

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.
Petitioner,

v.

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

Case IPR2012-00007
U.S. Patent 7,790,869

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

LEBOVITZ, *Administrative Patent Judge*.

**DECISION ON PETITION FOR
INTER PARTES REVIEW UNDER 35 U.S.C. § 311**

Columbia Exhibit 2036
Illumina, Inc. v. The Trustees of Columbia
University in the City of New York
IPR2018-00322

This is a decision on a petition¹ under 35 U.S.C. § 311 challenging the patentability under 35 U.S.C. §§ 102 and 103 of claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Pat. 7,790,869 B2. We have jurisdiction to decide the petition under 37 C.F.R. § 42.4(a) and 42.4(a). Pursuant to 35 U.S.C. § 314, we authorize inter partes review to be instituted on all of the challenged claims as follows:

I. Claims 12, 13, 17, 20-26, 28, 29, 31, and 33 under 35 U.S.C. § 102(b) as anticipated by Tsien.²

II. Claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I.³

III. Claims 12, 13, 17, 20-23, 25, 26, 28, 29, and 31 under 35 U.S.C. § 102(a) as anticipated by Stemple II.⁴

IV. Claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Stemple II and Anazawa.⁵

STATEMENT OF THE CASE

Illumina petitions under 35 U.S.C. § 311 to institute inter partes review of U.S. Patent 7,790,869 (“the ‘869 patent”) (Exhibit 1001). Petition 2. In their petition under 35 U.S.C. § 312, Illumina identifies 19 different

¹ Petition for Inter Partes Review of U.S. Pat. No. 7,790,869, dated September 16, 2012. Paper 5.

² Roger Tsien et al., WO 91/06678 (May 16, 1991), Exhibit 1002.

³ James Prober et al., A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides, 238 Science 336 (1987), Exhibit 1003.

⁴ Derek Stemple et al., WO 00/53805 (September 14, 2000), Exhibit 1007.

⁵ Takeshi Anazawa et al, WO 98/33939 (August 6, 1998), Exhibit 1010, citations are to English translation, Exhibit 1011.

grounds challenging the patentability under 35 U.S.C. §§ 102 and 103 of claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of the ‘869 patent. *Id.* at 5-8. Based on the prior art cited in each grounds, Illumina contends that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of the ‘869 patent invalid. The Patent Owner of the ‘869 patent is The Trustees of Columbia University in the City of New York (“Columbia”). Columbia filed a Preliminary Response under 37 C.F.R. § 42.107 to Illumina’s patentability challenge.⁶

The ‘869 Patent

The ‘869 patent issued September 7, 2010. It is subject to a terminal disclaimer. The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. The invention of the ‘869 patent involves sequencing DNA by incorporating a nucleotide analogue into a strand of newly synthesized DNA, and then detecting the identity of the incorporated analogue. A polymerase is used to incorporate the nucleotide analogue into the strand of DNA. ‘869 Patent, col. 2, l. 58 to col. 3, l. 3. The method is generally referred to as “sequencing DNA by synthesis” because the *sequence* of the DNA is determined by identifying the successive additions of labeled nucleotides to a newly *synthesized* strand of DNA. *Id.* at col. 2, ll. 8-12. The sequence is determined as the DNA is synthesized – using a complimentary DNA strand as a template to direct DNA synthesis. The claims of the ‘869 patent are directed to a nucleotide utilized in the DNA sequencing method.

⁶ Columbia’s Preliminary Response under 37 C.F.R. § 42.107. Paper 27 (December 21, 2012).

The '869 patent is the subject of the litigation styled *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 4. According to Illumina, Columbia alleges in that litigation that Illumina has infringed and continues to infringe the '869 patent. *Id.*

Related petitions for inter partes review

There are two pending inter partes petitions which are related to this petition for inter partes review of the '869 patent.

A petition for inter partes review was filed on September 16, 2012 in U.S. Pat. No. 7,713,698 B2 (“the ‘698 patent”).⁷ The ‘698 patent has the same lineage as the ‘869 patent, including tracing its ancestry back to a continuation-in-part of application of Appl. No. 09/684,670, filed October 6, 2000 and a provisional application filed June 26, 2001.

A petition for inter partes review was filed on October 3, 2012 in U.S. Pat. No. 8,088,575 B2 (“the ‘575 patent”)⁸ which is based on a continuation application of the ‘869 patent.

All three petitions have been decided concurrently.

The claims

The ‘869 patent was granted with 31 claims. Illumina challenges the validity of independent claim 12, and dependent claims 13, 15-17, 20-26, 28,

⁷ IPR2012-00006.

⁸ IPR2013-00011.

29, 31, and 33. Claim 12 is reproduced below (bracketed numbering 1-4 added to emphasize certain limitations in the claim):

12. A nucleotide having [1] a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has [2] a deoxyribose comprising a cleavable chemical group capping the 3' OH group, wherein [3] the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and wherein [4] the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.

15. The nucleotide of claim 12, wherein the base is a deazapurine.

16. The nucleotide of claim 15, wherein said deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.

CLAIM INTERPRETATION

Claim 15 recites that the base 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. ‘869 patent, col. 7, ll. 36-63. For example, in a 7-deazapurine (deaza-adenine or deaza-guanine), the natural 7-position nitrogen in the base ring is replaced with a carbon atom. *Id.*

1. ANTICIPATION

Claim 12 is directed to a nucleotide comprising the following features:

[1] a base that is attached to a detectable label through a cleavable linker; and

[2] a deoxyribose comprising a cleavable chemical group capping the 3' OH group.

