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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.
Petitioner

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2012-00007
Patent 7,790,869 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. BACKGROUND

A. Introduction

Petitioner, Illumina, Inc. ("Illumina"), filed a petition on September 16, 2012 (Pet.), for *inter partes* review of claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 ("the '869 Patent") pursuant to 35 U.S.C. §§ 311-319. The owner of the '869 Patent is The Trustees of Columbia University in the City of New York ("Columbia"). On March 12, 2013, the Board instituted *inter partes* review as to claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 on four grounds of unpatentability (Paper 38, Decision on Petition ("Dec. Pet." 2)). In a subsequent Decision on Illumina's Request for Rehearing (Paper 40), the Board modified two of the grounds of unpatentability by substituting a different patent publication for one of the cited patent publications, where both publications had the same inventors and shared specifications and disclosures (Paper 54, Dec. Pet. Reh'g 18).

After institution of the *inter partes* review, Columbia filed a response under 37 C.F.R. § 42.120 to the decision instituting *inter partes* review (Paper 78, "PO Resp.). Columbia also filed a Motion to Amend Claims (Paper 79) and a Motion to Exclude Evidence (Paper 122). Illumina filed a reply to Columbia's response under 37 C.F.R. § 42.120 (Paper 83, Pet'r Reply and a Motion to Exclude Evidence (Paper 119 (redacted); Paper 100 (unredacted)). An oral hearing was held on December 17, 2013, with both parties in attendance. (Record of Oral Hearing, Paper 124.)

Among the evidence cited in this proceeding are declarations by George L. Trainor, Ph.D. (Ex. 2033, Trainor Decl.) on behalf of Columbia, and by George Weinstock, Ph.D. (Ex. 1021, Weinstock Decl.) on behalf of Illumina. Dr. Trainor has a Ph.D. in Organic Chemistry and experience in

DNA sequencing (Ex. 2033, Trainor Decl. ¶¶ 3 and 6-8), qualifying him to testify on the prior art issues discussed in his declaration. Dr. Weinstock has a Ph.D. in Microbiology and experience in DNA sequencing, including as a director of large-scale genome centers (Ex. 1021, Weinstock Decl. ¶¶ 4, 6, 8, and 9), qualifying him to testify on the prior art issues discussed in his declaration.

The Board has jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Illumina has shown by a preponderance of the evidence that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of the ’869 Patent are unpatentable.

B. The ’869 Patent

The ‘869 Patent issued September 7, 2010. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the ’869 Patent involves sequencing DNA by incorporating a base-labeled nucleotide analogue into primer DNA strand, and then determining the identity of the incorporated analogue by detecting a label attached to the base of the nucleotide. A polymerase is used to incorporate the nucleotide analogue into the strand of DNA (’869 Patent, col. 3, ll. 1-3). The method is generally referred to as “sequencing DNA by synthesis,” or “SBS,” because the sequence of the DNA is determined by identifying the successive additions of labeled nucleotides to a strand of DNA as it is synthesized using a complimentary DNA strand as a template (*id.* at col. 2, ll. 8-12).

All the claims at issue in this *inter partes* review are drawn to a nucleotide analogue, which comprises: 1) a base that is attached to a

detectable label through a cleavable linker; and 2) a cleavable chemical moiety capping the 3'-OH group. Nucleotides, which are the building blocks of DNA, comprise a sugar (ribose or deoxyribose), phosphates attached to the 5'-position of the sugar, and a nitrogen base on the 1'-position of the sugar. During DNA synthesis, the 5'-position in the sugar of a new incoming nucleotide is linked by DNA polymerase to the 3'-OH group in the sugar of a preexisting nucleotide in the strand under synthesis. In order to identify the newly incorporated nucleotide, one approach described in the prior art is to attach a detectable label to the nucleotide at its 3'-OH group ('869 Patent, col. 2, ll. 34-38). For reference, the 3'-OH corresponds to 3'-position of the deoxyribose sugar of the nucleotide and serves as the site where a new nucleotide is added during DNA synthesis.

The approach described in the '869 Patent is to make nucleotide analogues by linking a unique label such as fluorescent dye through a cleavable linker to the nucleotide base, or to an analogue of the nucleotide base, and to use a small removable chemical moiety to cap the 3'-OH group of the deoxyribose to make it reversibly nonreactive ('869 Patent, col. 2, ll. 58-66). The reason the 3'-OH group is made reversibly nonreactive is to allow the sequencing reaction to be terminated after each nucleotide is added in order to determine its identity (*id.* at col. 2, l. 67 to col. 3, l. 3). According to the '869 Patent, the prior art teaches attaching the label to the 3'-OH group. The '869 Patent, in contrast, puts the label on the nucleotide base and the removable chemical moiety on the 3'-OH group. These latter features are at the center of the patentability challenges.

In summarizing the state of the art in Columbia's Patent Owner Response, Columbia states that, "[d]uring the 1990s, despite some interest in

base-labeled nucleotide analogues, efforts focused on including a label on the 3'OH group on the sugar in a nucleotide analogue and on the design and synthesis of new nucleotide analogues that could be incorporated by a polymerase into a primer extension strand." (Paper 78, PO Resp. 9.) Columbia cites paragraphs 30-35 of Dr. Trainor's declaration as evidence that "[r]esults were mixed and it was recognized that new nucleotide analogues were needed [for use in] BASS [sequencing by synthesis; also known as SBS] sequencing." (*Id*.)

As discussed in more detail below, Columbia's characterization of the prior art as having "some interest in base-labeled nucleotide analogues" understates the interest level shown in the prior art. Tsien[1] and Stemple III,[2] cited in this *inter partes* review, and Dower,[3] which is cited in related proceedings, describe SBS methods which use base-label nucleotides and nucleotides containing a removable chemical moiety at the 3'-OH position (Ex. 2033, Trainor Decl. ¶¶ 24 and 26-29). Columbia acknowledges that base-labeled nucleotides were described in the prior art (*id.* at 28). We understand it to be Columbia's position that because there is no single example in the cited prior art of a nucleotide with the base-label and removable 3'OH blocking group being used in a DNA sequencing reaction, the disclosure of such a nucleotide is somehow diminished and amounts only to "some interest." Columbia, however, has not identified disclosure in the prior art where a nucleotide analogue with a label on the base and removable

[1] Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002 ("Tsien").
[2] Derek Stemple et al., U.S. Patent 7,270,951 B1 (September 18, 2007), Exhibit 1008 ("Stemple III").
[3] William Dower et al., U.S. Pat. No. 5,547,839 (August 20, 1996), Exhibit 1005 ("Dower").

3'-OH chemical moiety was so disparaged that a person of ordinary skill in the art would have been dissuaded from using it in SBS methods. To the contrary, the disclosure in three publications of a label on the nucleotide base and of a removable 3'-OH group group (e.g., Tsien, Dower, and Stemple III) shows a recognition within the prior art that such nucleotides were useful and effective in SBS methods.

C. Related Proceedings

The '869 Patent is the subject of *The Trustees of Columbia University in the City of New York v. Illumina, Inc*., 1:12-cv-00376-UNA, currently pending in the United States District Court for the District of Delaware (Petition 3-4). According to Illumina, Columbia alleges in that proceeding that Illumina has infringed, and continues to infringe, the '869 Patent (*id*.).

There are two pending *inter partes* trials which are related to this trial:

A petition for *inter partes* review was filed on September 16, 2012, for U.S. Patent No. 7,713,698 B2 ("the '698 patent").[4] The '869 Patent is assigned to Columbia, has claims directed to related subject matter of the '698 patent, and has the same lineage as the '698 Patent. We instituted *inter partes* review on March 12, 2013.

A petition for *inter partes* review was filed on October 3, 2012 for U.S. Patent No. 8,088,575 B2 ("the '575 patent"),[5] which is based on a continuation application of the '869 Patent. The '575 patent is assigned to Columbia and has claims directed to related subject matter of the '869 patent. We instituted *inter partes* review on March 12, 2013.

[4] IPR2012-00006.
[5] IPR2013-00011.

D. The Alleged Grounds of Unpatentability

We instituted *inter partes* review on the following four grounds of unpatentability:

I. Claims 12, 13, 17, 20-26, 28, 29, 31, and 33 under 35 U.S.C. § 102(b) as anticipated by Tsien.[6]

II. Claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I.[7]

III. Claims 12, 13, 17, 20-23, 25, 26, 28, 29, and 31 under 35 U.S.C. § 102(a) as anticipated by Stemple III.[8]

IV. Claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Stemple III and Anazawa.[9]

E. Claims

The '869 Patent was granted with 33 claims. Illumina challenges the patentability of independent claim 12, and dependent claims 13, 15-17, 20-26, 28, 29, 31, and 33. Claims 12 and 15 are reproduced below (bracketed numbering 1-4 added to emphasize certain limitations in the claim):

> 12. A nucleotide having [1] a base that is attached to a detectable label through a cleavable linker, wherein the

[6] Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002 ("Tsien").
[7] James Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336 (1987), Exhibit 1003 ("Prober I").
[8] Derek Stemple et al., U.S. Patent No. 7,270,951 B1 (September 18, 2007), Exhibit 1008 ("Stemple III").
[9] Takeshi Anazawa et al, WO 98/33939 (August 6, 1998), Exhibit 1010, citations are to an English translation, Exhibit 1011 ("Anazawa").

