Trials@uspto.gov
572-272-7822

Paper 128
Mailed: March 6, 2014

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 IPR2012-00006
Patent 7,713,698 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 1-7, 11, 12, 14, 15, and 17 of U.S. Patent 7,713,698 B2 ("the '698 Patent") pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1 to 42.123. On March 12, 2013, the Board instituted *inter partes* review of claims 1-7, 11, 12, 14, 15, and 17 on three grounds of unpatentability (Paper 28, Decision on Petition ("Dec. Pet.")). Illumina requested rehearing on two of the grounds of unpatentability (Paper 30), which had been denied in the Decision on Petition. Upon reconsideration, the Board instituted *inter partes* review of one of these grounds of unpatentability as to claims 1-7, 11, 12, 14, 15, and 17 (Paper 43, Decision on Rehearing ("Dec. Reh'g")).

After institution of the *inter partes* review, Patent Owner, The Trustees of Columbia University in the City of New York ("Columbia"), filed a response under 37 C.F.R. § 42.120 to the decision instituting *inter partes* review (Paper 69, "PO Resp."). Columbia also filed a Motion to Amend Claims (Paper 70) and a Motion to Exclude Evidence (Paper 93). Illumina filed a reply to Columbia's response under 37 C.F.R. § 42.120 (Paper 76, "Pet'r Reply") and a Motion to Exclude Evidence (Paper 90 (redacted); Paper 107 (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 (Exhibit 2033, Trainor Decl. ¶¶ 3 and 6-8), qualifying him to testify on the 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 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 1-7, 11, 12, 14, 15, and 17 are unpatentable.

B. The '698 Patent

The '698 Patent issued May 11, 2010. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the '698 Patent involves sequencing DNA by incorporating a base-labeled nucleotide analogue into a primer DNA strand, and then determining the identity of the incorporated analogue by detecting the label attached to the base of the nucleotide. A polymerase is used to incorporate the nucleotide analogue into the strand of DNA ('698 Patent, col. 2, ll. 24-28). 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. 6-11).

Columbia does not argue the novelty of the steps utilized in the claimed method of "determining the identity of a nucleotide analogue

incorporated into a nucleic acid primer extension strand… ('698 Patent, cl. 1)," but rather focuses its arguments on the novelty and non-obviousness of the nucleotide analogue utilized in the sequencing method. Nucleotides, which are the building blocks of DNA, comprise a sugar (ribose or deoxyribose), a phosphate 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 ('698 Patent, col. 2, ll. 33-37). 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 '698 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 ('698 Patent, col. 2, ll. 57-65). 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. 64 to col. 3, l. 2). According to the '698 Patent, the prior art teaches attaching the label to the 3'-OH group. The '698 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.

All the claims at issue in this *inter partes* review involve a nucleotide analogue which comprises 1) a base labeled with a unique label, 2) a removable chemical moiety capping the 3'-OH group, and 3) a base which is deaza-substituted. A deaza-substituted nucleotide is a nucleotide analogue which includes a deazabase as the nitrogen base ('698 Patent, col. 7, ll. 44-63). A deazabase is a nitrogen base in which one of the natural nitrogen atoms in the base ring is substituted with a carbon atom (*id.*). For example, in a 7-deazapurine, the natural 7-position nitrogen in the base ring is replaced with a carbon atom (*id.*).

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 69, PO Resp. 8.) 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 Dower,[2]

[1] Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002 ("Tsien").
[2] William Dower et al., U.S. Pat. No. 5,547,839 (August 20, 1996), Exhibit 1005 ("Dower").

cited in this *inter partes* review, and Stemple III,[3] cited in related proceedings, describe SBS methods, which disclose base-labeled 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 working 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 where in the prior art a nucleotide with a label on the base and removable 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 several publications of nucleotides with a label on the nucleotide base with 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 '698 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

[3] Derek L. Stemple et al., U.S. Pat. No. 7,270,951 B1 (September 18, 2007), Exhibit 1008 ("Stemple III").