Illumina contends that independent claim 12 and various dependent claims are anticipated under 35 U.S.C. § 102(b) by each of Tsien, Dower,⁹ Rabani,¹⁰ Stemple II, and Stemple III.¹¹ Under 35 U.S.C. § 102(b), “a person shall be entitled to a patent unless the invention was patented or described in a printed publication . . . more than one year prior to the date of the application.” “Accordingly, invalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

Illumina, as the moving party, has the burden of proof to demonstrate that there is “a reasonable likelihood that [it] would prevail” in establishing unpatentability of the challenged claims. 35 U.S.C. §§ 311 & 314; 37 C.F.R. § 42.20(c). Thus, Illumina has the burden of establishing that there is reasonable likelihood it would prevail in establishing that the claimed invention of the ‘869 patent is described within the four corners of each of Tsien, Dower, Rabani, Stemple II, and Stemple III. We therefore must look

⁹ William Dower et al., U.S. 5,547,839 (August 20, 1996), Exhibit 1005.

¹⁰ Ely Rabani et al., WO 96/27025 (September 6, 1996), Exhibit 1006.

¹¹ Derek Stemple et al., U.S. 7,270,951 B1 (September 18, 2007), Exhibit 1008.

to the evidence put forth by Illumina in support of their challenge to the patentability of claim 12 and its dependents.

A. Patentability challenge based on Tsien (Petition 21)

Claims 12, 13, 17, 20-26, 28, 29, 31, and 33

Tsien describes a method of sequencing DNA. Tsien, p. 6, ll. 28-30. The method uses 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. Illumina contends that Tsien describes all the limitations of the claimed nucleotide. Petition 21-27.

In the Preliminary Response to the Petition, Columbia challenges Illumina's contention that Tsien describes a "nucleotide having a base that is attached to a detectable label through a cleavable linker." According to Columbia, there is no specific example of a nucleotide having a base that is attached to a detectable label through a cleavable linker. Columbia contends for Tsien to "anticipate claim 12, multiple features selected from different sections" of Tsien "as well as a specific combination of those features, would be required." Preliminary Response 14. Columbia argues that "the required selections and combinations" to have arrived at the subject matter of claim 12 "are contrary to Tsien's preferred selections and combinations." *Id.* Columbia conclude that therefore "[o]ne does not 'at once envisage' the claimed nucleotide from the Tsien disclosure." *Id.*

Specific working examples are not necessary to establish anticipation. For example, a very small genus can be a disclosure of each species within the genus. *In re Petering*, 301 F.2d 676, 682 (C.C.P.A. 1962); see also *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380

(Fed. Cir. 2001) (“[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.”). As held in *Petering*, in order to anticipate, one skilled in the art must be able to “at once envisage” the claimed structure in the disclosure. *Petering*, 301 F.2d at 681. On the other hand, “[i]f the members cannot be envisioned, the reference does not disclose the species and the reference is not enabling.” *Impax Labs., Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (“The ‘624 application does not identify riluzole by name. As found by the district court, riluzole is just one of hundreds of compounds included in formula I. . . . Here, with the large number of compounds included in formula I and no specific identification of riluzole by the ‘624 application, the ‘624 application does not disclose riluzole . . .”)

The evidence supports Columbia’s contention that there is no specific example of a nucleotide having a base that is attached to a detectable label through a cleavable linker as required by claim 1, feature [1]. However, there are separate disclosures, as acknowledged by Columbia, of 1) a detectable label attached to a *base* (Preliminary Resp. 10: 1-6) and of 2) a cleavable tether or spacer (*id.* at 9: 6-9). Thus, the issue in Illumina’s challenge to the patentability of independent claim 12 based on Tsien is whether there is a reasonable likelihood that Illumina would prevail in establishing that claimed [1] “base . . . attached to a detectable label through a cleavable linker” would be at once envisaged from these disclosures.

We first turn to the specific facts disclosed in Tsien.

Facts (“F”)

F1

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

Tsien, p. 27, l. 33-p. 28, l. 4.

F2

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

Tsien, p. 28, ll. 5-10.

F3

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.

Tsien, p. 28, ll. 19-23.

F4

The C-8 position of the purine structure presents an ideal position for attachment of a label. Sarfati et al. (1987) describes a derivatization of deoxyadenosine at C-8 of the purine to prepare, ultimately, an 8-substituted biotin aldyldamino dATP. The Sarfati et al. (1987) approach can be used to prepare the appropriate fluorescent, rather than biotinylated, analogues. A

number of approaches are possible to produce fluorescent derivatives of thymidine and deoxycytidine. One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags. Structures A, B, C and D below illustrate the type of fluorescent dNTPs that result from these synthetic approaches. The synthetic routes have a great flexibility in that the linker can be varied with respect to length or functionality.

Tsien, p. 29, pp. 3-19.

Analysis

Claims 12, 13, 17, 20-26, 28, 29, 31, and 33

There are two key disclosures that have been relied upon by Illumina in its contention that claim 12 is anticipated by Tsien. Both are factually supported.

First, Illumina cites explicit disclosure in Tsien of incorporating a fluorescent label into a base (F1, F2, & F4).

