex. 1053 at ¶ 119.

B. Stemple III Expressly Teaches Use the Deazapurine Bases

Stemple III expressly teaches use of Anazawa's attachment methods where

the label and linker are “attached directly to the base of the nucleotide.” Ex. 1053 at ¶ 127. A person of ordinary skill in the art would look to the linkage chemistry and methods for attachment, including position on the nucleotide bases where the linker is attached. Ex. 1053 at ¶¶ 128-130. A person of skill in the art would apply the teachings of Anazawa to analogues of all four nucleotides. Importantly, the only purine analogues shown in Anazawa having a label attached to the base are 7-deazapurines with the linker attached to the 7 position. Ex. 1011 at Figs. 7, 16 & 18; Ex. 1053 at ¶ 129. Thus, the disclosure of Stemple III directs a person of skill in the art to use attachment methods, including attachment to the 7-position of a 7-deazapurine for the purine analogues, as shown in Fig. 7 of Anazawa. Ex. 1053 at ¶ 130. Anazawa further directs the reader to Prober I. Ex. 1053 at ¶ 45.

C. Reasonable basis for expectation of success

For the same reasons set forth with respect to Tsien above, a person of skill in the art would reasonably expect to be able to synthesize nucleotide analogues of Stemple III having a chemically cleavable 3' blocking group and chemically cleavable label on a deazapurine base, based on the “well established” procedures set forth in Hobbs and Prober I. *See* Ex. 1053 at ¶¶ 138-140. Similarly, because Stemple III discloses SBS and deazapurine nucleotides were widely known to be incorporated by polymerases, a person of skill in the art would reasonably expect such nucleotides to be incorporated by a polymerase. Ex. 1053 at ¶¶ 142-145.

V. SECONDARY CONSIDERATIONS DO NOT DEMONSTRATE NON-OBVIOUSNESS, BUT RATHER, OBVIOUSNESS

Columbia did not show a nexus between anything novel in its claims and any secondary considerations. “Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus.” *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Where he identifies claim limitations, Dr. Trainor points to three supposedly novel features: “[1] a cleavable chemical group capping the 3'-OH position of the sugar and [2] a label attached to the nucleotide base via a cleavable linker ... [that are] [3] incorporated into a primer extension strand by a polymerase.” Ex. 2033 at ¶ 198; *see also* ¶¶ 222, 225-227, 231 & 237; Ex. 2094 at 430:10-16. But, as Dr. Trainor admitted, each feature is disclosed in Tsien (and is not novel). Ex. 2094 105:15-106:13 & 245:16-246:11. Also, feature [3] is not an element of claim 34, and Dr. Trainor’s opinion does not reflect a nexus with the claims.

None of Columbia’s generalized evidence about supposed praise for Dr. Ju’s work (e.g. his 2006 paper, Ex. 2034), or the Seo article (Ex. 2043) is tied to any novel, claimed aspect. *See* Ex. 2033, ¶¶ 211-220 (praise) and 244-251 (Seo). In fact, Dr. Ju’s 2006 paper has multiple features not in the patent (Ex. 2094 at 80:14-83:6, 85:17-86:5, & 397:12-404:11), and the Seo article lacks several features of the amended claims. *Id.* at 69:14-70:12; 71:7-72:7. Columbia identifies two specific items in support of “skepticism”: a potential need for different 3' blocking

groups, and a potential need for more than one polymerase. (Ex. 2033 at ¶¶ 262 & 263-264.) In addition to being unsupported by the evidence (Ex. 2094 at 75:12-77:25), neither feature is claimed in the '869 Patent (Ex. 2094 at 73:3-75:11).

With regard to commercial success, infringement is a matter the Board “does not determine” in *inter partes* review proceedings. IPR2012-00001, Paper 26, at 11-12, 35 U.S.C. §311(b) (Scope). No court has determined that Illumina infringes the '869 patent; thus, Columbia's argument based on the commercial success of Illumina's accused SBS products (ex. 2033, ¶¶ 221-251) should be disregarded.

In any event, Columbia has not presented any evidence supporting its commercial success argument. Both Mr. Sims and Dr. Trainor admitted they had no knowledge of the SBS market (Ex. 2094 at 422:13-424:16; Ex. 2095 at 51:6-55-14), so their opinions about reasons for Illumina's commercial success are sheer speculation. Mr. Sims relies on Dr. Trainor for a nexus (Ex. 2095 at 7:7-22 & 68:3-69:19), and Dr. Trainor admits he does not know if Illumina would have been equally successful using a non-claimed technology. Ex. 2094 at 423:2-425:12. In fact, despite hearing Dr. Weinstock, a major sequencing user, state that cost-benefit was a key factor (Ex. 1034 at 328:1-330:22), neither Dr. Trainor nor Mr. Sims even knew how Illumina's sequencing cost compared to competitors. Ex. 2094 at 425:13-22; Ex. 2095 22:7-22; 30:13-35:2. Columbia has not established a nexus.

Finally, the “strong inference of copying” advanced by Columbia is based

on misleadingly incomplete evidence. In truth, Solexa independently (and nearly simultaneously) had the same claimed ideas. Ex. 1037, 7:17-22, 8:13-9:23, 10:1-23, and Figs. 1 & 2; Ex. 2094 20:16-33:24; 43:16-50:16, & 416:18-422:10; Ex. 1038, p. 132998; Ex. 1053 at ¶¶ 105-113. Columbia knew of Solexa's application, as it is part of the co-pending litigation with the '869 patent, but inexplicably did not provide it to Dr. Trainor. Ex. 2094 42:16-25; 386:2-16. Dr. Trainor was also unaware, despite Amersham's work being cited in the IPR of Solexa's patents, that Amersham also arrived at the same "invention" before Dr. Ju (filing prior to Dr. Ju, but in the UK). Ex. 1048, 3:14-16, 4:25-5:2, 5:30-31, 6:16-20, 7:12-30, 8:12-17, 9:9-32, 11:3-5, & Figs. 1 & 2; Ex. 2094 413:2-6; 430:17-443:14; Ex. 1053 at ¶ 109. The contemporaneous, independent invention by others is evidence of obviousness, not non-obviousness. *Geo M. Martin Co. v. Alliance Machine Systems Intern, LLC*, 618 F.3d 1294, 1305-1306 (Fed. Cir. 2010).

VI. CONCLUSION

For the foregoing reasons, Illumina respectfully submits that each of the challenged claims of the '869 Patent (both in their original form, and as proposed for amendment by Patent Owner) are invalid.

Dated: September 27, 2013

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of: Jingyue Ju et al.
Title: MASSIVE PARALLEL METHOD FOR DECODING
 DNA AND RNA
Patent No.: 7,790,869
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Alexandria, VA 22313-1450

CERTIFICATE OF SERVICE

Copies of the following were served electronically this 27th day of
September 2013 to Columbia at jwhite@cooperdunham.com,
ColumbiaIPR@fchs.com and dthibode@nsf.gov:

1. Petitioner Illumina's Reply to Patent Owner Columbia's Response to
Petition.

Dated this 27th day of September 2013.

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