> nucleotide has [2] a deoxyribose comprising a cleavable chemical group capping the 3' OH group, wherein [3] the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and wherein [4] the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.
>
> 15. The nucleotide of claim 12, wherein the base is a deazapurine.

PATENTABILITY CHALLENGES

II. TSIEN

Illumina contends in their Petition for *Inter Partes* Review that Tsien describes all the limitations of the nucleotide of claim 12 and the limitations of dependent claims 13, 17, 20-26, 28, 29, 31, and 33 (Petition 21-27).

Claim 12 is directed to a nucleotide comprising the following features: (1) a base that is attached to a detectable label; (2) through a cleavable linker; and (3) a deoxyribose comprising a cleavable chemical group capping the 3' OH group. The means for cleaving the linker and group are "selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light."

Tsien is a published PCT international patent application which discloses a sequencing by synthesis method in which 3' OH blocked and fluorescent labeled nucleotides are sequentially added to a primer during sequencing of a template DNA strand (Tsien, p. 6, l. 34 to p. 7, l. 34; p. 10, l. 1-15). Tsien teaches using nucleotides with 3'-OH capping groups and methods for removing the capping group (*id*. at p. 21, ll. 9-33; p. 23, l. 28 to

p. 25, l. 25) and thus describes "a cleavable chemical group capping the 3' OH group" as recited in claim 12.

In order to detect the incorporated nucleotide, Tsien describes using a detectable label (*id.* at p. 26, ll. 1-26). In the Petition, Illumina cited explicit disclosure in Tsien of incorporating a detectable fluorescent label into a base:

> The C-8 position of the purine [base] structure presents an ideal position for attachment of a label. Sarfati et al. (1987) describes a derivatization of deoxyadenosine at C-8 of the purine to prepare, ultimately, an 8-substituted biotin aldylamino dATP. The Sarfati et al. (1987) approach can be used to prepare the appropriate fluorescent, rather than biotinylated, analogues. A number of approaches are possible to produce fluorescent derivatives of thymidine and deoxycytidine. One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags.

(Tsien, p. 29, ll. 3-14 (emphasis added).)

> While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of alternatives - particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position such as the base. This dNTP can be incorporated and the fluorescence measured and removed according to the methods described below.

(*Id.* at p. 27, l. 33-p. 28, l. 4 (emphasis added).)

The "methods described below" teach attaching the label through a cleavable linker:

> One method involves the use of a fluorescent tag attached to the base moiety. The tag may be chemically cleaved (either separately from or simultaneously with the deblocking step) and measured either in the reaction zone before deblocking or in the reaction [eluent] after cleavage.

(*Id.* at p. 28, ll. 5-10 (emphasis added).)

> In another type of remote labeling the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The tether can be cleavable if desired to release the fluorophore or other label on demand.

(*Id.* at p. 28, ll. 19-23 (emphasis added).)

There is no express statement in Tsien to use the cleavable linker to attach the fluorescent label to the base. However, in the Decision to Institute *Inter Partes* Review, we found that such configuration would have been envisaged clearly by one of ordinary skill in the art upon reading the Tsien disclosure (Dec. Pet. 10-11). We found that Tsien describes linkers as useful to attach a label to a nucleotide (Tsien, p. 28, ll. 19-23). The base of the nucleotide is also expressly taught as a position where labels can be attached (Tsien, p. 29, ll. 3-14; p. 27, l. 33-p. 28, l. 4). Consequently, we determined that the skilled worker would have been guided to use the cleavable linker to attach the fluorescent label to the base of the nucleotide (Dec. Pet. 10-11). In reaching this determination, we found that although there was no specific example of a base that is attached to a detectable label through a cleavable linker, specific examples are not necessary to establish anticipation when there is a small genus disclosed and each member can be at once envisaged, the factual scenario we found to be the case here (*id.* at 7-8). *In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001).

With respect to the claimed cleaving means, Tsien discloses use of "3'-O-acyl blocking groups and other blocking groups [which are] hydrolysable under basic conditions." (Tsien, p. 22, l. 34 to p. 23, l. 2). Tsien further discloses removal of 3'-OH blocking groups using other

chemistries, light, and enzymes (*id.*, p. 23, l. 27 to p. 25, l. 34), making any one of the three choices anticipatory.

Columbia challenged Illumina's contentions in their preliminary response, but we found their arguments to be unpersuasive and instituted the trial on Tsien as an anticipatory publication (Dec. Pet. 11). In the response under § 42.120, Columbia did not address further the anticipation rejection based on Tsien, but rather indicated that challenged claims had been cancelled in a motion to amend the claims (Paper 78, PO Resp. 13). The motion is a contingent motion and has not been granted. Illumina's patentability challenge of claim 12 based on Tsien as an anticipatory publication is supported by a preponderance of the evidence as explained above. We find it fully persuasive for the reasons stated here and in the Decision to Institute *Inter Partes* Review.

With respect to claims 13, 17, 20-26, 28, 29, 31, and 33, Illumina identified specific disclosure in Tsien where each limitation is found (Petition 22-26). We find Illumina's assertions to be supported by a preponderance of the evidence.

III. STEMPLE

We instituted i*nter partes* review of claims 12, 13, 17, 20-23, 25, 26, 28, 29, and 31 on the grounds that these claims would have been anticipated under 35 U.S.C. § 102(a) by Stemple III (Dec. Pet. 17-19; Dec. Reh'g 12-13).

Stemple III is a U.S. patent that describes DNA sequencing by synthesis. As indicated in Illumina's patentability challenge of claim 12, Stemple III describes chain terminating nucleotides that include a blocking

group at the 3'-OH of the ribose (limitation (2) of claim 12) and a fluorescent label attached to the nucleotide base (limitation (1) of claim 12) (Petition 48). To illustrate this teaching, Illumina relied upon Figure 1B of Stemple III. Figure 1B, as annotated by Illumina with arrows and boxes, is reproduced below.

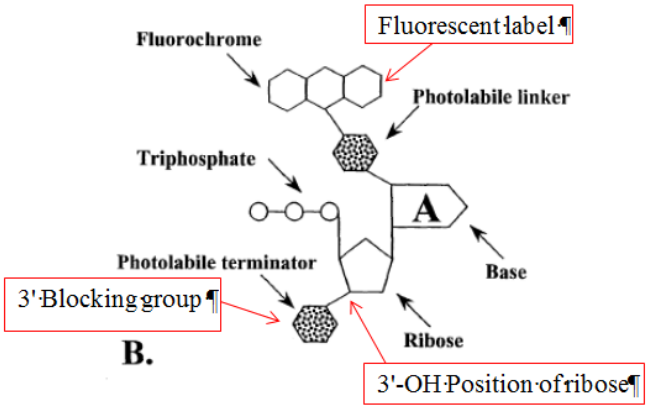


Figure 1B shows the following elements of claim 12.

A base ("Base") attached to a detectable label ("Fluorochrome") through a cleavable linker ("Photolabile linker"); and a deoxyribose ("Ribose") comprising a cleavable chemical group capping the 3'-OH group ("Photolabile terminator"). The claimed "cleavable linker" and "cleavable chemical group" correspond to Stemple III's Photolabile linker and Photolabile terminator, respectively, and are each described as being removable by illumination (Stemple III, col. 22, ll. 53-57) and, thus, are cleavable by light as recited in claim 12. Stemple III also discloses that "[t]he labeling group and the 3' blocking group can be removed enzymatically, chemically, or photolytically" (Stemple III, col. 3, ll. 34-36; Petition 49) as in claim 12, making any one of three choices anticipatory. Thus, Illumina's contention in the Petition that claim 12 is anticipated by Stemple III is supported by a preponderance of the evidence.

Columbia did not challenge Illumina's contentions in their preliminary response (Paper 27). In their Patent Owner Response (Paper 78), Columbia did not address the anticipation rejection of claim 12 based on Stemple III, but rather indicated that challenged claim had been cancelled by a motion to amend the claims (Paper 78, PO Resp., p. 13). The motion is a contingent motion and has not been granted. Illumina's patentability challenge of claim 12 based on Stemple III is supported by a preponderance of the evidence as explained above. We find it persuasive for the reasons stated here and in the Decision to Institute *Inter Partes* Review.