Second, Illumina cites to Tsien's disclosure of attaching a detectable label to a nucleotide through a cleavable spacer or tether (F3). The spacer or tether corresponds to the claimed "linker."

What is missing is an express statement by Tsien to use the cleavable linker to attach the fluorescent label to the base. However, Tsien describes linkers as useful to attach a label to a nucleotide (F3 & F4). The base of the nucleotide is expressly taught as a position where labels can be attached (F1). Consequently, the skilled worker would have been guided to use the linker to attach the fluorescent label to the base of the nucleotide. Thus, while there is no specific example of a base that is attached to a detectable label through a cleavable linker, it would have been envisaged clearly by one of ordinary skill in the art upon reading the Tsien disclosure, particularly the disclosures at F1-F4.

Columbia points to more general disclosure in the Tsien patent as to where the linker and detectable label could be attached to the nucleotide. Preliminary Response 9-11 & 12-13. However, Columbia has not explained how this more general disclosure would detract from the more specific disclosures of F1 to F4 that comprise an immediately envisaged description of the nucleotide of claim 12. Accordingly, we find that the evidence as a whole establishes a reasonable likelihood, the pertinent standard under 35 U.S.C. § 314, that Illumina would prevail in showing that claim 12 is anticipated by Tsien. Accordingly, we authorize an inter partes review of claims 12 to be instituted with respect to Illumina's patentability challenges based on Tsien as anticipatory reference.

With respect to claims 13, 17, 20-26, 28, 29, 31, and 33, Illumina identified specific disclosure in Tsien where each limitation is found. Petition 22-26. We find Illumina's assertions to be factually supported, and authorize an inter partes review of claims 13, 17, 20-26, 28, 29, 31, and 33 to be instituted with respect to Illumina's patentability challenge based on Tsien as anticipatory reference.

Claims 15 and 16

Claim 15 is dependent on claim 12 and reads as follows:

15. The nucleotide of claim 12, wherein the base is a deazapurine.

Claim 16 is dependent on claim 15.

Tsien is not said by Illumina to disclose a deazapurine nucleotide expressly. Rather, Illumina contends that the nucleotides are present by virtue of the incorporation of the Prober I publication by Tsien which is said to disclose a deazapurine. Petition 23-24. Tsien refers to a disclosure by

Prober I which is said by Illumina to disclose a deazapurine base as claimed. The passage in Tsien said by Illumina to describe deazapurine nucleotides is reproduced below:

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) show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™[.]

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

An anticipatory document must “disclose all elements of the claim within the four corners of the document” and “arranged as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). However, “[m]aterial not explicitly contained in the single, prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document.” *Advanced Display*, 212 F.3d at 1282. Accordingly, the question before us is whether Illumina met its burden in establishing that Prober I is incorporated into Tsien in a manner that complies with the requirement of 35 U.S.C. § 102, i.e., that the invention be described within the four corners of the anticipatory reference.

Advanced Display 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.” *Advanced Display*, 212 F.3d 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).

Under *Advanced Display*, it must be clear that Prober I is being cited in Tsien for its disclosure of deaza-substituted nucleotides. Illumina did not meet its burden in establishing this fact.

Tsien does not indicate that Prober I is being referenced for its teaching of a deazapurine nucleotide. Tsien refers to Prober I for its teaching that fluorescent ddNTPs can be incorporated by two different enzymes, but did not identify the fluorescent ddNTPs as comprising a deazapurine base as recited in claim 15, or point to a passage in Prober I where the latter could be found.

Illumina points to Tsien’s disclosure on page 3, lines 13-16, “that the documents identified in the specification are to be used ‘for their teaching of synthetic methods, coupling and detection methodologies, and the like.’” Petition 26. However, such generic disclosure does not remedy Tsien’s failure to identify deazapurine nucleotides as the specific teaching incorporated by its reference to Prober I.

Illumina provided testimony by Dr. George Weinstock¹² that Prober I is incorporated by Tsien for “its teaching regarding attachment of a linker to

¹² Dr. Weinstock received a Ph.D. in Microbiology from the Massachusetts Institute of Technology in 1977. Weinstock Decl. ¶ 4 (Exhibit 1021) (dated Sept. 15, 2012). At the time the declaration was executed, Dr. Weinstock was Professor of Genetics and a Professor of Molecular Microbiology and Associate Director of The Genome Institute at Washington University

the 7 position in the 7-deazapurine,” but these words do not appear in Tsien. Weinstock Decl. ¶ 63. Dr. Weinstock did not provide a factual basis for his testimony as to why this teaching would have been recognized by one of ordinary skill in the art. *Id.*

Because Illumina did not provide adequate evidence that Tsien clearly identified the deazapurine nucleotides as the material to be incorporated by their reference to Prober I, we find that it is not reasonably likely that Illumina would prevail in establishing that claims 15 and 16 are anticipated by Tsien. Since the proper standard under 35 U.S.C. § 314 was not met, we do not authorize an inter partes review of claims 15 and 16 to be instituted with respect to Illumina’s patentability challenge based on Tsien as an anticipatory publication.

B. Patentability challenge based on Dower (Petition 32)

Illumina contends that Dower describes all the features of the claimed nucleotide. With respect to the claimed requirement of [1] “a base that is attached to a detectable label through a cleavable linker,” Illumina cites the following disclosures:

Nucleotide analogs used as chain-terminating reagents will typically have both a labeling moiety and a blocking agent while remaining compatible with the elongation enzymology.

