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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 IPR2013-00011
Patent 8,088,575 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 October 3, 2012, for *inter partes* review of claims 1-3 and 6 of U.S. Patent 8,088,575 B2 ("the '575 Patent") pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1 - 42.123. On March 12, 2013, the Board instituted *inter partes* review of claims 1-3 and 6 on four grounds of unpatentability (Paper 26, Decision on Petition ("Dec. Pet.")). Illumina requested rehearing on two of the grounds of unpatentability (Paper 29), 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 claim 6 (Paper 44, Decision on Rehearing ("Dec. Reh'g")). This corresponded to one of the same grounds of unpatentability authorized for claims 1-3.

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 70, "PO Resp."). Columbia also filed a Motion to Amend Claims (Paper 56) 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). An oral hearing was held on December 17, 2013 with both parties in attendance. (Record of Oral Hearing, Paper 126.)

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 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 1-3 and 6 are unpatentable.

B. The '575 Patent

The '575 Patent issued January 3, 2012. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the '575 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 ('575 Patent, col. 3, ll. 2-3). 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. 9-13).

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," but rather focuses its arguments on the novelty and unobviousness of the nucleotide utilized in the sequencing method. 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 ('575 Patent, col. 2, ll. 35-39). 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 '575 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 (*id*. at col. 2, ll. 59-65). 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. 3, ll. 1-4). According to the '575 Patent, the prior art teaches attaching the label to the 3'-OH group. The '575 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.

Claims 1-3 in this *inter partes* review involve a nucleotide analogue that comprises: 1) a base labeled with a unique label; and 2) a removable chemical moiety capping the 3'-OH group. Claim 6 further requires a base that is deaza-substituted. A deaza-substituted nucleotide is a nucleotide analogue that includes a deazabase as the nitrogen base (*id.* at col. 7, ll. 46-65). 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 70, 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., US 5,547,839 (August 20, 1996), Exhibit 1005 ("Dower").

cited in this *inter partes* review, and Stemple III,[3] which is cited in related proceedings, describe SBS methods that use base-label nucleotides and nucleotides containing a removable chemical moiety at the 3'-OH position (Ex. 2033, Trainor Decl. ¶¶ 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 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 and a removable 3'-OH group (e.g., Tsien, Dower, and Stemple III) shows a recognition within the prior art that such nucleotide analogues were useful and effective in SBS methods.

C. Related Proceedings

The '575 Patent is the subject of the litigation, *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

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

alleges in that proceedings that Illumina has infringed, and continues to infringe, the '575 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. Pat. No. 7,713,698 B2 ("the '698 patent").[4] The '698 patent is assigned to Columbia, has claims directed to related subject matter, and has a similar lineage as the '575 Patent. We instituted *inter partes* review on March 12, 2013.

A petition for *inter partes* review was filed on September 16, 2012 for U.S. Pat. No. 7,790,869 B2 ("the '869 patent").[5] The '869 patent is assigned to Columbia and has claims directed to related subject matter. The '575 Patent is a continuation of the '869 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 1-3, and 6 under 35 U.S.C. § 102(b) as anticipated by Dower;

II. Claims 1-3, under 35 U.S.C. § 102(b) as anticipated by Tsien;

III. Claim 6 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I;[6] and

[4] IPR2012-00006.
[5] IPR2012-00007.
[6] James M. Prober et al., *A System for Rapid DNA Sequencing with Flourescent Chain-Terminating Dideoxynucleotides*, 238 SCI. 336 (1987), Exhibit 1003 ("Prober I").

IV. Claim 6 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Seela I.[7]

E. The Claims

The '575 Patent was granted with claims 1-6. Illumina challenges the patentability of independent claim 1 and claims 2, 3, and 6, which depend from claim 1. Claims 1 and 6 read as follows (bracketed numerals added to emphasize certain claim limitations):

> 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 [1] a base labeled with a unique label and contains [2] a small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, wherein said small cleavable chemical group does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate; and c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.
>
> 6. The method of claim 1, wherein said base of at least one of said nucleotide analogues is a deazapurine.