With respect to claims 13, 17, 20-26, 28, 29, 31, and 33, Illumina identified specific disclosure in Stemple III where each limitation is found (Petition 22-26). We find Illumina's assertions to be supported by a preponderance of the evidence.

IV. STEMPLE AND ANAZAWA

We instituted *inter partes* review of claims 15 and 16 on the grounds that these claims would have been obvious under 35 U.S.C. § 103 in view of Stemple III and Anazawa (Dec. Pet. 30; Dec. Reh'g 18).

Claim 15 depends on claim 12, and recites that the base is a deazapurine, further limiting the claim. In the Petition, Illumina cited Anazawa, an international PCT application published in Japanese, for its teaching of a deazapurine base coupled to a detectable label.

Figure 7 of Anazawa shows a nucleotide 7-deazaguanine (natural nitrogen at position 7 replaced with a carbon) labeled with the fluorescent marker Texas Red at the 7-position (Anazawa, Fig. 7 and p. 6, ll. 5-7). Anazawa teaches that the labeled nucleotide "can be incorporated by

polymerase-based complementary-chain elongation reactions, as has been confirmed by various experiments" (*id.* at p. 6, ll. 10-12), providing an expectation that it could be used successfully in sequencing by synthesis methods. The marker or label can be dissociated by photo-irradiation (*id.* at p. 5), and is, therefore, photolabile.

Stemple III provides a reason to have modified its nucleotides with Anazawa's teachings[10] (Petition 55). Stemple III teaches:

> In an alternative configuration a photolabile group is attached to the 3'-OH using succinimide or other chemistry and a fluorochrome-photolabile linker conjugate is attached directly to the base of the nucleotide as described by Anasawa [sic, Anazawa] et al., WO 98/33939. The 3' attached photolabile group will serve as a reversible chain terminator . . . and the base-attached fluorochrome-photo labile linker will serve as a removable label. In this configuration with each cycle both photolabile groups will be removed by photolysis before further incorporation is allowed. Such a configuration may be preferred if it is found that steric hindrance of large fluorochrome groups attached to the 3'-OH of the nucleotide prevent the nucleotide from entering the polymerase.

(Stemple III, col. 22, ll. 52-67).

Based on the suggestion of Stemple III to use the photolabile linkers described in Anazawa, the skilled worker would have had reason to have turned to the Anazawa publication and to have replaced the natural nitrogen base of Stemple III's nucleotide with a deazapurine as in Anazawa, where the latter base comprises a photolabile linker. Even absent this disclosure, it would have been obvious to one of ordinary skill in the art to have used Anazawa's deazapurine labeled nucleotide for its known use in DNA

[10] In addition to the deazaguanine, Anazawa teaches other base types and base labeled nucleotides (Anazawa, p. 6, ll. 7-9; 12-16 and 30-34).

sequencing (Anazawa, pp. 5-6). It would have been obvious to one of ordinary skill in the art to have used a material for its known and expected function. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (". . . a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.")

Relying on the Declaration of Dr. Trainor, Columbia argues that Stemple III describes nucleotides with detectable labels at the 3'-OH capping group and an alternate structure where the label is attached to the base (Ex. 2033, Trainor Decl. ¶ 89). Dr. Trainor testified that the starting point would have been the nucleotide analogue with the label on the 3'-OH group because this is the only synthesis which is exemplified (*id.* ¶¶ 90, 91, and 95). Dr. Trainor also testified about reasons why one of ordinary skill in the art would have preferred to use nucleotides with the label attached to the 3'-OH (*id.* ¶¶ 92-93). Dr. Trainor states there are deficiencies in the descriptions of the labeling chemistries in Stemple III and Anazawa, making it even less likely that label on the base would have been a starting point (*id.* ¶ 96, n.7).

Dr. Trainor's testimony is not persuasive. Figure 1B of Stemple III shows a nucleotide with a removable blocking group on the 3'-OH group, which has all the features of claim 15 except for the deazapurine base. Although there may be other preferred nucleotides, the presence of other examples, which differ in structure from Figure 1B, would not have led the skilled worker away from the nucleotide in Figure 1B because it is expressly described by Stemple III as a choice to use in Stemple's sequencing method (Stemple III, col. 3, ll. 56-58). With respect to replacing the naturally occurring base in Stemple III with a deazapurine base comprising the

photolabile linker, there are two publications cited for base labeling chemistry – Anazawa in Stemple III at columns 21 and 22; and Prober I in Anazawa at page 5, line 40 – indicating that one of ordinary skill in the art would have known how to accomplish the desired result, even if certain deficiencies were present in one of the publications. Stemple III's statement that Anazawa's teaching about photolabile linkers could be applied to Stemple III's nucleotides strongly suggests that it was within the purview of the ordinary skilled worker to have made such chemical modifications. Dr. Trainor's testimony about how to design new chemical procedures to convert Stemple III's 3'-OH labeled nucleotides into the nucleotide of claim 15 (Ex. 2033, Trainor Decl. ¶ 107) is unavailing because Figure 1B of Stemple III would not have required such changes.

Dr. Trainor also testified that if the starting point were the nucleotide of Figure 1B, then four differences from the claimed invention at issue would need to be addressed:[11]

> 1. replace the photocleavable linker (described in both Stemple Figure 1B and in Anazawa) on the base with a linker cleavable by a means other than light;
> 2. include at 3'-OH position of the nucleotide analogue a capping group that is cleavable by means other than light;
> 3. change the purine base to a deazapurine base; and
> 4. retain the property of being incorporated onto a primer extension strand.

[11] Differences (1) and (2) do not appear in either claim 1 or claim 15, but rather appear in claim 34 which was proposed in Columbia's contingent Motion to Amend Claims in which claim 15 was narrowed by canceling light as a cleaning means from the recited Markush group (Paper 79). This motion has not been entered. However, since the other means involving physical and chemical are recited in the claim, we shall address Dr. Trainor's arguments.

(Ex. 2033, Trainor Decl. ¶ 108).

With regard to changes (1) and (2), Stemple III discloses that "[t]he labeling group and the 3' blocking group can be removed enzymatically, chemically, or photolytically" (Stemple III, col. 3, ll. 34-36; Petition 49). Thus, reason exists to have used any of the three cleaving techniques to remove the label and capping group from the nucleotide analogue.

Columbia contends that a person of ordinary skill

> would not know how to arrive at a nucleotide analogue which includes a cleavable chemical group capping the 3'-OH group, wherein the cleavable linker is cleaved by a means other than light or a base that is a deazapurine and is attached to a detectable label through a cleavable linker, where the cleavable linker is cleaved by means other than light, from the combined descriptions of Stemple III and Anazawa.

(Ex. 2033, Trainor Decl. ¶ 136). Dr. Trainor cites Stemple III's lack of any working example other than light as the cleaving agent (*id.* ¶ 137).

This argument is not persuasive. Illumina met its burden in establishing that the claimed limitation was met by showing express disclosure in Stemple of cleaving the claimed linker by chemical means (Stemple III, col. 3, ll. 34-36; Petition 49). Columbia appears to be arguing that Stemple III's disclosure is not enabling, but this argument is not supported by convincing evidence. As discussed above, Columbia argues that Stemple III only shows photocleavable groups (Ex. 2033, Trainor Decl. ¶¶ 136-137), but Columbia did not provide evidence that utilizing chemical means requires anything more than conventional techniques within the purview of the ordinary skilled worker.

Columbia also argues that there would not have been a reasonable expectation of success that the claimed nucleotide could be incorporated by

polymerase (Ex. 2033, Trainor Decl. ¶¶ 87, 90, 92, and 135). Dr. Trainor stated that were "no reports of successful incorporation by a polymerase of a nucleotide analogue that had been modified both by placing a removable capping group at the 3'-OH position of the sugar and by placing any label, let alone a label through a chemically linker, on the base." (*Id.* ¶ 92). Dr. Trainor cited published reports that he testified establish unpredictability about the polymerase activity on nucleotide analogues with the claimed features (*id.* at ¶ 135).

However, Stemple III gives an example of a modified nucleotide comprising a 3'-OH cap and base label (Fig. 1B) that can be used its sequencing, indicating a reasonable belief that such a nucleotide is a viable substrate for DNA polymerase. There is no other purpose for which it is disclosed. Moreover, Stemple stated:

> The 3' attached photolabile group will serve as a reversible chain terminator . . . and the base-attached fluorochrome-photo-labile linker will serve as a removable label. In this configuration with each cycle both photolabile groups will be removed by photolysis before further incorporation is allowed. Such a configuration may be preferred if it is found that steric hindrance of large fluorochrome groups attached to the 3'-OH of the nucleotide prevent the nucleotide from entering the polymerase.

(Stemple III, col. 22, ll. 57-67; underlining added).

It is evident from the passage that Stemple III had considered the question of whether a nucleotide with a cap on the 3' end and label on the base would serve as a polymerase substrate and had found it "preferred" in some cases over a modified nucleotide with the label on the 3' end. Stemple III expressed no reservation that a nucleotide with the claimed features would work.