School of Medicine in St. Louis, Missouri. *Id.* at ¶ 3. Dr. Weinstock stated that he has “over 40 years of experience working in the field of genomics, including over 15 years managing DNA sequencing projects, and first-hand experience in the use of DNA sequencing platforms.” *Id.* at ¶ 8. Dr. Weinstock’s expertise is in DNA sequencing, which is the field of the claimed invention. We therefore find that Dr. Weinstock is qualified to testify in this proceeding.

As the blocking agent will usually be on the 3'hydroxyl position of the sugar on a nucleotide, it would be most convenient to incorporate the label and the blocking agent at the same site, providing for a single reaction for simultaneous removal of the label and blocking agent. However, it is also possible to put a label on another portion of the nucleotide analog than the 3' hydroxyl position of the sugar, thereby requiring a two-step reaction cycle for removing the blocking and labeling groups.

Dower, col. 15, 62 to col. 16, 6.

(b) The fluorophore is placed in a position other than the 3'OH of the nucleoside, and a different group placed on the 3'OH of the dNTPs to function as a chain terminator. The fluorophore and the 3' blocking group are removed by the same treatment in a single step (preferably), or they may be removed in separate steps

Dower, col. 25, ll. 35-40.

The cited disclosures in Dower do not expressly identify a “cleavable linker” as joining the “base” to the “detectable label.” Removal of a detectable label from a nucleotide is described, but such disclosure does not specify that removal occurs at cleavable linker which joins the label to the base. In the absence of such description, there is not a reasonable likelihood that Illumina would prevail in demonstrating unpatentability based on Dower, alone. Since the proper standard under 35 U.S.C. § 314 was not met, we do not authorize an inter partes review to be instituted with respect to Illumina’s patentability challenges based on Dower as anticipatory publication.

C. Patentability challenge based on Rabani (Petition 42)

Illumina contends that Rabani describes all the features of the claimed nucleotide. With respect to the claimed requirement of “a base that is

attached to a detectable label through a cleavable linker,” Illumina cites the following specific disclosures from Rabani:

Labeling moieties are favorably in communication with or coupled to nucleotides via a linker of sufficient length to ensure that the presence of said labeling moieties on said nucleotides will not interfere with the action of a polymerase enzyme on said nucleotides.

Rabani, p. 32, ll. 10-13 (emphasis added).

For example, a beam of predetermined frequency may be used to effect the photobleaching of the labeling moiety on a particular sample molecule, to selectively remove a photocleavable protecting group on a particular sample molecule, **to selectively remove a moiety joined to a sample molecule by a photocleavable linker**, or selectively control any photochemical reactions in a highly localized but non-invasive manner.

Rabani, p. 17, ll. 15-21 (emphasis added).

Cleavability may be provided for in a number of ways which will be obvious to those skilled in the arts of organic and synthetic chemistry. For example, said linker may include along its length one or more ester linkages, which will be susceptible to hydrolysis, which may be sufficiently mild for various ester functional groups. Amide linkages may similarly be employed.

Rabani, p. 32,¹³ ll. 24-29.

Analysis

Rabani describes coupling a labeling moiety to a nucleotide using a linker (p. 32, ll. 10-13; p. 17, ll. 15-21), but does not expressly identify the base as the position at which the label and linker are attached. Illumina, in the claim chart on pages 42-43 of the Petition, cites the passages of Rabani reproduced above for disclosure of “a base that is attached to a detectable

¹³ Page 43 of the Petition listed page 34 for this disclosure; however the quoted disclosure appear on page 32.

label through a cleavable linker,” but does not explain – in the absence of explicit disclosure – where or how this limitation is described by Rabani. Consequently, we find that Illumina did not meet its burden in establishing it would prevail in showing that claim 12 is anticipated by Rabani. Since the proper standard under 35 U.S.C. § 314 was not met, we do not authorize an inter partes review to be instituted with respect to Illumina’s patentability challenges based on Rabani as anticipatory publication.

D. Patentability challenges based on Stemple II and Stemple III (Petition 47 and 54)

Illumina contends that Stemple II and Stemple III anticipate the subject matter of claims 12, 13, 15-17, 20-26, 28, 29, 30, 31, and 33 of the ‘869 patent. Columbia did not respond to Illumina’s evidence of unpatentability in view of Stemple II and Stemple III. We address the sufficiency of Illumina’s evidence below.

Claim 12

Illumina states that Stemple II utilizes chain terminating nucleotides that include a blocking group at the 3'-OH of the ribose (limitation [2] of claim 12] and a fluorescent label attached to the nucleotide base (limitation [1] of claim 12). Petition 48. To illustrate this teaching, Illumina relied upon Figure 1B of Stemple II. Figure 1B, as annotated by Illumina with arrows and boxes, is reproduced below. This figure appears in Stemple III, as well.