[7] Frank Seela, US 4,804,748 (February 14, 1989), Exhibit 1014 ("Seela I".

PATENTABILITY CHALLENGES

II. CLAIM INTERPRETATION

Claim 6 recites that the base of at least one of the nucleotide analogues is a "deazapurine." One of ordinary skill in the art would understand that a "deazapurine" is a nitrogen base in which one of the natural nitrogen atoms in the base ring is substituted with a carbon atom. ('575 Patent, col. 7, ll. 39-65.) For example, in a 7-deazapurine, the natural 7-position nitrogen in the base ring is replaced with a carbon atom. ***Id.***

ANTICIPATION

Independent claim 1 is directed to a method of "determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand," comprising three recited steps using a nucleotide analogue with "a base labeled with a unique label" and "small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue." Claim 6 further recites that the base is a deazapurine. Columbia does not dispute that the claimed methods steps were known in the art, but rather argues that the claimed nucleotide analogue was not.

III. DOWER

Claims 1-3

We instituted *inter partes* review of claims 1-3 based on Dower as an anticipatory publication. Dower describes methods for sequencing DNA (Dower, col. 6, ll. 19-20). In one embodiment, a primer is elongated, one nucleotide at a time, using labeled nucleotide analogues in a polymerase-catalyzed enzymatic reaction (*id.* at col. 14, ll. 37-59; col. 15, l. 56 to col. 16,

l. 21). As explained in more detail below, Dower describes nucleotides with a label attached to the base and a small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, the two structural features of the nucleotide utilized in the claimed method of "determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand" ('575 Patent, claim 1). We address each of these features below.

A. "a base labeled with a unique label"

The phrase "unique label" is not defined in the '575 patent. We adopt the ordinary meaning of "unique" as "being the only one of its kind."[8] Therefore, the phrase "unique label" would be understood to mean that each of the recited four nucleotides has a different label (*see* '575 patent, col. 21, ll. 31-35). Dower has express disclosure of each nucleotide bearing its own distinct label (Dower, col. 23, ll. 22-24 ("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 . . .")).

Illumina also points to disclosure in Dower, which is said to describe a label attached to a base of a nucleotide (Petition 20).

> FIG. 9 schematically illustrates the synthesis of a generic protected nucleotide. A suitable nucleotide is labeled with the FMOC fluorescently detectable label by reaction under the conditions described, e.g., in Ser. No. 624,114 filed Dec 6, 1990, FMOC-Cl, and H_2O. A protection moiety will be added using conditions also described there.

(Dower, col. 18, l. 64-col. 19, l. 2.)

Figure 9 is reproduced below:

[8] http://www.thefreedictionary.com/unique. Accessed February 9, 2013.

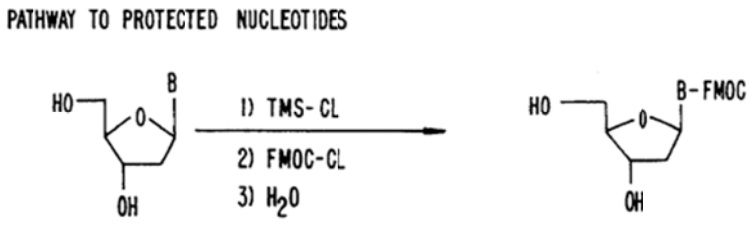


Figure 9 shows a fluorescent label, FMOC, attached to the base of a nucleoside. Dower states that "the FMOC may be attached to adenine, cystosine [sic, cytosine], or guanine" (Dower, col. 5, ll. 35-37), and thus, has express disclosure of a unique label attached to the base of a nucleotide as required by claim 1.

B. "small removable chemical moiety capping the 3'-OH of the sugar"

Illumina provided factual support for its contention that Dower describes a small removable chemical moiety at the 3'-OH of the sugar (Petition 21). This evidence includes the following disclosures:

> For a nucleic acid, a unit for addition would typically be a single nucleotide. . . . To prevent elongation by a unit length greater than one monomer, the nucleotide should be blocked at the position of 3' elongation. Usually, the nucleotide will be blocked at the 3' hydroxyl group where successive nucleotides would be attached.