The claimed nucleotide also incorporates a deazapurine base into the nucleotide, another source of unpredictability alleged by Columbia. However, Anazawa teaches that nucleotides with a label attached to the base are effective polymerase substrates, including a nucleotide with a deazapurine base (Fig. 7):

> As seen in the substance diagrammed in Fig. 7, substances labeled at the position of the base of the nucleotide can be incorporated by polymerase-based complementary-chain elongation reactions, as has been confirmed by various experiments. It has been confirmed, for example, that dideoxy nucleotide ddNTPs, the positions of the bases whereof are labeled by various fluorophores, that is, that the terminators of the complementary chain synthesis, are incorporated by complementary chain synthesis (Nucleic Acids Respectively. 20, 2471 – 2483 (1992)).

(Anazawa, p 6, ll. 10-16).

In sum, based on the evidence before us, we are persuaded that Illumina established by a preponderance of the evidence that claim 15 is unpatentable in view of Stemple III.

V. TSIEN AND PROBER

We instituted *inter partes* review of claims 15 and 16 on the grounds that the Columbia claims would have been obvious under 35 U.S.C. § 103 in view of Tsien and Prober I. We first turn to the description in Tsien and Prober I of key elements of the claims, and then to the reason for combining Tsien and Prober I to have arrived at the claimed invention.

Claim 15 is directed to a nucleotide analogue comprising the following features: (1) a base that is attached to a detectable label; (2) through a cleavable linker; (3) a deoxyribose comprising a cleavable

chemical group capping the 3'-OH group; and 4) a deaza-substituted base. [12]

A. Tsien

Tsien describes a DNA sequencing by synthesis method (Tsien, pp. 6-7). The method uses nucleotides labeled with reporter groups to identify when they are incorporated into the newly synthesized strand (*id*. at p. 7, ll. 3-14).

The following evidence from Tsien supports Illumina's contention that structures or featuers 1) and 2) of claim 15 set forth above are described in Tsien (*see also* Petition, 27-29 (In the Petition for *Inter Partes* Review of the '869 Patent, Illumina cited disclosure from Tsien to meet the claim limitations) (Petition 27-29).

1) Unique label attached to a base

Tsien has the following teachings:

> When they [deoxynucleotide triphosphates or dNTPs] are each tagged or labeled with different reporter groups, such as different fluorescent groups, they are represented as dA'TP, dC''TP, dG'''TP and dT''''TP. As will be explained in more detail below, the fact that the indication of labeling appears associated with the "nucleoside base part" of these abbreviations does not imply that this is the sole place where labeling can occur. Labeling could occur as well in other parts of the molecule.

(Tsien, p. 10, ll. 7-15 and Fig. 2.)

> While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of alternatives - particularly the formation of

[12] The claim does not specify that deaza-substitution is in the nucleotide base, but that would be understood by one of ordinary skill in the art upon reading the '869 Patent (*see, e.g.*, '869 Patent, col. 7, ll. 44-47 and 58-63).

> a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position such as the base.

(*Id.* at p. 27, l. 33 to p. 28, l. 2.)

> One method involves the use of a fluorescent tag attached to the base moiety . . . This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence.

(*Id.* at p. 28, ll. 5-12.)

2) Cleavable linker

The following passage in Tsien is cited for its description of "a cleavable linker":

> In another type of remote labeling the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The tether can be cleavable if desired to release the fluorophore or other label on demand. There are several cleavable tethers that permit removing the fluorescent group before the next successive nucleotide is added--for example, silyl ethers are suitable tethers which are cleavable by base or fluoride, allyl ethers are cleavable by Hg(II), or 2,4-dinitrophenylsulfenyls are cleavable by thiols or thiosulfate.

(Tsien, p. 28, ll. 19-29).

Tsien, in this passage, thus describes a "space or tether" – the "linker" in claim 15 – which can attach the label to the nucleotide analogue ("dNTP" in Tsien). The tether is expressly taught by Tsien to "be cleavable if desired to release the fluorophore or other label on demand" and therefore is a "cleavable linker" as recited in the claim. This passage does not describe the label attached via a linker to the base of the nucleotide as required by claim 15. However, Tsien in the preceding passage describes "a fluorescent tag

attached to the base moiety" (Tsien, p. 28, ll. 5-6) and, thus, reasonably suggests the tether to attach the fluorescent tag to the base.

3) Removable 3'-OH capping group

During DNA synthesis, nucleotides are sequentially added to the 3'-OH group of the nucleotide sugar. The 3'-OH group contains a removable blocking group in Tsien's sequencing method so the labeled nucleotides can be added one at a time. After each addition, the label is detected and the 3'-OH group is deblocked and new nucleotide is added (Tsien, p. 13). Specifically, Tsien teaches:

> A deblocking solution is added via line 28 [Fig. 2] to remove the 3' hydroxyl labeled blocking group. This then generates an active 3' hydroxyl position on the first nucleotide present in the complementary chain and makes it available for coupling to the 5' position of the second nucleotide.

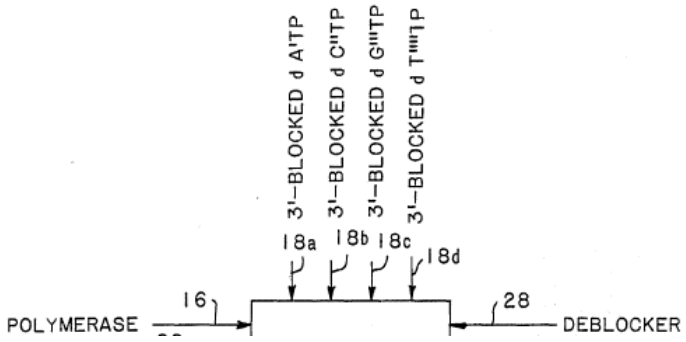
(Tsien, p. 13, ll. 17-22).

> The coupling reaction generally employs 3' hydroxyl blocked dNTPs to prevent inadvertent extra additions [of nucleotides to the 3'-OH end].

(*Id.* at p. 20, ll. 25-27 (emphasis added).

Structures 1) and 3) combined

Figure 2 of Tsien, set forth below, shows nucleotides used in a sequencing reaction, each with a unique label and a blocked 3'-OH group (18a, 18b, 18c, and 18d) (Tsien, p. 12, ll. 14-18; p. 9, l. 35 to p. 10, 15):



A portion of Tsien's Figure 2, reproduced above, shows nucleotides each with a unique label attached to the nucleotide and a blocked 3'-OH group. The figure indicates that the labeling is on the base, but "these abbreviations [do] not imply that this is the sole place where labeling can occur." (Tsien, p. 10, ll. 7-15 and Fig. 2).

4) A deaza-substituted base

Tsien does not disclose a deaza-substituted base, but references Prober I which does. Specifically, Tsien teaches:

> One method involves the use of a fluorescent tag attached to the base moiety. . . . This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. [refers to Sarfati et al. (1987)] . . . Prober et al. (1987) [Prober I] show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™.

(Tsien, p. 28, ll. 5-18).

Prober I discloses "[t]he set of four fluorescence- tagged chain-terminating reagents we have designed and synthesized is shown in Fig. 2A. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base . . . The linker is attached . . . to the 7 position in the 7-deazapurines." (Prober I, p. 337.) In sum, Prober I describes a

nucleotide comprising a deazapurine base to which a label has been attached.

C. Reason to combine

In making an obviousness determination, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. Illumina contends that Tsien's reference to Prober I's fluorescent nucleotides would have provided one of ordinary skill in the art with a reason to have used Prober I's labeling technique in Tsien's method (Pet. 28).

Even absent disclosure of Prober I in Tsien, Dr. Weinstock testified that it would have been obvious to have used Prober I's teachings in Tsien.

> Prober I specifically teaches that nucleotide analogues incorporating 7-deazapurines may be used in sequencing reactions. Thus, the combination of Tsien and Prober I is the use of the known techniques of Prober I to improve similar Tsien systems and methods in the same way that the known features improve the methods and reagents of Prober I. Furthermore, use of the features taught by Prober I for their intended purpose, as disclosed by Prober I, would enhance the capability of the Tsien systems and methods in the same way they enhance the capability of the Prober I methods and reagents.

(Ex. 1021, Weinstock Decl. ¶ 66.)

D. Discussion

Columbia did not separately address claim 15 in their Patent Owner Response. However, in the Motion to Amend, new claim 34 was proposed that incorporates all the limitations of claim 15 into claim 1 (Paper 79, pp. 4-

5). In addressing claim 34, Columbia provided arguments and reasons as to why specific limitations, the same as those in claim 15, would not have been obvious to one of ordinary skill in the art in view of Tsien and Prober I. We address these arguments below.