(Petition 3-4). According to Illumina, Columbia alleges in that proceeding that Illumina has infringed, and continues to infringe, the '698 Patent (*id*.).

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

A petition for *inter partes* review was filed on September 16, 2012, for U.S. Pat. No. 7,790,869 B2 ("the '869 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. Pat. 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 '698 patent. We instituted *inter partes* review on March 12, 2013.

D. The Alleged Grounds of Unpatentability

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

I. Claims 1-7, 11, 12, 14, 15, and 17 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I[6] (Petition 27).

II. Claims 5 and 12 under 35 U.S.C. § 103(a) as obvious in view of Tsien, Prober I, and Rabani[7] (Petition 52).

---

[4] IPR2012-00007.
[5] IPR2013-00011.
[6] James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336-341 (1987), Exhibit 1003 ("Prober I").

III. Claims 1-7, 11, 12, 14, 15, and 17 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Seela I[8] (Petition 56).

IV. Claims 1-7, 11, 12, 14, 15, and 17 under 35 U.S.C. § 102(b) as anticipated by Dower (Petition 30).

E. Claims

Claims 1 and 11 are the only independent claims under review. Claims 2-7, 14, 15, and 17 depend from claim 1. Claim 12 depends from claim 11.

Claims 1 and 11 are reproduced below:

> 1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:
>
> a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template;
>
> b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, and wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and
>
> c) detecting the unique label of the incorporated nucleotide analogue,

---

[7] Ely Rabani et al., WO 96/27025 (September 6, 1996), Exhibit 1006 ("Rabani").
[8] Frank Seela, U.S. Pat. No. 4,804,748 (February 14, 1989), Exhibit 1014 ("Seela I").

so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.

11. A plurality of nucleic acid templates immobilized on a solid surface, wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue, at least one of which is deaza-substituted, wherein each labeled nucleotide analogue comprises a base labeled with a unique label and contains a removable chemical moiety capping the 3'-OH group of the sugar of the of the nucleotide analogue.

PATENTABILITY CHALLENGES

II. TSIEN AND PROBER I

We instituted *inter partes* review of claims 1-7, 11, 12, 14, 15, and 17 on the grounds that the 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.

A. Claim 1 and others

Claim 1 is drawn to nucleic acid sequencing involving steps of: a) contacting a nucleic acid template with a primer; b) contacting the template hybridized with a polymerase and four nucleotide analogues, where each base has a unique label and a removable chemical moiety capping the 3'-OH group of the nucleotide sugar; and c) detecting the unique label of the nucleotide analogue which is incorporated into the primer as the primer is extended. At least one of the four nucleotide analogues is deaza-substituted.

A nucleotide analogue of claim 1 has the following structures or features: 1) a unique label attached to a base; 2) a removable chemical moiety capping the 3'-OH group of the nucleotide sugar; and 3) a deaza-substituted base.

Tsien

Tsien describes a DNA sequencing by synthesis method (Tsien, p. 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 features 1) and 2) are described in Tsien (*see also* Pet. 19-25).

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

(*Id*. at 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 28, ll. 5-6, 10-12.)

2) Removable 3'-OH chemical moiety (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.

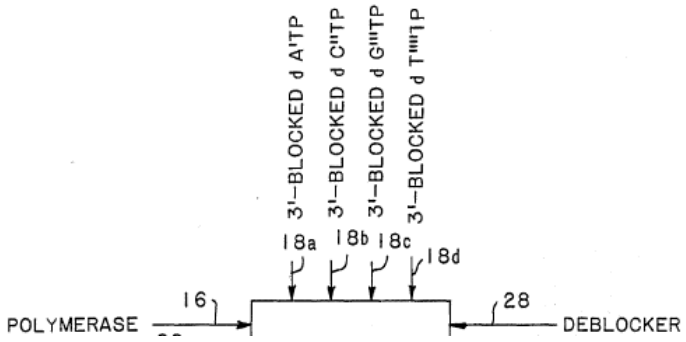
(Tsien, p. 13, ll. 17-22.)