(Dower, col. 15, ll. 25, 33-37.)

> . . . typically the blocking agent will be a reversible blocking agent thereby allowing for deblocking and subsequent elongation.

(*Id.* at col. 15, ll. 38-40.)

> Appropriate blocking agents include, among others, light sensitive groups such as 6-nitoveratryloxycarbonyl (NVOC), 2-nitobenzyloxycarbonyl (NBOC), α,α-dimethyl-dimethoxybenzyloxycarbonyl (DDZ), 5-bromo-7-

> nitroindolinyl, o-hydroxy-2-methyl cinnamoyl, 2-oxymethylene anthraquinone, and t-butyl oxycarbonyl (TBOC).

(*Id.* at col. 18, ll. 52-77.)

C. Discussion

In its preliminary comments, Columbia argued, unsuccessfully, that Dower is not anticipatory because there is no single example of a nucleotide with both structural features [1] and [2]. However, a single example is not required to establish anticipation. *In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *WM. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361-62 (Fed. Cir. 2012). For a prior art reference to anticipate a claim, it must disclose all of the limitations of the claim, "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008).

With respect to limitation [2], Dower expressly describes blocking the 3'-OH group of the sugar molecule in order to halt polymerase catalyzed elongation of the primer strand (Dower, col. 15, ll. 35-37 (reproduced above)). The blocking group is, thus, necessary for Dower's one-step process (*id.* at Fig. 8; col. 23, ll. 26-30). The nucleotide must also be detectably labeled in order to determine whether it was added to the primer end. Thus, the reversibly blocked nucleotide must be labeled as recited in limitation [1] of claim 1. Dower expressly teaches a nucleotide detectably labeled on a base, for example, as shown in Figure 9 (*id.* at col. 5, ll. 35-37; col. 18, l. 64-col. 19, l. 2; Figure 9). While Figure 9 does not depict the nucleotide with a blocked 3'-OH group, the skilled worker would have understood that a blocked nucleotide is needed to carry out Dower's process (*see infra*).

Columbia did not respond substantively to the patentability challenge of claims 1-3 based on Dower under 35 U.S.C. § 102 in their subsequent response under 37 C.F.R. § 42.120. The evidence as outlined above persuades us that Illumina has met its burden of proof by a preponderance of the evidence in showing that claims 1-3 of the '575 Patent are anticipated by Dower under 35 U.S.C. § 102.

Claim 6

Claim 6 depends from claim 1, and further recites that the sequencing method employs a nucleotide which comprises a deazapurine as a base. Dower is not said by Illumina to expressly describe a deazapurine base in its written disclosures. Rather, Illumina contends a nucleotide with a deazapurine is present by virtue of the incorporation by reference to the Prober I publication by Dower. "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." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). When making such determination, the standard "of one reasonably skilled in the art should be" applied. *Id.* at 1283.

The following passages were cited in the Decision on Rehearing to establish that Dower incorporated Prober I for its teaching a deazapurine base.

> 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.

(Dower, 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.)

> (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.

(*Id.* at col. 25, ll. 41-47.)

Upon reconsideration, we agreed with Columbia that Prober I is <u>not</u> incorporated by reference into Dower for a teaching a deazapurine base in a nucleotide with a reversible 3'-OH cap (Paper 44, Dec. Reh'g 6-9.) The primary flaw is that Prober I's nucleotides with the deazapurine substituent have an irreversible 3'-OH blocking group (chain terminating dideoxy ddNTPs) because they were employed in chain terminating sequencing. Illumina did not identify a teaching in Dower where Dower describes using Prober I to modify Dower's nucleotides with a reversible 3'-OH capping group.