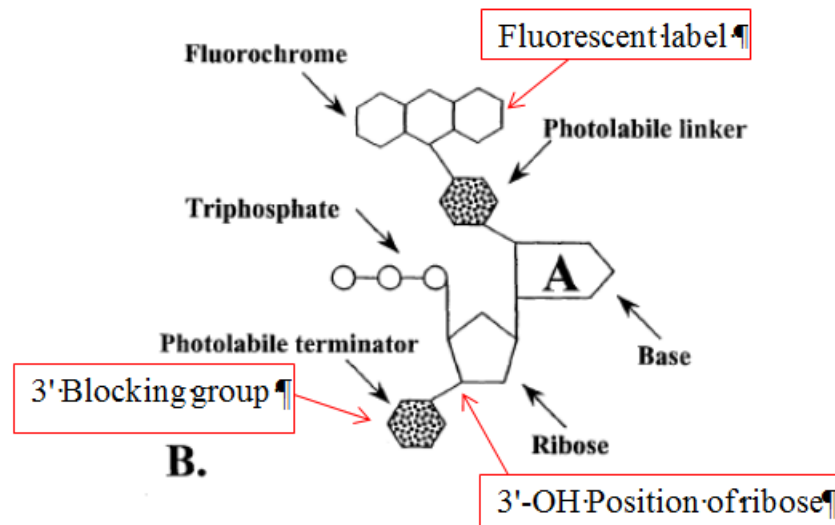


Figure 1B shows the following elements of claim 12:

- [1] a base (“Base”) that is attached to a detectable label (“Fluorochrome”) through a cleavable linker (“Photolabile linker”);
- [2] a deoxyribose (“Ribose”) comprising a cleavable chemical group capping the 3' OH group (“Photolabile terminator”);

[3] & [4], the claimed “cleavable linker” and “cleavable chemical group correspond to Stemple II’s Photolabile linker and Photolabile terminator, respectively, are each removed by illumination and thus are cleaved by light as recited in claim 12. Stemple II, p. 14, ll. 28-30. Stemple II also discloses that “[t]he labeling group and the 3’ blocking group can be removed enzymatically, chemically, or photolytically.” Stemple II, page 4, ll. 8-9; Petition 49.

Thus, Illumina’s evidence that claim 12 is anticipated by Stemple II is supported by factual evidence. Accordingly, we find that Illumina has met its burden to establish a reasonable likelihood, the pertinent standard under

35 U.S.C. § 314, that they will prevail in showing that claim 12 is unpatentable under 35 U.S.C. § 102 as anticipated by Stemple II.

With respect to claims 13, 17, 20-23, 25, 26, 28, 29, 30, and 31, Illumina identified specific disclosure in Stemple II where each limitation is found. Petition 50-53. We find Illumina's assertions to be factually supported, and authorize an inter partes review of claim 13, 17, 20-23, 25, 26, 28, 29, 30, and 31 to be instituted with respect to Illumina's patentability challenge based on Stemple II.

Claims 15 and 16

Claim 15 is directed to the nucleotide of claim 12, wherein the base is a deazapurine. Stemple II is not said by Illumina to expressly disclose deazapurine. Rather, Stemple II refers to a disclosure by Anazawa which is said by Illumina to disclose a 7-deaza-guanine base – a deazapurine as claimed. Petition 50.

Anazawa [footnote omitted] discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. Fig. 7 and page 5, l. 36 - page 6, line 9 (also citing "Science 238, 336 – 341, 1987," i.e. Prober I).

Id. at 50-51.

The complete passage in Stemple II said by Illumina to describe a deazapurine is reproduced below:

In an alternative configuration a photolabile group is attached to the 3'-OH using succinimide or other chemistry and **a fluorochrome-photo labile linker conjugate is attached directly to the base of the nucleotide as described by** Anasawa [sic, Anazawa] et al., WO 98/33939. The 3' attached photolabile group will serve as a reversible chain terminator [Metzker, et al., Nucleic Acids Res 22: 4259-4267 (1994)] and the base-attached fluorochrome-photo labile linker will serve as

a removable label. In this configuration with each cycle both photo labile groups will be removed by photolysis before further incorporation is allowed.

Stemple II, p. 31, ll. 10-18 (emphasis added).

Illumina argues:

In particular, Stemple II states that labels should be attached to the base using the method disclosed in Anazawa. The method of Anazawa converts the 7 position of purines to a carbon (making them “deaza”) to increase the stability of the nucleotide. Thus, following the method of Anazawa as instructed by Stemple II necessarily requires the use of deaza bases.

Petition 53-54.

The question before us is whether Illumina met its burden in establishing that Anazawa is incorporated into Stemple II in a manner that complies with the requirement of 35 U.S.C. § 102, i.e., that the invention be described within the four corners of the anticipatory reference.

Stemple I clearly references Anazawa for teaching a detectable label attached to a base by a cleavable linker. *See* passage reproduced above. However, Stemple II does not state that the linker is attached to deazapurine, i.e., a purine base in which nitrogen has been substituted with a carbon. Nor does Stemple II “clearly indicate where that material is found” as required under *Advanced Display*. To make up for this deficiency, Illumina argues “following the method of Anazawa as instructed by Stemple II necessarily requires the use of deaza bases.” However, this is a conclusory statement without evidentiary support. Because there is insufficient evidence to support its patentability challenge based on Stemple II, we find that there is not a reasonable likelihood that Illumina would prevail in establishing that claims 15 and 16 are anticipated by the publication. Since the proper

standard under 35 U.S.C. § 314 was not met, we do not authorize an inter partes review to be instituted with respect to Illumina's patentability challenge of claims 15 and 16 based on Stemple II as anticipatory publication.