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

(Tsien, p. 20, ll. 25-27.)

Structures 1) and 2) combined

Figure 2 of Tsien, reproduced 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.)

3) 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. [citing Sarfati 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 the "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.

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 Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). 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

> because the nucleotide analogues disclosed in Prober I, wherein "a linker is attached to the 5 position in the pyrimidines and to the 7 position in the 7-deazapurines," is shown to be an effective way to attach a fluorescent label to a nucleic acid base while maintaining the ability of the Sequenase™ polymerase used by Tsien to incorporate the associated dNTP into the primer extension strand.

(Petition 29.) 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.)

Discussion

Columbia did not respond substantively to the patentability challenge of claim 1 based on Tsien and Prober I under 35 U.S.C. § 103 in either the Preliminary Response (Paper 21) or Patent Owner Response (Paper 69). However, in arguing for the patentability of a claim with narrower scope than claim 1 (i.e., proposed claim 18), 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 69, PO Resp. 18). 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 which disparages these alternative nucleotide analogues, or which would have led one of ordinary skill in the art to conclude that they were unsuitable for the SBS purpose described by Tsien.

B. Claim 15

Claim 15 depends on claim 1 and further adds the limitation that "each of said unique labels is attached to the nucleotide analogue via a cleavable linker."

Although Illumina identified where in Tsien the "cleavable linker" limitation in claim 15 was described, Columbia did not separately address claim 15 in their Patent Owner Response. However, in the Motion to Amend the Claims, proposed new claim 18, which incorporates all the limitations of claim 15 into claim 1 (Paper 70, p. 4), was submitted by

Columbia along with arguments for its patentability over the cited art (Paper 69, PO Resp.). We consider these arguments below.

Tsien

Illumina cites the following passage in Tsien for a description of "a cleavable linker," as recited in claim 15 (Petition 26):

> 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, and claim 1 from which it depends. However, Illumina cited Tsien for its teaching "of a fluorescent tag attached to the base moiety" (Tsien, p. 28, ll. 5-6) to meet this limitation of the claim (Petition 21). A person of ordinary skill in the art reading Tsien would have recognized that its teaching of a cleavable tether to release the label would have been useful when the label is attached to the base moiety.

Columbia contends that the patentability challenge based on Tsien and Prober I is insufficient because "no starting point is identified and no rationale for the obviousness of the novel nucleotide analogue is provided." (Paper 69, PO Resp. 17.)

Columbia's argument is not persuasive. In the petition, Illumina 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." (Petition 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 "starting point" argument is, therefore, unsubstantiated. A rationale to combine the publications was also described above in Section A 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 69, PO Resp. 21.) Relying on Dr. Trainor's testimony, Columbia asserts that one of skill in the art would have had to make the following changes (Ex. 2033, Trainor Decl. ¶ 92):

> 1. remove the identical (non-unique) 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. change the identical labels on the pyrimidines to unique labels;

> 4. replace the uncleavable, acetylenic linker (described in Prober I) on the pyrimidines with a cleavable linker;
> 5. replace the uncleavable alkylamino linker on the purines with a cleavable linker);
> 6. include removable 3'-OH capping groups on the uncapped 3'-OH groups of the nucleotide analogues; and
> 7. incorporate such a novel nucleotide analogue into the end of a primer extension strand.

(Ex. 2033, Trainor Decl. ¶ 92.)

We address each of these differences, below.