With respect to col 23, ll. 18-24 of Dower, Dr. Trainor testified:

> [T]he material being referenced in Dower in the phrase "where each of four dNTP analogues is identified by a distinct dye" is <u>only the description of the four distinct dyes</u> used to label four

> ddNTPs. The only dNTPs described in Prober I are unlabeled nucleotides which are used with four labeled ddNTPs in a Sanger dideoxy sequencing experiment. Since there is no disclosure in Prober I of labeled dNTP analogues, one of ordinary skill would not have understood the referenced material to be dNTP analogues identified by distinct dyes, but only the four dyes used to label the ddNTPs.

(Ex. 2033, Trainor Decl. ¶ 52.)

We agree with Dr. Trainor's analysis and conclusion.

Similarly, we agree with Dr. Trainor that Dower's disclosure at col. 25, ll. 4-10, is not adequate because it appears to be only a description of the conditions that one of ordinary skill in the art would use to accomplish the polymerase reaction, and not of using the analogues themselves (Ex. 2033, Trainor ¶ 54). In addition, the passage cited at column 24, lines 41-47, is also inadequate because it only concerns the four fluorescently labeled, dideoxy ddNTP chain terminators described in Prober I (*id.* at ¶ 56).

At col. 25, ll. 41-64, Dower describes an alternative (c). This embodiment refers to nucleotides that have irreversible blocking groups on the 3'-OH position of the sugar, and thus, do not teach using Prober I's deazapurine in nucleotide with a reversible 3'-OH group as claimed (Ex. 2033, Trainor ¶ 57).

Illumina cites to column 15, lines 37-40 of Dower, which states: "In contrast to a dideoxy nucleotide, typically the blocking agent will be a reversible blocking agent thereby allowing for deblocking and subsequent elongation." Illumina states this disclosure supports the position that Dower discloses dNTPs for sequencing synthesis methods (Paper 76, p. 12.) We agree with this statement, but the issue is whether the disclosure of SBS nucleotides with reversible 3'-OH caps coupled to the reference to Prober's

dideoxy irreversibly capped ddNTPs having a deazapurine base is a description of the claimed nucleotide analogue having a deazapurine base with a reversible 3'-OH cap. Illumina has not pointed to anything convincing in Dower that teaches replacing Dower's dideoxy terminated nucleotide with a removable 3'-OH cap or vice-versa.

Accordingly, we find that Illumina has not established by a preponderance of the evidence that Dower anticipates claim 6.

IV. TSIEN

We instituted *inter partes* review of claims 1-3 based on Tsien as an anticipatory publication. Tsien describes a method of sequencing DNA (Tsien, p. 6, ll. 28-30). The method involves the sequential addition to a primer of labeled nucleotides (dNTP), each with a different detectable label attached to it (*id.* at p. 7, ll. 3-14; p. 10, ll. 7-10; p. 14, ll. 12-26). Tsien describes the claimed [1] detectable label attached to a base (*id.* at p. 10, ll. 10-15; Tsien, p. 27, l. 33 to p. 28, l. 2; p. 28, ll. 5-6), in addition to other locations on the nucleotide analogue (p. 26, ll. 2-5; p. 26, ll. 17-19). Tsien also describes "[2] a small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue" to prevent inadvertent multiple additions during the sequencing method (*id.* at p. 12, ll. 27-29).

Columbia had argued in the Preliminary Response that "the large number of alternative approaches and features disclosed by Tsien form a 'genus' of many possible methods, from which the specific method of claim 1 cannot be immediately envisaged." (Paper 22, Preliminary Response 16.) We agreed that there were choices to be made, but find that each selection is made from a defined set of possible choices. Citing *Wrigley*, 683 F.3d at

1361-62, in which anticipation was found where each of the specific ingredients in the claimed formula was recited in a longer list of alternative agents, we determined that there was a factual and legal basis on which Illumina would prevail in establishing anticipation by Tsien of claims 1-3, despite the need for choosing (Paper 26, Dec. Pet. 16).