In arguing the patentability of claim 34, Columbia contends that Tsien's base label nucleotide would not have been the "starting point" to make novel nucleotide analogues because of a preference for nucleotides with the label attached to the 3'-OH group (Paper 78, PO Reply, p. 14). We do not find this argument persuasive because there is an explicit description of base-labeled nucleotides in Tsien, and no specific disclosure has been identified in Tsien by Columbia that disparages these alternative nucleotide analogues or that would have led one of ordinary skill in the art to conclude that they were unsuitable for the SBS purpose described by Tsien.

Columbia also contends that the patentability challenge based on Tsien and Prober I is insufficient because "no rationale for the obviousness of the novel nucleotide analogue is provided." (Paper 78, PO Reply, p. 14).

The Columbia argument is not persuasive. Illumina in the Petition cited Tsien's reference to Prober I for teaching labeled nucleotides and expressly stated that "Tsien thus provides an express teaching, suggestion, and motivation to combine Tsien with the disclosures of Prober I with respect to 'base moiety derivatized' nucleotide analogues." (Pet. 28). Furthermore, Illumina stated that Tsien teaches that "the synthesis scheme for ddNTPs used in Prober I should be used in Tsien to produce 'fluorescent dNTPs.' Tsien, p. 29, ll. 10-19." (*Id.*) Columbia's argument is therefore unsubstantiated. A rationale to combine the publications was also described above based on testimony by Dr. Weinstock.

Columbia argues that if one of skill in the art would have used the base-labeled nucleotide analogues of Tsien as a "starting point," several differences between those nucleotide analogues and the claimed nucleotide analogues would "have had to be addressed." (Paper 78, PO Reply, p. 18). Relying of Dr. Trainor's testimony, Columbia asserts that one of skill in the art would have had to make the following changes to have made the claimed invention:

> 1. remove the labels from the C-8 positions of the two purines despite the C-8 position being described by Tsien as the "ideal" position for the attachment of the labels to purines;
> 2. change the purine bases of the purines to deazapurines;
> 3. replace the uncleavable, acetylenic linker (described in Prober I) on the pyrimidines with a cleavable linker;
> 4. replace the uncleavable alkylamino linker on the purines with a cleavable linker);
> 5. attach the label to the base with a linker cleavable by a means other than light;
> 6. include removable 3'-OH capping groups on the uncapped 3'-OH groups of the nucleotide analogues;
> 7. use a capping group at 3'-OH position of the nucleotide analogue that is cleavable by means other than light; and
> 8. retain the property of being incorporated onto a primer extension strand.

(Ex. 2033, Trainor Decl. ¶ 67.)

We address each of these differences, below.

Deaza-substituted nucleotide (Nos. 1 and 2 in Ex. 2033, Trainor Decl. ¶ 67).

Citing the Trainor Declaration, Columbia argues "there was no reason to use a deaza-purine labeled at the 7-position given Tsien's specific guidance to the contrary that a label on the 8-position of a non-deaza purine was 'ideal.' (Ex. 2033, Trainor Decl., ¶§70-73 [ ])." (Paper 78, PO Reply, p.

19). Columbia further argues that there would have been no reason "to change the uncleavable linkers on the 8-position of the purine labeled nucleotide analogues of Tsien to a cleavable linker, particularly since the linker in Prober I is uncleavable (Exhibit 2033, Trainor Decl., ¶73.)" (*Id.*)

Dr. Trainor cites Tsien's statement that the "C-8 position of the purine structure presents an ideal position for attachment of a label." (Tsien, p. 29, ll. 3-4). Dr. Trainor acknowledges that Tsien cites Prober I in the same paragraph in which purine labeling is described and that Prober I describes producing labeled deazapurines (Ex. 2033, Trainor Decl. ¶ 72). However, Dr. Trainor states that Tsien ignored Prober's teaching because Tsien "refers to Prober I for teaching an approach to producing fluorescently labeled derivatives of pyrimidines." (*Id.*) The mentioned teaching in Prober I is reproduced below:

> A number of approaches are possible to produce fluorescent derivatives of thymidine and deoxycytidine. One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags.

(Tsien, p. 29, ll. 10-14).

Columbia's argument is not persuasive or consistent with the full labeling disclosure in Tsien. Beginning at page 26, Tsien describes reporter groups on dNTPs and how they can be incorporated into a dNTP. Tsien states that one "approach employs fluorescent labels. These can be attached to the dNTP's via the 3'OH blocking groups or attached in other positions." (Tsien, p. 26, ll. 17-19). After describing approaches to label the 3'-OH blocking group, Tsien goes on to state that "there are a number of alternatives - particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position

such as the base. This dNTP can be incorporated and the fluorescence measured and removed according to the methods described below." (*Id.* at 27, l. 33 to p. 28, l. 4). In the following paragraph, Tsien describes attaching a fluorescent label to the base, and states:

> This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. Sarfati et al, (1987) demonstrates the incorporation of biotinylated dATP in nick translations, and other biotinylated derivatives such as 5-biotin (19)-dUTP (Calbiochem) are incorporated by polymerases and reverse transcriptase. Prober et al. (1987) [Prober I] show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™.

(*Id.* at p. 28, ll. 10-18).

This passage, expressly mentions Prober I's method in its discussion of base labeling, reasonably suggesting that Tsien considered it suitable for Tsien's sequencing method. While Tsien discloses that the C-8 position of the nucleotide base is "ideal" for labeling a purine, that disclosure would not have dissuaded one of ordinary in the art from labeling at other positions in the base. "[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). For a reference to "teach away" from using a particular approach, it must be shown that "the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Gurley*, 27 F.3d at 553.

Dr. Trainor, himself, admitted that fluorescently labeled deazapurines had been used in the prior art (Ex. 2033, Trainor Decl. ¶¶ 20-21).

In this case, as mentioned above, there is generic disclosure in Tsien of labeling the base moiety, including a specific reference to Prober I, the latter describing C-7 deaza-labeled purine bases. Thus, even if labeling at the C-8 position is superior, Prober I's method is still reasonably suggested by Tsien, which characterizes Prober I as showing "enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™" (Tsien, p. 2, ll. 6-9; p. 19, ll. 9-18). Thus, those of skill in the art would have found the use of Prober I's analogues to be useful and effective, even if nucleotide analogues with a label on the 8-position of a non-deaza purine might have been better.

Cleavable linker between a base and a label in a nucleotide analogue (Nos. 3-5 in Ex. 2033, Trainor Decl. ¶ 67).

In claim 15, the label is attached to the nucleotide by a "cleavable linker." As discussed above, Illumina argued that this limitation was described in Tsien, an assertion supported by the evidence. Columbia challenges that the limitation is met, arguing that "none of the approaches to attaching labels to nondeazabases discussed by Tsien on page 29 at lines 3-18 and illustrated in the structures on page 30 involve use of a cleavable linker." (Ex. 2033, Trainor ¶ 73.)

This argument is not persuasive. Illumina did not argue that Tsien described cleavable linkers at the pages cited by Dr. Trainor, but rather cited page 28, lines 19-29, of Tsien for this disclosure as discussed above in 2) above. Columbia contends there would have been no reason to change the uncleavable linkers on the 8-position of the purine labeled nucleotide

analogues of Tsien to a cleavable linker, particularly since the linker in Prober I is uncleavable (Ex. 2033, Trainor Decl. ¶ 73). However, Tsien gives an express reason to use a cleavable linker when attaching a label to the deaza-substituted nucleotide: "to release the fluorophore or other label on demand." (Tsien, p. 28, ll. 22-23). Dr. Trainor acknowledged in his declaration that Tsien describes "nucleotide analogues which include a label attached to the base (Exhibit 1002, page 28, ll. 5-6) and the possibility of the label being attached to the nucleotide analogue by means of a cleavable tether (Exhibit 1002, page 28, ll. 19-21 [])." (Ex. 2033, Trainor Decl. ¶ 28; emphasis added). Accordingly, we are persuaded that Tsien teaches a cleavable linker.

Removable chemical moiety capping the 3'-OH group of the sugar (No. 6 and 7 in Trainor Decl. ¶ 67)

In paragraph 67 of Dr. Trainor's declaration, he mentions one difference between Tsien and the claimed nucleotides as having to "include removable 3'-OH capping groups on the uncapped 3'-OH groups of the nucleotide analogues."

Dr. Trainor did not identify where uncapped 3'-OH groups were found in Tsien. The claims require a removable 3'-OH capping group. Tsien, as discussed above, also describes capped 3'-OH groups, a fact acknowledged by Dr. Trainor (Ex. 2033, Trainor Decl. ¶ 28). A blocking group on the 3'-OH is required to prevent inadvertent multiple additions (Tsien, p. 12, ll. 27-29).