Deaza-substituted nucleotide (Nos. 1 and 2 in Ex. 2033, Trainor Decl. ¶ 92)

Citing the Trainor Declaration, Columbia argues "there was no reason to use a deaza-purine labeled at the 7-positiResn given Tsien's specific guidance to the contrary that a label on the 8-position of a non-deaza purine was 'ideal.' (Exhibit 2033, Trainor Decl., ¶§95-98 [])." (Paper 69, PO Resp. 22.) 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., ¶98 [])" (*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. ¶ 96). However, Dr. Trainor states that Tsien ignored Prober I'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 p. 27, l. 33 to p. 28, l. 4.) In the following paragraph, Tsien describes attaching a label to the base, and states:

> 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. 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. 5-18.)

This passage, cited by Illumina on page 28 of the Petition, 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." *Id*. 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'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.

Unique labels (No. 3 in Ex. 2033, Trainor Decl. ¶ 92)

In his declaration, Dr. Trainor testifies that to have arrived at the claimed nucleotides from Tsien, a person of ordinary skill would have had to change the identical labels on the pyrimidines to unique labels. As explained by Illumina and in the section above on claim 1, Tsien has an express disclosure of using different reporter groups of each dNTP (*see* Section A). *See also* the following passage of Tsien:

> The detected florescence is then correlated to the fluorescence properties of the four different labels present on the four different deoxynucleotide triphosphates to identify exactly which one of the four materials was incorporated at the first position of the complementary chain. This identity is then noted.

(Tsien, p. 13, ll. 8-13.)

Thus, Tsien gives an express reason for using a unique label on each of the four different dNTPs: to identify what nucleotide is incorporated into the newly synthesized DNA molecule.

Cleavable linker between a base and a label in a nucleotide analogue (Nos. 4 and 5 in Ex. 2033, Trainor Decl. ¶ 92; original claim 15)

In claim 15 (and 18), the unique 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 Decl. ¶ 98.)

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. 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. ¶ 98, identified difference Nos. 4 and 5; Paper 69, PO Resp. 22). 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 Ex. 2033, Trainor Decl. ¶ 92)

In paragraph 92 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 testimony unavailing. Tsien teaches the nucleotides are added to the 3'-OH of the primer, extending it (Tsien, p. 11, 1-13; No. 6 and 7 in Ex. 2033, Trainor Decl. ¶ 92).

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

Columbia contends:

> [T]here 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 69, PO Resp. 19.) 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. ¶ 75.) 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. 13-15 (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 I 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, and 86), 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 discouraged or abandoned over the other. We have not been directed to evidence that base-labeled nucleotides would have been ignored or seen as an unworkable alternative for 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, but did not sufficiently explain the pertinence of these publications.

Dr. Trainor cites page 4263 of Metzker[9] (Ex. 2033, Trainor Decl. ¶ 112). 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. Dr. Trainor did not explain how these results with different nucleotides than those which are claimed make it unpredictable that two structures which are known to work with polymerase would not work when combined in the same nucleotide molecule. In fact, the publication shows the routineness of testing for the ability of an analogue to be incorporated into DNA by a polymerase.

Dr. Trainor also cites page 3 of Canard and Sarfati (1994),[10] but without explaining its significance. The abstract of the paper describes synthesizing nucleotide analogs which "acted as substrates with several DNA polymerases leading to chain termination." Page 3 appears to describe some differences in the effectiveness of the synthesized nucleotides with the

[9] Michael L. Metzker et al., *Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphoshpates*, 22 Nucleic Acids Res. 4259-4267 (1994), Exhibit 2015.
[10] Bruno Canard et al., *DNA polymerase fluorescent substrates with reversible 3'-tags*, 148 Gene 1-6 (1994), Exhibit 2030.

different polymerases, but Dr. Trainor did not point to any specific instance or what relevance it had to unpredictability in view of the success pointed out in the abstract.