Columbia did not respond substantively to the patentability challenge of claims 1-3 based on Tsien under 35 U.S.C. § 102 in their subsequent Patent Owner Response. The evidence as outlined above persuades us that Illumina has met its burden of proof by a preponderance of the evidence in showing that claims 1-3 of the '575 Patent are anticipated under 35 U.S.C. § 102 by Tsien.

V. TSIEN AND PROBER

We instituted *inter partes* review of claim 6 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.

A. Claim 6

Claim 6 is drawn to the nucleic acid sequencing method of claim 1, and further recites that at least one of the labeled bases is a "deazapurine." We instituted *inter partes* review of claim 6 under 35 U.S.C. § 103 as obvious in view of Tsien and Prober I.

A nucleotide analogue of claim 6 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. Features 1) and 2) are said to be described by Tsien. Prober I describes deazapurines. The issue to be decided is whether it would have been obvious to one of ordinary skill in the art to have used Prober I's deazapurines in Tsien's sequencing method.

B. Tsien and Prober I disclosures

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 structures 1) and 2) are described in Tsien (*see also* Pet. 31-38 (where Illumina cited disclosure from Tsien to meet the claim limitations).

> 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

> 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. 5-6.)

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.

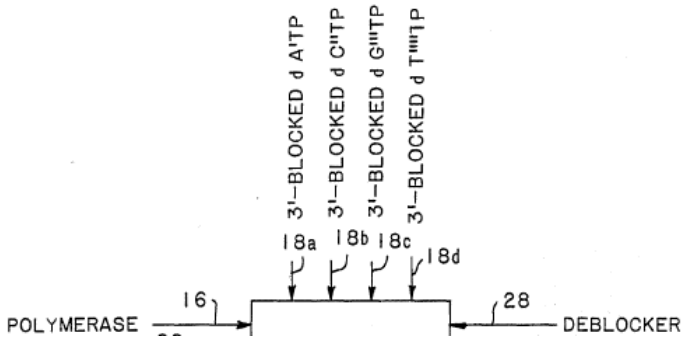
(*Id.* at p. 13, ll. 17-19.)

> 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. 25-26.)

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) (*id.* at 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:

> 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.

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 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 (Ex. 1021, Weinstock Decl. ¶ 83).

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.

> 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. See Tsien, page 28, lines 5-18. The combination of Tsien and Prober I would additionally offer the benefit of the "stable linker arm attachment" taught by Prober I. Prober I, p. 337, col. 1.

(Ex. 1021, Weinstock Decl. ¶ 85)

D. Discussion

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 70, PO Resp. 15-16).

Columbia's 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." (Petition 37.) 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 described above.

Columbia identified five differences between the nucleotide described in Tsien and the nucleotide recited in claim 6 (Ex. 2033, Trainor Decl. ¶ 79), The differences, as stated in Dr. Trainor's Declaration, are as follows:

> 1. remove the labels from the 3'-OH capping group of the sugars and place them on the bases;
> 2. include removable chemical capping groups that did not include labels on the 3'-OH of the sugar;
> 3. attach four unique labels to the bases;
> 4. change at least one purine base to a deazabase; and
> 5. retain the property of being incorporated onto a primer extension strand.

(Ex. 2033, Trainor Decl. ¶ 79.)

We address these differences below:

Deaza-substituted nucleotide (No. 4 in Ex. 2033, Trainor Decl. ¶ 79)

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' (Exhibit 2033, Trainor Decl., ¶88-96.)" (Paper 70, PO Resp. 20). 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. ¶ 91). 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." (*Id.* at p. 26, ll. 17-19). After describing approaches to label the 3'-OH blocking group, Tsien goes on to write 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 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 subsequently Tsien discloses C-8 position of the nucleotide base as "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 F3d 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 I's analogues to be useful, 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. ¶ 79)

In his Declaration, Dr. Trainer testifies that to have arrived at the claimed nucleotide analogues from Tsien, a person of ordinary skill would have had to change the identical labels on the pyrimidines to unique labels. Tsien has express disclosure on using different reporter groups on each dNTP.