The nucleotide analogues of Prober I are chain terminating and do not have an -OH group on the 3' carbon of the sugar (Prober I, Fig. 2). However, Tsien was relied upon for the 3'-OH capping group, not Prober I.

Consequently, we find Dr. Trainor's argument unavailing. Tsien teaches the nucleotides are added to the 3'-OH of the primer, extending it (Tsien, p. 11, ll. 1-13); Nos. 6 and 7 in Ex. 2033, Trainor Decl. ¶ 67).

Using cleaving means other than light (No. 7 in Ex. 2033, Trainor Decl. ¶ 67)

As discussed in the section on Tsien as anticipatory to the subject matter of claim 12, Tsien describes various cleaving means, including chemical and enzymatic, making any one of them obvious to have used. Columbia has not presented arguments to the contrary.

Was there a reason to move the label from the 3'-OH group to the base?

Columbia contends that there would have been no reason

> . . . to change the preferred reversibly terminating 3'OH labeled nucleotide analogues of Tsien to move the label from the 3'OH group to the base since introducing modifications at two positions in a nucleotide analogue would have been understood by a person of ordinary skill to be more likely to result in a nucleotide analogue that a polymerase would not incorporate into a primer extension strand.

(Paper 78, PO Reply, p. 16).

Dr. Trainor testifies that having the label on the 3'-OH group "was to accomplish both labeling and removable capping at a single position on the nucleotide in a single series of chemical reactions." (Ex. 2033, Trainor Decl. ¶ 50). Dr. Trainor states that there were no reports of incorporating a nucleotide analogue into a primer, where the analogue had a removable cap on the 3'-OH group and a label on a base (*id.*)

As already discussed, Tsien expressly teaches placing the label on the base, rather than the 3'-OH group. Columbia's arguments to the contrary ignore the explicit disclosure by Tsien of base-labeled nucleotides. Moreover, Columbia's argument that a nucleotide with a label on the 3'-OH group is the appropriate starting point is factually incorrect because Tsien teaches nucleotides with the label on the base and the capping group on the 3'-OH. Even were there a preference for 3'-OH labeled nucleotides, this would not detract from the explicit disclosure of base-labeled nucleotides. Columbia's argument to the contrary is contradicted by the passages from Tsien reproduced below:

> As will be explained in more detail below, the fact that the indication of labeling appears associated with the "nucleoside base part" of these abbreviations does not imply that this is the sole place where labeling can occur. Labeling could occur as well in other parts of the molecule.

(Tsien, p. 10, ll. 10-15(emphasis added).)

> One simple labeling approach is to incorporate a radioactive species within the blocking group or in some other location of the dNTP units.

(*Id*. at p. 26, ll. 13-14 (emphasis added).)

> Another labeling approach employs fluorescent labels. These can be attached to the dNTP's via the 3'OH-blocking groups or attached in other positions.

(*Id*. at p. 26, ll. 17-19 (emphasis added).)

> While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of alternatives - particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a remote position such as the base.

(*Id*. at p. 27, l. 33 to p. 28, l. 2) (emphasis added).)

> One method involves the use of a fluorescent tag attached to the base moiety.

(*Id*. at p. 28, ll. 5-6 (emphasis added).

Columbia attempts to distinguish Prober I because Prober teaches chain terminating nucleotides which lack a removable group. But Prober I was only relied upon for its teaching of how to label a purine base with a detectable label. Tsien was relied upon for its teaching DNA sequencing using nucleotides with removable 3'-OH groups.

Dr. Trainor cited several publications for describing on-going efforts to create modified nucleotides with labels on the 3'-OH (Ex. 2033, Trainor ¶¶ 27, 28, 49, 61, and 102), said to teach against labeling the nucleotide base. Columbia's argument ignores explicit disclosure in Tsien of a base-labeled nucleotide. The fact that more than one type of nucleotide was being pursued for sequencing is not evidence that one approach would have been dropped over the other. We have not been directed to evidence that base-labeled nucleotides would have been ignored or seen as an unworkable alternative to use in sequencing by synthesis methods.

In addition to requiring a reason to have combined the prior art, the skilled worker must also have had a reasonable expectation of success of doing so. *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1361 (Fed. Cir. 2007). Columbia raises the issue of whether there would have been a reasonable expectation of success that a nucleotide analogue with a label on the base and a capping group on the 3'-OH would be incorporated into a DNA. A preponderance of the evidence supports an affirmative answer.

Prober I teaches that base labeled nucleotides can be incorporated into a newly synthesized DNA strand by appropriate enzymes (Prober I, p. 337, col. 2; p. 340, col. 1, second paragraph). Dr. Trainor admitted that 3'-OH

removably capped nucleotides had been used in DNA sequencing methods (Ex. 2033, Trainor Decl. ¶¶ 26-28). Dr. Trainor cites several publications in support of unpredictability.

Dr. Trainor cites Metzker (Ex. 2033, Trainor Decl. ¶ 87). On page 4263, Metzker describes testing 3'-OH modified terminators for their ability to be substrates for polymerases. As shown in Table 2 of Metzker, terminators had different activities when tested against various polymerases. However, the publication shows the routineness of testing for activity. Dr. Trainor did not explain how these results with different nucleotides than claimed make it unpredictable that two structures which are known to work with polymerase would not work when combined in the same nucleotide molecule.

Finally, Dr. Trainor contrasts these publications with page 200 of Welch and Burgess (1999). According to Dr. Trainor, Welch shows that preliminary tests of compounds 1a and 1b as polymerase substrates did not show evidence of incorporation (Ex. 2033, Trainor Decl. ¶ 30). However, Dr. Trainor did not explain the pertinence of these compounds and their underlying chemistry to a nucleotide having a labeled deaza-purine and a removable 3'-OH group.

In sum, the preponderance of the evidence establishes that there was a reasonable expectation of success, and Columbia has not directed us to sufficient evidence to establish that it was unpredictable to have used the claimed nucleotide as a polymerase substrate for DNA sequencing.

Was there a basis for reasonably expecting that a nucleotide with a removable 3'-OH group and a label attached to the base could be made?

Columbia contends that neither Tsien nor Prober I discloses any chemistry relevant to making a nucleotide analogue with the claimed features, requiring a person of ordinary skill "to design new chemical procedures to attempt to address the differences between the nucleotide analogues described by Tsien and the nucleotide analogue recited in the claim." (Paper 78, PO Resp., p. 17). Furthermore, Dr. Trainor testifies that Prober I's nucleotides do not include a cleavable linker and cannot be modified to include, a 3'-OH group (Ex. 2033, Trainor Decl. ¶¶ 79-80). Dr. Trainor concludes that new chemical procedures would have been needed, the development of which were complex and fraught with difficulties. (*id*. ¶¶ 81-82).

This argument is not persuasive. First, the patentability challenge is not based on converting Prober I's nucleotide into the claimed nucleotide. Rather, the analysis begins with Tsien, who describes nucleotides with a cleavable linker and 3'-OH removable blocking group. Second, a preponderance of evidence establishes a reasonable expectation of success as addressed above

VI. SECONDARY CONSIDERATIONS FOR UNPATENTABILITY CHALLENGES II AND IV BASED ON OBVIOUSNESS

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of

nonobviousness, if any. *Graham v. John Deere Co. of Kansas*, 383 U.S. 1, 17 (1966). Secondary considerations are "not just a cumulative or confirmatory part of the obviousness calculus but constitute independent evidence of nonobviousness … [and] enables the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks and citations omitted). "[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). "This objective evidence must be 'considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.' *Id.* at 1538-39." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012).

Columbia contends that Illumina's obviousness challenges fail because objective evidence shows: 1) the claimed invention has yielded unexpectedly improved properties and results not present in the prior art; (2) the claimed invention has received praise and awards; (3) the claimed invention is responsible for Illumina's commercial success; (4) Illumina copied the claimed nucleotide analogues; (5) others in the art were skeptical that the claimed nucleotides and methods would be successful; and (6) Illumina attempted to license the claimed nucleotides and methods (Paper 78, PO Resp., pp. 26-27). We have considered this evidence along with all the other evidence before us, but do not find it persuasive.

A. "unexpectedly improved properties"

Relying on data in Ju's 2006 publication[13] in which sequencing of a 20 nucleotide template was accomplished using "four nucleotide analogues, each having both a unique detectable label attached through a chemically cleavable linker to the base (two pyrimidines and two deazapurines), and a chemically cleavable chemical group capping the 3'-OH group of the sugar," Dr. Trainor testified that the properties of the claimed nucleotides "have revolutionized the DNA sequencing industry." (Ex. 2033, Trainor Decl. ¶¶ 199-200). Specifically, Dr. Trainor testified that Ju's results show that the sequencing with the claimed nucleotides are unexpectedly better than pyrosequencing by facilitating clear identification of all 20 nucleotides in the DNA template while pyrosequencing did not (*id*. at ¶¶ 200-201). Dr. Trainor testified that this "accurate identification was made possible by the fact that Dr. Ju's nucleotide analogues separated the cleavable chemical group at the 3'-OH position of the sugar from the detectable label, which was placed instead on the base" (*id.* at ¶ 203). Dr. Trainor further cited additional publications said to have reported similar successes (*id.* ¶¶ 206-208).