Finally, Dr. Trainor contrasts these publications with page 200 of Welch and Burgess (1999).[11] According to Dr. Trainor, Welsh showed that preliminary tests of compounds 1a and 1b as polymerase substrates did not show evidence of incorporation (Ex. 2033, Trainor Decl. ¶ 31). 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 69, PO Resp. 20-21.) Furthermore, Dr. Trainor testifies that

[11] Mike B. Welch et al., *Synthesis of Fluorescent, Photolabile 3'-O-Protected Nucleoside Triphosphates for the Base Addition Sequencing Scheme*, 18 Nucleosides & Nucleotides 197-201 (1999), Exhibit 2027.

Prober I's nucleotides do not include a cleavable linker and cannot be modified to include, a 3'-OH group (Ex. 2033, Trainor Decl. ¶¶ 104-105). Dr. Trainor concludes that new chemical procedures would have been needed, the development of which were complex and fraught with difficulties (*id.* ¶¶ 106-107).

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. Secondly, a preponderance of evidence establishes a reasonable expectation of success as addressed above.

C. Claim 11

Independent claim 11 is drawn to a plurality of nucleic acid templates hybridized with a primer, where the primer has incorporated a nucleotide which is 1) deaza-substituted; 2) has a based labeled with a unique label; and 3) has a removable chemical moiety capping the 3'-OH group of the sugar. All three structures present in the nucleotide have been discussed above and are described or suggested by the combination of Tsien and Prober I. Columbia did not separately argue claim 11 in their response under 37 C.F.R. § 42.120.

III. TSIEN, PROBER I, AND RABANI

We instituted *inter partes* review of claims 5 and 12 on the grounds that the claims would have been obvious under 35 U.S.C. § 103(a) in view of Tsien, Prober I, and Rabani (Dec. Pet. 29-30). Columbia did not in their

response under § 42.120 (PO Resp., Paper 69) identify a defect in the factual findings or reasoning which led to the institution of the patentability challenge. We therefore adopt the findings and reasoning set forth in the Decision on Petition.

IV. TSIEN AND SEELA I

We instituted *inter partes* review of claims 1-7, 11, 12, 14, 15, and 17 on the grounds that the claims would have been obvious under 35 U.S.C. § 103(a) in view of Tsien and Seela I (Dec. Pet. 26-28). Tsien has been discussed in detail above. In this challenge, instead of Prober I, Seela I was cited for its disclosure of deaza-modified nucleotides. The reason for combining the cited publications is the same as for Tsien and Prober (*id.* at 27-28).

Columbia relies upon the same arguments as made for Tsien and Prober I (Paper 69, PO Resp. 25). We find those arguments unpersuasive for the same reasons as above.

V. SECONDARY CONSIDERATIONS

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] enable[] 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 69, PO Resp., p. 26). 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[12] in which sequencing of a 20 nucleotide template was accomplished using "four nucleotide analogues,

[12] Jingyue Ju et al., *Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators*, 103 Proc. Nat'l Acad. Sci.

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 that the properties of the claimed nucleotides "have revolutionized the DNA sequencing industry." (Ex. 2033, Trainor Decl. ¶¶ 203-204.) 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.* ¶¶ 205-206). 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.* ¶ 207). Dr. Trainor further cited additional publications said to have reported similar successes (*id.* ¶¶ 210-211).

Ju 2006 reported DNA sequencing in which "four nucleotides (A, C, G, and 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 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. ¶ 207). Claim 1 of the '698 Patent is drawn to a method which has a nucleotide with the removable capping group and the fluorophore label on the base, but does not require that the label be cleavable. Thus, the evidence is not commensurate

---

19635-19640 (2006), Exhibit 2034. The Ju publication is said to correspond to the claimed invention with respect to the nucleotides and methods.

with the full scope of claim 1. Claim 15, on the other hand, requires that the label is attached to the nucleotide analogue via a cleavable linker – as in the nucleotide utilized in Ju's sequencing.

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 of a nucleotide

analogue with the 3'-OH and label on the base is better than pyrosequencing is merely recognizing an advantage of a nucleotide analogue described by Tsien. The description is not anticipatory to the Columbia claim 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. ¶ 213). 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.* ¶ 214.) 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 Dep. 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 Dep. 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. In sum, Dr. Weinstock's testimony is both credible and factually-supported.