> 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. 8-12.)

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.

Removable chemical moiety capping the 3'-OH group of the sugar (No. 2 in Ex. 2033, Trainor Decl. ¶ 79)

In paragraph 87 of his declaration, Dr. Trainor mentions one difference between Tsien and the claimed nucleotide analogues 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. Trainer (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, 1-13; No. 5 in Ex. 2033, Trainor Decl. ¶ 79).

> *Was there a reason to move the label from the 3'-OH group to the base? (No. 1 in Ex. 2033, Trainor Decl. ¶ 79)*
>
> 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 70, PO Resp. 17). 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." (Trainer Decl. ¶ 70). 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 position. 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, as shown 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 I teaches chain terminating nucleotides that lack a removable group. But Prober I was relied upon only 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 ¶¶ 26-28), 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. ¶ 106). 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

[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.

testing for activity. Dr. Trainor did not explain how these results with different nucleotides than those which are claimed make it unpredictable that two structures (3-OH cap and base-label) 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 (Ex. 2033, Trainor Decl. ¶ 106). 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 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) (Ex. 2033, Trainor Decl. ¶ 106). According to Dr. Trainor, Welsh showed that preliminary tests of compounds 1a and 1b as polymerase substrates did not show evidence of incorporation (*id.* at ¶ 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

[10] Bruno Canard et al., *DNA polymerase fluorescent substrates with reversible 3'-tags*, 148 GENE 1-6 (1994), Exhibit 2030.

sufficient evidence to establish that it was unpredictable to have used the claimed nucleotide analogue 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 disclose 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 70, PO Resp. 18-19), Furthermore, Dr. Trainor testifies that Prober I's nucleotides cannot be modified to include a removable 3'-OH group (Ex. 2033, Trainor Decl. ¶¶ 98-99). Dr. Trainor concludes that new chemical procedures would have been needed, the development of which were complex and fraught with difficulties (*id.* at ¶ 101).

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

VI. TSIEN AND SEELA I

We instituted *inter partes* review of claim 6 on the grounds that the Columbia claims would have been obvious under 35 U.S.C. § 103 in view of Tsien and Seela I. Columbia in their response under § 41.120 states the

claim is patentable for the same reasons discussed in the section on Tsien and Prober I (Paper 70, p. 22).

VII. 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 City*, 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 (Fed. Cir. 2013) (internal quotations and citation 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) (citing *Stratoflex*, 713 F.2d 1538-39).

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 nucleotide analogues and methods would be successful; and (6) Illumina attempted to license the challenged patents (Paper 70, p. 24). We have considered this evidence, but do not find it persuasive.

A. "unexpectedly improved properties"

Relying on data in Ju's 2006 publication[11] 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 nucleotide analogues "have revolutionized the DNA sequencing industry." (Ex. 2033, Trainor Decl. ¶¶ 191-92). Specifically, Dr. Trainor testified that Ju's results show that the sequencing with the claimed nucleotide analogues are unexpectedly better than pyrosequencing by facilitating clear identification of all 20 nucleotides in the DNA template while pyrosequencing did not (*id.* ¶¶ 193-196). 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.* ¶ 195). Dr.

[11] 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.

Trainor further cited additional publications said to have reported similar successes (*id.* ¶¶ 198-199).

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 substrates." (Ju, p. 19635 (Exhibit 2034).) 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. (Trainor Decl. ¶¶ 192 and 195). Claims 1 and 6 of the '575 Patent are drawn to methods which have a nucleotide with the removable capping group and the fluorophore label on the base, but do not require that the label be cleavable. Thus, the evidence is not commensurate with the full scope of the claims.

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. *Id.* 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. *Id.* at 391. The court concluded that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Id.* at 392. Likewise, Tsien has a written description of a nucleotide 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 6 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. ¶ 201). 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 ¶ 202.) 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. (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, ll. 14-20).