Ju 2006 reported DNA sequencing in which "four nucleotides (A, C, G, T) are modified as reversible terminators by attaching a cleavable fluorophore to the base and capping the 3-OH group with a small chemically reversible moiety so that they are still recognized by DNA polymerase as

[13] Jingyue Ju et al., *Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators,* 103 PROC. NAT'L ACAD. SCI. 19635-19640 (2006), Exhibit 2034. The Ju publication is said to correspond to the claimed invention with respect to the nucleotides and methods.

substrates." (Ju, p. 19635). Dr. Trainor attributes Ju's success to this configuration, i.e., the label on the base and the 3-OH removable cap, but not to the deazA substitution. (Ex. 2033, Trainor Decl. ¶ 203). Both these features are present in claim 12.

While there is no working example in Tsien of a nucleotide with the claimed features, as explained above, Tsien suggests attaching a label to the base moiety and utilizing a cleavable tether to release the label before the next successive nucleotide is added (Tsien, p. 28, ll. 5-25). Tsien's method also requires removable 3'-OH groups in its sequencing (*id.*at p. 21, ll. 9-12; p. 23, ll. 28-32). In considering the weight of the evidence militating in favor of the "unexpectedly improved properties" over pyrosequencing, we must take into account that a single reference describes both features, i.e., attachment of a label to the base and a cleavable linker as the attachment means. This implicates the legal principles enunciated in *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

In *Baxter*, the applicant had argued that the claimed plasticized blood donor bag comprised of DEHP had unexpected properties in suppressing hemolysis of red blood cells stored inside it. *Baxter*, 952 F.2d at 389. The court found that such evidence did not rebut prima facie obviousness because the prior art disclosed a DEHP-plasticized donor bag, and therefore, Baxter's blood bag had the same hemolytic-suppressing function as the prior art – albeit unappreciated at the time of the invention. *Baxter*, 952 F.2d at 391. The court concluded that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Baxter*, 952 F.2d at 392. Likewise, Tsien has a written description of a nucleotide analogue with the features relied upon by Columbia as possessing

unexpected properties. Thus, it could be said that the finding that a nucleotide analogue with the 3'-OH and label on the base is better than pyrosequencing, is merely recognizing an advantage of a nucleotide described by Tsien. The description is not anticipatory to claim 15 because the claim further requires a deazapurine base. However, the deazapurine is not said by Columbia to be responsible for the unexpected result.

Dr. Trainor also testified that an "unexpected benefit" associated with the claimed nucleotide analogues was identified by Illumina's expert Dr. Weinstock (Ex. 2033, Trainor Decl. ¶ 209). According to Dr. Trainor, Dr. Weinstock stated during his deposition that "nucleotide analogues having a label on the base have the beneficial property of being useable in sequencing methods that require repetitive incorporation of nucleotide analogues, in particularly dGTPs, to sequence DNA having G:C rich regions." (*Id.*) Dr. Trainor stated that he "was surprised to learn that nucleotide analogues having a label on the base have solved the problem of sequencing G:C rich regions." (*Id.* at ¶ 210). This testimony is not persuasive.

Dr. Weinstock, in his deposition, specifically stated that Prober I had used "2'-deoxy-7-deazaguanosine triphosphates . . . in place of dGT to minimize" the effects of secondary structure when sequencing GC-rich regions. (Ex. 1034, Weinstock Tr. 141:5-18; 145:10-22). Dr. Weinstock also testified that GC-rich regions "had a tendency to form secondary structures that were difficult for a DNA polymerase to get through during a DNA synthesis reaction and that the addition of deazabases to the end of the primer may have some benefit" in sequencing (*id.* at 147:8-13; *see also* 148:24 to 150:5). Based on this deposition testimony, it is evident that

Dr. Weinstock believed that the problem of sequencing in GC-rich areas had already been addressed by Prober I in their use of the deazaguanosine, inconsistent with Dr. Trainor's testimony that the problem was solved using analogues with a label on the base. Indeed, Dr. Weinstock's testimony is supported by Prober I , which taught that 2'-deoxy-7-guanosine triphosphates had been used to minimize secondary structure in sequencing (Prober I, p. 341, 1st column).

In response to questioning about the effect of a labeled deazabase, Dr. Weinstock added that "if a small change of substituting a carbon for a nitrogen has a benefit on reducing secondary structure in GC-rich regions, sticking anything larger than that at that position is likely to have an even bigger benefit." (Ex. 1034, Weinstock Tr. 151:13-21). We understand Dr. Weinstock to be saying that further attaching a label to the deazapurine base would have been expected ("is likely") to have "an even bigger benefit" than the deazapurine alone, which is inconsistent with Dr. Trainor's statement of unexpected benefit of the deazapurine labeled base.

A showing of "new and unexpected results" must be "relative to the prior art." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004). To establish unexpected results, the claimed subject matter must be compared with the closest prior art. *In re Baxter Travenol Labs*., 952 F.2d at 392. In this case, Patent Owner's comparison was performed with pyrosequencing, but pyrosequencing is not the closest prior art. Rather, closer prior art is described in Tsien of a nucleotide with a label and removable group on the 3'-OH group. Patent Owner thus did not perform a comparison with the closest prior art.

B. Commercial success

Illumina sells products used in sequencing by synthesis (SBS), the same type of sequencing described in the Tsien and Stemple III publications. Columbia introduced evidence that Illumina's SBS products included nucleotide analogues with a removable chemical moiety capping the 3'-OH group and a label on the base and that these features were "crucial to the commercial success" of Illumina's SBS products (Ex. 2033, Trainor Decl. ¶¶ 221-222). A nucleotide analogue with the latter two features is embodied by claim 15 of the '869 Patent. These Illumina products are also the subject of a patent infringement action by Columbia against Illumina (Paper 78, PO Resp., p. 37).

Commercial success involves establishing success in the marketplace of a product encompassed by the claims and a nexus between the commercial product and the claimed invention. "Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Technology Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). "For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). "While objective evidence of nonobviousness lacks a nexus if it exclusively relates to a feature that was 'known in the prior art,' *Ormco Corp. v. Align Tech., Inc*., 463 F.3d 1299, 1312 (Fed. Cir. 2006), the obviousness inquiry centers on whether 'the claimed invention as a whole' would have

been obvious, 35 U.S.C. § 103." *Rambus Inc. v. Rea*, 731 F.3d. 1248, 1257-58 (Fed. Cir. 2013).

With regard to whether a nexus has been established between the products upon which commercial success has been based and the claimed invention, Dr. Trainor testified that he reviewed Illumina's technical documents and that each of the nucleotide analogues "has a cleavably-linked label on the nucleotide base, namely a fluorescent dye molecule." (Ex. 2033, Trainor Decl. ¶¶ 227-230). Dr. Trainor also testified these commercial nucleotide analogs have a removable chemical moiety capping the 3'-OH group of the nucleotide sugar (*id.* at ¶ 231-234). With regard to the deazapurine, Dr. Trainor reproduced a nucleotide which appears to be a C-substituted guanine at position 7 as it would be for deazapurine, although Dr. Trainor did not provide specific testimony in support. To the extent the nucleotides used by Illumina are not deazapurines, a nexus is not established because claim 15 requires a deazapurine base.

As evidence that these features are responsible for the success of the commercial products, Dr. Trainor cited a February 17, 2006 email from Dr. Colin Barnes – a scientist at the predecessor company to Illumina – written to two other scientists at the same company. In the email, Dr. Barnes stated: "Our original concept of having a very small 3'-block and leaving the fluor on the base is the reason our SBS works so well." (Ex. 2033, Trainor Decl. ¶ 239). Dr. Barnes's email was written in 2006 at the time Mr. Sims[14] stated Illumina entered the SBS sequencing market with its

[14] Exhibit 2091 is the declaration of Raymond Sims which was provided by Columbia to establish commercial success of Illumina's products said to

nucleotide analogues having removable 3'OH groups and cleavable labels on the nucleotide base (Sims Decl. ¶ 14). Dr. Trainor also cited a deposition from Dr. Xiaohai Liu, Illumina's Director of SBS Sequencing Chemistry Research, who testified that he agrees with Dr. Barnes assessment, stating it "is part of a jigsaw." (Ex. 2033, Trainor Decl. ¶ 240; Ex. 2049, Liu Tr. 202:17-21).

As held in *J. T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997), "the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art."