A showing of "new and unexpected results" must be "relative to 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. *Baxter*, 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 Tsien. Columbia introduced evidence that Illumina's SBS products included nucleotide analogues with a removable chemical moiety capping the 3'-OH group and a unique label on the base and that these features were "crucial to the commercial success" of Illumina's SBS products (Ex. 2033, Trainor Decl. ¶¶ 225-226). A nucleotide analogue with the latter two features is embodied by claim 15 of the '698 Patent. These Illumina products are also the subject of a patent infringement action by Columbia against Illumina (Paper 69, PO Resp. 40). In response, Illumina contends that Columbia has not presented any evidence supporting its commercial success argument (Paper 76, Pet'r Reply 14).

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. ¶ 231; *see also* ¶¶ 232-234.) Dr. Trainor also testified these commercial nucleotide analogs have a removable chemical moiety capping the 3′-OH group of the nucleotide sugar (*id.* ¶¶ 235-238). 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 a deazapurine, although Dr. Trainor did not provide specific testimony in support (*id*. ¶ 237). To the extent the nucleotides used by Illumina are not deazapurines, a nexus is not established because claims 1 and 15 require 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. ¶ 243 (emphasis omitted).) Dr. Barnes's email was written in 2006 at the time Mr. Sims[13] stated Illumina entered the SBS sequencing market with its

[13] Exhibit 2091 is the declaration of Raymond Sims which was provided by Columbia to establish commercial success of Illumina's products said to embody the claimed subject matter. Based on Mr. Sims's education and

nucleotide analogues having removable 3'OH groups and cleavable labels on the nucleotide base (Ex. 2091, 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. (Ex. 2033, Trainor Decl. ¶ 244; Ex. 2049, Liu Tr. 202:17-21.)

However, 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 – [(1)] a cleavable chemical group capping the 3′-OH position of the sugar and [(2)] a label attached to the nucleotide base via cleavable linker" were responsible for the nucleotides success. (Ex. 2033, Trainor Decl. ¶ 202; *see also* ¶¶ 226, and 229.) 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 (*id*. ¶ 247). Both these features, however, are described in Tsien, making them known and "readily available 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

---

experience, we find him qualified to give opinions on financial data, the topic of his declaration.

§ 42.120 (Paper 69, PO Resp.), nor Trainor, in his 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 non-obviousness because it can indicate the licensor recognizes the merits of the invention by licensing it. *Stratoflex*, 713 F.2d at 1539.

In this case, Columbia provided evidence that Illumina sought to license the technology developed by Dr. Ju (Paper 69, PO Resp. 37-39). Columbia states that it elected to license the technology to another company, not Illumina (*id.* at 39). Subsequently, Columbia states that Illumina had discussions about acquiring the company which gained a license to Ju's technology (*id.* at pp. 37-39). 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 § 42.120 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 (Paper 69, PO Resp. 37-40). 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 1 and 15 are unpatentable over I) Tsien and Prober I; II) Tsien, Prober I, and Rabani; and III) Tsien and Seela I. Columbia made no substantive arguments that would differentiate claims 2-7, 11, 12, 14, and 17 from claims 1 and 1. These claims are therefore unpatentable for the same reasons as claims 1 and 15, and the reasons set forth in the Petition.

VI. DOWER

In the Decision on the Request for Rehearing, the Board authorized the patentability challenge to claims 1-7, 11, 12, 14, 15, and 17 based Dower as anticipatory publication (Dec. Reh'g 7). Upon reconsideration and in view of Columbia's Response under § 42.120 (Paper 69) and the Trainor Declaration, we shall not sustain this challenge.