Claims 24 and 33

Claim 24 depends on claim 23, and further recites "wherein said [nucleic acid] template is immobilized on a solid surface." Claim 33 depends on claim 24. In the related IPR2012-00006 of U.S. Pat. No. 7,713,698 B2 ("the '698 patent"), we construed "immobilized on a solid surface" to mean "that the DNA, itself, is affixed to the solid surface without intervening structures." IPR2012-0006 Decision on Petition, pp. 7-8. The '869 patent has the same patent application lineage as the '698 patent. The specifications appear to be the same, as well. We therefore adopt the construction of "immobilized" set forth in the Decision on Petition in IPR2012-0006. Under this construction, Stemple II does not meet the limitations of claims 24 and 33 because the nucleic acid in Stemple II is immobilized on a solid surface through the intervening structure of the DNA polymerase. IPR2012-0006 Decision on Petition, pp. 14-17. Accordingly, we do not authorize an inter partes review to be instituted with respect to Illumina's patentability challenge of claims 24 and 33 based on Stemple II as anticipatory publication.

E. Patentability challenge based on Stemple III (Petition 54)

Stemple II is a PCT application published September 14, 2000 having an international filing date of March 10, 2000 and claiming priority to U.S.

Application Serial No. 09/266,187, filed March 10, 1999. Stemple III is US 7,270,951 B1, a national phase Application of Stemple II. Illumina relies on substantially the same disclosure for Stemple III as they did for Stemple II. The evidence does not show that Stemple III is any more complete than Stemple II in providing a description of the claimed subject matter. The claim chart showing the correspondence between the claim limitations and the Stemple II and III does not indicate any differences between the two publications. The rejections appear to be duplicative. Accordingly, as the rejection appears to be redundant and based on the same set of facts as Stemple II, we shall not authorize an inter partes review at this time for ground 11 based on Stemple III an anticipatory publication. 37 C.F.R. § 42.108(a). *See also Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM-2012-00003 (Paper No. 7), at *2 (PTAB Oct. 25, 2012) (not proceeding on redundant grounds in absence of meaningful distinction); *see also* 37 C.F.R. § 42.1(b) (“This part [i.e., Part 42 of Title 37, Code of Federal Regulations] shall be construed to secure the just, speedy, and inexpensive resolution of every proceeding.”)

2. OBVIOUSNESS

Illumina cites the Tsien, Dower, Rabani, Stemple II, and Stemple III publications for teaching the claimed nucleotide with a deazapurine base as recited in claims 15 and 16. Contingent upon the Board deciding that Illumina did not meet its burden in establishing the latter publications described the nucleotide with a deazapurine base, Illumina proposed additional grounds of rejection under 35 U.S.C. § 103. These rejections combined each of Tsien, Dower, Rabani, Stemple II, and Stemple III with

either Prober I, Prober II,¹⁴ Hobbs,¹⁵ and Anazawa, the latter which Illumina contends establish that deazapurine nucleotides were known in the art prior to the invention. Based on the combined teachings, Illumina contends there was reason to have made a nucleotide with a deazapurine base.

The patentability challenges to the claims under 35 U.S.C. § 103 each involve the same issue of whether it would have been obvious to have made a nucleotide of Tsien, Dower, and Stemple II & III with a deazapurine base.

To establish obviousness under 35 U.S.C. § 103, the following factors must be taken into consideration: (a) the scope and content of the prior art; (b) the differences between the prior art and the claimed subject matter; (c) the level of skill in the pertinent art; and (d) evidence of secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). 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).

A. Deaza-substituted nucleotides

Illumina contends that the “use of nucleotide analogues including deazapurines was well known in the nucleic acid sequencing field at least as early as the mid-1980s as shown in a wide variety of prior art documents.”
Petition 14. To establish this fact, Illumina cites published scientific journal articles and expert testimony. The evidence cited by Illumina as follows:

(1) Prober I

¹⁴ James Prober et al., U.S. 5,242,796 (September 7, 1993), Exhibit 1004.

¹⁵ Frank Hobbs et al., U.S. 5,047,519 (September 10, 1991), Exhibit 1013.

Prober I describes DNA sequencing methods using fluorescent tagged chain terminating reagents. Prober I, Abstract. Prober I teaches using ddNTP's to which a fluorescent label is attached to the 7-position in a 7-deazapurine. *Id.* at p. 337, col. 1. The modified labeled nucleotides were successfully incorporated into synthesized DNA by T7 DNA polymerase. *Id.* at p. 337, col. 2; p. 340, col. 1.

Prober I teaches at p. 341, column 1:

In practice there are regions of DNA which are difficult to sequence due to aberrations in electrophoretic mobility caused by secondary structure (17). . . 2'-Deoxy-7-deazaguanosine triphosphate has been used (c⁷dGTP) in place of dGTP to minimize these effects.

(2) Prober II

Prober II describes a process for DNA sequencing using a modification of a Sanger chain termination method, where the terminator can be a 7-deazaadenine or 7-deazaguanine which carries a fluorescent marker attached to the 7-position of the deazapurine. Prober II, col. 7, l. 50 to col. 8, l. 39. Prober II teaches that "art shows that . . . the 7-position on purines may carry even a relatively bulky substituent without significantly interfering with overall binding or recognition [R.M. K. Dale et al., *Proc. Nat. Acad. Sci. USA*, 70, 2238-2242 (1973)]. Prober II, col. 18, l. 64 to col. 19, l. 2.