In this case, Dr. Trainor testified that "a nucleotide analogue combining all the features arranged as in Columbia patent claims – a cleavable chemical group capping the 3'-OH position of the sugar and a label attached to the nucleotide base via a cleavable linker" were responsible for the nucleotides success. (Ex. 2033, Trainor Decl. ¶¶ 198, 222, and 225). Dr. Barnes also attributed the success to these features. Illumina marketed its SBS products as having the cleavable label and removable 3'OH group ("using a proprietary reversible terminator-based method that enables detection of single bases as they are incorporated into growing DNA strands. A fluorescently-labeled terminator is imaged as each dNTP is added and then cleaved to allow incorporation of the next base"), the same features embodied in claim 15 (Ex. 2033, Trainor Decl. ¶ 243). Both these features, however, are described in Tsien, making them known and "readily available

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embody the claimed subject matter. Based on Mr. Sims's education and experience, we find him qualified to give opinions on financial data, the topic of his declaration.

in the prior art." The record indicates therefore that the success did not stem from the merits of the claimed invention. Neither Columbia in their response under § 42.120 (Paper 78, PO Resp.) or in Trainor's declaration described any other feature of the invention, as a whole, that should be considered when evaluating commercial success. *Rambus*, 731 F.3d at 1257-1258.

As discussed above, Tsien's nucleotides have a cleavable chemical group capping the 3'-OH position of the sugar in order to prevent inadvertent additions during the sequencing by synthesis method. A detectable label is described by Tsien on either the 3'-OH position or on the nucleotide base, and thus a nucleotide with label on the nucleotide base is one of two choices. The label on the nucleotide base is cleavable in order to identify subsequent nucleotide additions during the sequencing by synthesis method (Tsien, p. 13, ll. 1-29; p. 14, ll. 19-26; p. 17, ll. 14-16). The features said by Dr. Barnes, Dr. Liu, and Illumina to have been responsible for the commercial success of Illumina's product are thus described and "readily available" in Tsien. Indeed, Tsien's Figure 2 shows four unique labeled nucleotides, each with a removable 3'OH blocking group and removable label (*id.* at p. 11, l. 28 to p. 13, l. 29). The removable label is depicted on the nucleotide base ("As will be explained in more detail below, the fact that the indication of labeling appears associated with the "nucleoside base part" of these abbreviations does not imply that this is the sole place where labeling can occur.") (*Id*. at p. 10, ll. 10-14).

C. Evidence of attempted licensing

Licensing of a patented technology can be evidence of nonobviousness because it can indicate the licensor recognizes the merits of the invention by licensing it. *Stratoflex, Inc.*, 713 F.2d at 1539.

In this case, Columbia provided evidence that Illumina sought to license the technology developed by Dr. Ju (Paper 78, PO Resp. pp. 37-41). Columbia states that it elected to license the technology to another company, not Illumina (*id.* at 40). Subsequently, Columbia states that Illumina had discussions about acquiring the company, which gained a license to Ju's technology (*id.* at 40). Columbia states that Illumina tried to acquire the licensed technology just prior to Columbia suing Illumina for patent infringement (*id.* at 40). Illumina did not challenge Columbia's description of its attempt to license the technology in their response to Columbia's § 41.120 filing. The only response was in their motion to exclude the evidence of attempted licensing as either hearsay or on lack of relevance.

Columbia has direct knowledge of Illumina's licensing attempts. While Illumina never licensed the technology, Columbia argued that this was because Columbia had licensed to another company. Nonetheless, based on statements by Illumina witness Dr. Barnes and Illumina's own marketing literature, the invention recognized by Illumina as having merit, is one which is described in Tsien with the removable 3-'OH capping group and base label. There is insufficient evidence that Illumina's licensing strategy was driven by recognition of the merits of the claimed invention, rather than knowledge of a patent potentially covering their own product.

D. Praise and skepticism

We have considered Columbia's evidence of praise and skepticism, but find it of insufficient weight and relevance to deem it persuasive as to the merits of the claimed invention particularly when we consider it within the totality of the evidence before us.

E. Summary

After considering the evidence of record, including the secondary considerations, we are persuaded that a preponderance of the evidence supports Illumina's contention that claims 15 and 16 are unpatentable over II) Tsien and Prober I; and IV) Stemple III and Anazawa.

MOTIONS

VII. COLUMBIA'S MOTION TO AMEND

A motion to amend the claims under 37 C.F.R. § 42.121 was filed by Columbia on August 30, 2013 (Paper 79). In the motion, Columbia proposed canceling claims 12-33 and replacing them with substitute claims 34-54.

Proposed claim 34 is identical to original claim 15, rewritten in independent form and reciting all of the features of original claim 12. The only difference is that the word "light" has been deleted from two Markush groups as an alternative cleaving means. The claim is thus narrower than original claim 15.

Proposed claims 35-54 are identical to original claims 13-14 and 16-33, respectively, except that they depend directly or indirectly from

proposed claim 34 and therefore incorporate the features of original claim 15.

Columbia argued that proposed claim 34 is not anticipated by Tsien or by Stemple II (Paper 79, pp. 9 and 10). However, claim 34 is said by Columbia to correspond to claim 15, and *inter partes* review of claim 15 was not instituted on the basis of Tsien and Stemple III as anticipatory publications. Rather, review was instituted on claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I and as obvious in view of Stemple III and Anazawa. Columbia stated that the proposed claim obviates two grounds upon which the trial was instituted (Paper 79, p. 12), but trial was not instituted on claim 15, upon which claim 34 was based, for either of these grounds. The proposed amendments therefore do "not respond to a ground of unpatentability involved in the trial."[15] Nonetheless, we considered the amended claim language and found that the amended claims remain unpatentable because the alternative claimed cleaving means are described in Tsien and Stemple. See *supra* at pp. 11 (Tsien), 12 (Stemple III), 16-17 (Stemple III), and 31 (Tsien).

For the foregoing reason, we deny the motion to amend.

VIII. COLUMBIA'S MOTION TO EXCLUDE

A motion to exclude evidence under 37 C.F.R. § 42.64 was filed by Columbia on November 12, 2013 (Paper 103).

[15] A motion to amend may be denied where: "(i) The amendment does not respond to a ground of unpatentability involved in the trial; or (ii) The amendment seeks to enlarge the scope of the claims of the patent or introduce new subject matter." 37 C.F.R. § 42.121(a)(2).

A. Columbia seeks to exclude Exhibits 1029-1033 which were said to have been introduced for the first time at the deposition of Illumina's expert, Dr. Weinstock, during redirect examination by Illumina's counsel (Paper 103, p. 1). As, we did not rely on this portion of Dr. Weinstock's testimony or the exhibits cited in it, we dismiss this part of the motion as moot.

B. Columbia seeks to exclude Exhibits 1041-1049 which were introduced at Dr. Trainor's deposition (Paper 103, p. 4.)

Exhibits 1041-1048 were introduced by Illumina for the purpose of impeaching Dr. Trainor's opinions in his declaration regarding the non-obviousness of the claimed subject matter (Ex. 2094, Trainor Tr. 277: 21 to 278: 6). Columbia contends that these references were belatedly introduced so that they could be cited in Illumina's Reply and in Exhibit 1053 (Declaration of Kevin Burgess, Ph.D.) in order to make out Illumina's prima facie case, in violation of the Trial Practice Guide. (77 Fed. Reg. 48,756, 48,767, Aug. 14, 2012) (Paper 103, p. 6). Exhibit 1049 is a declaration from an IPR to which Columbia is not a party, previously introduced as Ex. 1024, which was previously expunged by the Board as improperly filed (Paper 46).

We have determined there was a reason to have made the claimed nucleotides based on the combination of Tsien and Prober I, without relying on Exhibits 1041-1048. Thus, we dismiss this part of the motion as moot.

C. Columbia seeks to exclude Exhibits 1050-1054 (Paper 103, p. 7). Exhibits 1050, 1051, 1052, and 1054 are said by Columbia to belatedly raised new issues and evidence to make out its prima facie case (*id*.). Exhibit 1053 is a declaration of Kevin Burgess filed by Illumina and cited for the first time in their response (Paper 76, p. 2) to Columbia's response under § 42.120 (Paper 76).

We determine that the Columbia claims are unpatentable without relying on Exhibits 1050-1054 and, thus, we dismiss this portion the motion as moot as well.

IX. ILLUMINA'S MOTION TO EXCLUDE

A motion to exclude evidence was filed by Illumina on November 12, 2013 (Paper 119). This evidence goes to the secondary considerations that were argued by Columbia in their response to the petition under § 42.120. As we conclude that the Columbia claims are unpatentable even if we consider this evidence, we need not and do not decide this motion and dismiss it as moot.

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X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 are cancelled;

FURTHER ORDERED that Columbia's motion to amend claims is denied;

FURTHER ORDERED that Columbia's motion to exclude evidence is dismissed as moot; and

FURTHER ORDERED that Illumina's motion to exclude evidence is dismissed as moot.

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