Dower describes a DNA sequencing method which uses base-labeled nucleotides (col. 18, l. 64 to col. 19, l. 10) and a reversible blocking agent on the 3'-OH of the nucleotide sugar to allow for deblocking and subsequent elongation (col. 14, ll. 50-53; col. 15, ll. 33-35, 38-40, and 52-56) (Petition 34).

Dower was not said by Illumina to expressly describe a deazapurine base. Rather, Illumina contends in the petition that a nucleotide comprising a deazapurine base is present by virtue of the incorporation by reference of

the Prober I publication which is said to disclose nucleotides with deazapurine bases (Request Reh'g 2-3). The issue addressed in the Request for Rehearing with respect Dower was whether Illumina met its burden in establishing whether Prober I is incorporated into the host document in a manner that complies with the requirement of 35 U.S.C. § 102. The following three passages were cited in the Request for Rehearing to support this determination:

> (c) An alternative polymer stepwise synthetic strategy can be employed. In this embodiment, the fluorophores need not be removable and may be attached to irreversible chain terminators. Examples of such compounds for use in sequencing DNA include, but are not limited to, dideoxynucleotide triphosphate analogs as described by Prober et al. (1987) *Science* 238:336-341.

(Dower, col. 25, ll. 41-47.)

> DNA polymerase, or a similar polymerase, is used to extend the chains by one base by incubation in the presence of dNTP analogs which function as both chain terminators and fluorescent labels. This is done in a one-step process where each of the four dNTP analogs is identified by a distinct dye, such as described in Prober et al. *Science* 238:336-341 . . . .

(*Id.* at col. 23, ll. 18-24.)

> Fluorescent chain terminators (analogs of dATP, dCTP, dGTP, and TP, each labeled with fluorophore preferably emitting at a distinguishable wavelength) are added to the reaction at a sufficient concentration and under suitable reaction conditions (time, temperature, pH, ionic species, etc., See Sambrook et al. (1989) *Molecular Cloning*, vols. 1-3, and Prober et al.) . . . .

(*Id.* at col. 25, ll. 4-10.)

Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272 (Fed. Cir. 2000), set forth the test for anticipation when material is incorporated by reference. "Incorporation by reference provides a method for integrating

material from various documents into a host document . . . by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein." *Id.* at 1282 (citations omitted). "To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents." *Id.* (citations omitted).

In this case, the passage at column 25, lines 41-47, refers to Prober I in the context of using nucleotides which are "irreversible chain terminators." An irreversible chain terminator is a termination dideoxynucleotide which lacks the removable 3'-OH group (Ex. 2033, Trainor Decl. ¶¶ 24 and 29). In contrast, the claims require a removable blocking group at the 3'-OH group. Thus, this reference to Prober I does not, when combined with Tsien, describe a nucleotide with a "removable chemical moiety capping the 3'-OH group of the sugar" as required by the claim.

The passage at column 23, lines 18-24, refers to chain terminators in reference to Prober I which only describes irreversible chain terminator. In this passage, Prober I is referenced for its teaching of identifying "each of the four dNTP analogs . . . by a distinct dye, such as described in" Prober I (Dower col. 23, ll. 18-24). It therefore appears that Prober I is cited for its disclosure of the concept of using a distinct dye for each nucleotide, and not necessarily for using a deaza-substituted base attached to the dye (Ex. 2033, Trainor Decl. ¶ 55).

In the passage at column 25, lines 4-10, Dower refers to fluorescent chain terminators as being used in sufficient concentrations and suitable

reaction conditions, and then references Sambrook and Prober I. Dr. Weinstock testified that in this passage Dower "expressly teaches the combination with Prober I to make the labeled nucleotides." (Ex. 1021, Weinstock Decl. ¶ 70.) However, this passage refers to analogs of dATP, dCTP, dGTP, and TP which are not the same as the irreversible chain terminators in Prober I. The passage also refers to concentrations and condition to carry out reactions. Therefore, it is not clear from the sentence what Prober I is being cited for and the passage does not state "with detailed particularity what specific material it incorporates and clearly indicate where that material is found" as required under *Advanced Display*.