(3) Hobbs

Hobbes describes using deaza-substituted nucleotides (Hobbs, col. 10, line 67 to col. 11, line 11) as chain terminating substrates for DNA sequencing using polymerase (*id.* at Abstract). Hobbs teaches attachment of

a linker to the 7-position of purine nucleotides to “provide labeled chain-terminating substrates that do not interfere excessively with the degree or fidelity of substrate incorporation.” *Id.* at col. 8, ll. 58-61. Hobbs discloses that the nucleotides include a heterocyclic base and that “[p]referred heterocyclic bases include: . . . 7-deazaadenine [and] (j), 7-deazaguanine . . . The unnatural 7-deazapurines can be employed to attach the linker without adding a net charge to the base portion and thereby destabilizing the glycosidic linkage.” *Id.* at col. 10, line 67 - col. 11, line 4.

(4) *Anazawa*

Figure 7 of Anazawa shows a nucleotide 7-deazaguanine (natural nitrogen at position 7 replaced with a carbon) labeled with the fluorescent marker Texas Red at the 7-position. Anazawa (translation), Fig. 7 and p. 6, lines 5-6. Anazawa teaches that the labeled nucleotide “can be incorporated by polymerase-based complementary-chain elongation reactions, as has been confirmed by various experiments.” *Id.* at p. 6, ll. 10-12.

Anazawa [footnote omitted] discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. Fig. 7 and page 5, l. 36 - page 6, line 9 (also citing “Science 238, 336-341, 1987,” i.e. Prober I).

Petition 50-51.

(5) *Weinstock Declaration*

Dr. Weinstock stated:

37. The use of nucleotide analogs including deazapurine, and a label attached at the 7-position thereof, was known in the nucleic acid sequencing field at least as early as the late 1980s.

42. It was widely known to use deazapurine-based nucleotides in the sequencing by synthesis methods at least 10 years prior to the filing date of the '869 patent. See e.g., Dower, Tsien, Stemple II and the references cited therein, including Prober I and Anazawa.

43. Multiple prior art references recognized a number of advantages for using deazapurines as the base in nucleotide analogs for sequencing.

To support paragraph 43, Dr. Weinstock cited specific passages in Seela I,¹⁶ Prober I, Hobbs, and Prober II, which show that deazapurines were used in DNA sequencing and were capable of being incorporated into DNA by polymerase during the sequencing reaction. Weinstock Decl., ¶¶ 43-48 & 51-54.

B. Summary

We credit Dr. Weinstock's testimony and find persuasive the other evidence discussed above which sufficiently establish that 1) DNA sequencing by synthesis was known in the art; and 2) that deaza-substituted nucleotides had been used in DNA sequencing prior to the earliest filing date of the '869 Patent. We note that in the Preliminary Response under 37 C.F.R. § 42.107 Columbia did not dispute Illumina's evidence of 1) and 2) as summarized above. In sum, we find that 1) and 2) are representative of the scope and content of the prior art at the time the '869 Patent was filed.

Reason to combine & analysis

¹⁶ Frank Seela, U.S. 4,804,748 (February 14, 1989), Exhibit 1014.

It is important to have a reason to have combined the cited publications to have arrived at the claimed invention. *KSR*, 550 U.S. at 418. Illumina's reasons for combining the prior art, and the sufficiency of these reasons, are addressed below.

Obviousness based on Tsien

C. Patentability challenge based on Tsien and Prober I (Petition 27)

The issue is whether it would have been obvious to one of ordinary skill in the art to have replaced a nitrogen base of the nucleotide described in Tsien with a deazapurine nitrogen base as taught by Prober I. Illumina's evidence that the modified nucleotide of claim 15 is obvious in view of Tsien and Prober I includes:

- Evidence that deazapurines had been used in DNA sequencing prior to the earliest filing date of the '869 Patent. *Supra* section "A. Deazapurines" (1)-(5); Petition 13-16.

- Specific disclosure by Prober I of a nucleotide comprising a fluorescent label attached to the 7-position of a deazapurine and that such nucleotide could be used in polymerase mediated sequencing. *Supra* section A(1).

- Disclosure by Tsien that Prober I's fluorescent ddNTPs could be incorporated by polymerase into DNA. *Supra* section A(1); Petition 26-28.

Illumina also provided evidence of a reason to have modified Tsien's nucleotides with a deazapurine:

Tsien further states 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. Prober I specifically teaches that nucleotide analogues incorporating 7-deazapurines may be

used in sequencing reactions. In fact, using the synthetic methods of Prober I to attach labels to purine bases requires and necessarily results in the use of 7 deazapurines. See Weinstock Decl. ¶ 66. Thus, it would have been obvious for one of ordinary skill in the art to combine Tsien's teachings with the 7-deazapurine feature disclosed in Prober I because it is merely the use of known techniques to improve similar Tsien systems and methods in the same way that the known features improve the methods and reagents of Prober I, and as expressly taught by Tsien.

Petition 28.

Based on the suggestion of Tsien and the known advantage of using a deazapurine in sequencing as taught by Prober I (see A(1) *supra*), the skilled worker would have had reason to replace the natural nitrogen base of Tsien's nucleotide with a deazapurine to have made the claimed invention. Consequently, we conclude that Illumina has provided sufficient evidence to establish a reasonable likelihood, the pertinent standard under 35 U.S.C. § 314, that they will prevail in establishing that claims 15 and 16 are unpatentable under 35 U.S.C. § 103. Accordingly, we authorize an inter partes review of claims 15 and 16 to be instituted with respect to Illumina's patentability challenge based on Tsien and Prober I.