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." (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. *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 the Tsien and Dower publications. Columbia introduced evidence that Illumina's SBS products included nucleotide analogues with a removable chemical moiety capping 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. ¶¶ 213-214). A nucleotide analogue with the latter two features is embodied by claim 6 of the '575 patent. These Illumina products are also the subject of a patent infringement action by Columbia against Illumina (Paper 70, PO Resp. 34).

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 Tech. Inc.*, 463 F3d 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, Trainer Decl., ¶ 219-222.) Dr. Trainor also testified these commercial nucleotide analogs have a removable chemical moiety capping the 3'-OH group of the nucleotide sugar (*id.* at ¶ 223-227). Dr. Trainor reproduced a nucleotide which appears to be a C-substituted guanine at position 7 as it would be for deazapurine, although Dr. Trainer did not provide specific testimony in support (*id.* at ¶ 224). To the extent the nucleotides used by Illumina are not deazapurines, a nexus is not established because claim 6 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. ¶ 231). Dr. Barnes's email was written in 2006 at the time Mr. Sims[12] stated Illumina entered the SBS sequencing market with its 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, stating it "is part of a jigsaw." (Ex. 2033, Trainor Decl. ¶ 232-233; 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 – [1] a cleavable chemical group capping the 3'-OH position of the sugar and [2] a label attached to the nucleotide base via a cleavable linker" were responsible for the nucleotides success. (Ex. 2033, Trainor Decl. ¶¶ 190, 214, and 217). 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

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

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 6. 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 § 42.120 (Paper 70, 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.

In addition to this, Columbia argues that the success is due to a label attached to the base by a cleavable linker. However, the claim 6 does not require a cleavable linker in this position. Commercial success cannot be established by relying on an unclaimed feature. *Ormco Corp.*, 463 F.3d at 1312.

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 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 label 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." (Tsien, 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*, 713 F.2d at 1539.

In this case, Columbia provided evidence that Illumina sought to license the technology developed by Dr. Ju (Paper 70, PO Resp. 34-38). Columbia states that it elected to license the technology to another company, not Illumina (*id.* at p. 37). Subsequently, Columbia states that Illumina had discussions about acquiring the company which gained a license to Ju's technology (*id.*). Columbia states that Illumina tried to acquire the licensed technology just prior to Columbia suing Illumina for patent infringement (*id*). 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 relevance.

Columbia has direct knowledge of Illumina's licensing attempts (Paper 70, PO Resp. 34-38). While Illumina never licensed the technology, Columbia argued that this was because Columbia had licensed to another company. Nonetheless, based on statements by Illumina's witness Dr. Barnes and their 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 claim 6 is unpatentable over the combination of I) Tsien and Prober I; and II) Tsien and Seela I.

MOTIONS

VIII. COLUMBIA'S MOTION TO AMEND

A motion to amend the claims under 37 CF.R. § 42.121 was filed by Columbia on June 25, 2013 (Paper 56). In the motion, Columbia proposed cancelling claims 1-6 and replacing them with claims 7-11 (*id.* at 4). Proposed claim 7 is identical to original claim 6, rewritten in independent form and reciting all of the features of original claim 1. Proposed claims 8-11 are identical to original claims 2-5, respectively, except that they depend directly or indirectly from proposed claim 7 and therefore also incorporate the feature of original claim 6.

Claim 7 is drawn to the identical subject matter as claim 6. Since claim 6 is already under *inter partes* review, it is unclear why claim 7 is necessary or how it is a response to a ground of unpatentability under 37 C.F.R. § 42.121(a)(2)(i). It is merely duplicative to a claim already under *inter partes* review.

In any event, 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.

IX. 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 do 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. at 48,767.)" (Paper 93, 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 No. 46.)

We have determined there was a reason to have made the claimed nucleotide analogues 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 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 reply (Paper 76, p. 2) to Columbia's response under § 42.120 (Paper 70).

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.

X. 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.

XI. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1-3 and 6 of U.S. Patent 8,088,575 B2 are cancelled;

FURTHER ORDERED that Columbia's motion to amend claims is dismissed as moot;

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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