Accordingly, we find that Illumina has not established by a preponderance of the evidence that Dower anticipates claims 1 and 11, and dependent claims 2-7, 12, 14, 15, and 17.

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 70). In the motion, Columbia proposed: 1) cancelling claim 1; 2) cancelling claims 2-7 and replacing them with claims 19-24; 3) canceling claims 11 and 12 and replacing them with claims 25 and 26; 4) canceling claims 14, 16 and 17 and replacing them with claims 27-29, and 5) cancelling claim 15 and replacing it with claim 18.

Proposed claim 18 is identical to original claim 15, rewritten in independent form and reciting all the features of original claim 1.

Proposed claims 19-23 are identical to original claims 2-6, respectively, except they depend from proposed claim 18.

Proposed claim 24 is identical to original claim 7, except that it depends from proposed claim 23.

Proposed claims 25 is identical to original claim 11 except that it specifies a plurality of different nucleic acid templates. Proposed claim 26 is identical to claim 12, except that it depends on proposed claim 25.

Proposed claims 27-29 are identical to claims 14, 16, and 17.

The main differences between the original claims and the proposed claims are that 1) claim 1 has been amended by incorporating the limitation of claim 15 requiring that "each of said unique labels is attached to the nucleotide analogue via a cleavable linker," and designating it as proposed claim 18; and 2) claim 11 has been amended by adding the limitation that the recited nucleic acid templates are "different," and designating it as proposed claim 25. The latter limitation was not in original claim 11 or in any of the original claims, which depended on claim 11. However, Columbia cited support in the '698 Patent for the limitation (Paper 70, p. 8-9).

Claim 25 adds the limitation "different" to claim 11, but the claim is otherwise identical to claim 11. Columbia, in adding this term, did not give a reason as to why the proposed claim is patentably distinct over the prior art or how it responds to a ground of unpatentability under 37 C.F.R. § 42.121(a)(2)(i). Indeed, Columbia stated that the amendment "merely clarifies the original patent claim, as the original patent claim would have been understood by a person skilled in the art" because a person of ordinary skill in the art would have understood original claim 11 to mean different nucleic acid templates (Paper 70, p. 13). Thus, by Columbia's own admission, claims 25 is of the same scope as original claim 11.

Accordingly, all the claims proposed in the Columbia amendment are of the same scope as claims already before us in this review, and which have been determined to be unpatentable. In the opposition to the motion, Illumina contends that Columbia's motion is defective (Paper 74, p. 1). We need not, and do not, reach Illumina's contention, however, since the claims, even as Columbia proposes to amend them, are unpatentable.

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 93).

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 93, 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 93, 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. 48756, 48767 (Aug. 14, 2012)). (Paper 93, p. 6). Exhibit 1049 is a declaration from an *inter partes* review to which

Columbia is not a party, previously introduced as Ex. 1024, which was previously expunged by the Board as improperly filed (Paper 34).

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 1041-1049. Thus, we dismiss this part of the motion as moot.

C. Columbia seeks to exclude Exhibits 1050-1054 (Paper 93, p. 7). Exhibits 1050, 1051, 1052, and 1054 are said by Columbia belatedly to raise 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 to Columbia's response under § 42.120 (Paper 76, Pet'r Reply 2).

We determine that the 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 90). 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.

X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1-7, 11, 12, 14, 15, and 17 of U.S. Patent 7,713,698 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.

Petitioner:

Robert Lawler

And

James Morrow
Reinhart Boerner Van Deuren s.c.
ipadmin@reinhartlaw.com

Patent Owner:

John P. White
Cooper & Dunham LLP
jwhite@cooperdunham.com

and

Anthony M. Zupcic
Fitzpatrick, Cella, Harper & Scinto
ColumbiaIPR@fchs.com