D. Patentability challenge based on Tsien and Prober II (Petition 29)

The issue is whether it would have been obvious to one of ordinary skill in the art to have modified a nucleotide described in Tsien with a deazapurine base as taught by Prober II. Illumina explained that Prober II discloses the deazapurine synthesis scheme "underlying" Prober I. Petition 30. Thus, both Prober I and Prober II are being relied upon for the same deazapurine nucleotides. The evidence does not show that Tsien in

combination with Prober II would be more likely than Tsien in combination with Prober I to establish the obviousness of the claimed subject matter. The rejections appear to be duplicative. *See* 37 C.F.R. § 42.108(a) and discussion above about duplicative rejections. Accordingly, we shall not authorize an inter partes review at this time for the grounds based on the combination of Tsien and Prober I.

E. Patentability challenge based on Tsien and Hobbs (Petition 57)

The issue, as with the Prober I and Prober II publications, is whether it would have been obvious to one of ordinary skill in the art to have modified a nucleotide described in Tsien with a deazapurine base as taught by Hobbs. In characterizing Hobbs, Illumina states that “Hobbs reflects the synthesis scheme used to make the nucleotides of Prober I.” Petition 15. Based on this statement, it appears that Hobbs is being relied upon for same teachings in Prober I. Accordingly, as the rejections appear to be duplicative and there is insufficient information to establish that Illumina would be more likely to prevail in establishing obviousness than with the challenge based on Tsien and Prober I, we shall not authorize an inter partes review at this time for the grounds based on the combination of Tsien and Hobbs. *See* 37 C.F.R. § 42.108(a) and discussion above about duplicative rejections.

Obviousness based on Dower & Rabani

F. Patentability challenges based on Dower and Rabani

The obviousness rejections of claims 15 and 16 based on Dower and Rabani are substantially the same as those based on Tsien, i.e., the obviousness of modifying a “nucleotide having [1] a base that is attached to

a detectable label through a cleavable linker, wherein the nucleotide has [2] a deoxyribose comprising a cleavable chemical group capping the 3' OH group” with the teachings in the prior art of a nucleotide with a deazapurine. We found Dower and Rabani to be less complete than Tsien in not teaching all the features of claim 12, leading us to conclude that it was not likely that Illumina would prevail in establishing claim 12 as anticipated by Dower and Rabani. In view of this deficiency and the lack of evidence from Illumina that either Dower or Rabani in combination with the cited secondary references would be more likely than the Tsien rejections to establish the obviousness of the claimed subject matter, we shall not authorize an inter partes review at this time for the grounds based on the combination of Dower with Prober I, Prober II, or Hobbs; or Rabani with Prober I or Prober II.

Obviousness based on Stemple II & III

Stemple II

G. Patentability challenge based on Stemple II and Anazawa (Petition 55)

The issue is whether it would have been obvious to one of ordinary skill in the art to have modified a nucleotide described in Stemple II with a deazapurine base as taught by Anazawa. Illumina’s evidence that a modified nucleotide of claims 15 and 16 is obvious in view of Stemple II and Anazawa includes:

- Evidence that deazapurines had been used in DNA sequencing prior to the earliest filing date of the ‘869 Patent. *Supra* section A(1); Petition 13-16. We note that this evidence is not disputed by Columbia.

- Specific disclosure by Anazawa of a nucleotide comprising a fluorescent label attached to the 7-position of a 7deaza-guanine base. *Supra* section A(4); Petition 51 & 54.

Illumina also provided evidence of a reason to have modified Tsien's nucleotides with a deazapurine:

Stemple II states that a fluorescent label and linker "is attached directly to the base of the nucleotide as described by Anasawa [sic], WO 98/33939." Stemple II, col. 22, ll. 53-57. Stemple II thus provides an express teaching, suggestion, and motivation to combine Stemple II with the disclosures of Anazawa with respect use of 7-deazapurine nucleotide analogues in methods for sequencing by synthesis. See, e.g., Anazawa, Figs. 3-7 (also citing Prober I) and page 5, l. 36 - page 6, line 9; see also Weinstock Decl., ¶ 83.

Petition 27-28.

Columbia did not respond to Illumina's challenge to the patentability of claims 15 and 16 based on Stemple II and Anazawa.

Based on the suggestion of Stemple II, the skilled worker would have had reason to replace the natural nitrogen base of Tsien's nucleotide with a deazapurine to have made the claimed invention. Consequently, we conclude that Illumina has provided sufficient evidence to establish a reasonable likelihood, the pertinent standard under 35 U.S.C. § 314, that they will prevail in establishing that claims 15 and 16 are unpatentable under 35 U.S.C. § 103. Accordingly, we authorize an inter partes review of claims 15 and 16 to be instituted with respect to Illumina's patentability challenge based on Stemple II and Anazawa.

H. Patentability challenges based on Stemple II and Prober I or Hobbs (Petition 55 & 59).

Illumina challenges the patentability of claims 15 and 16 based the combination of Stemple II and Prober I and Stemple II and Hobbs. The patentability challenges are based on the obviousness of using a deazapurine base in the nucleotide described by Stemple II. This the same issue as the challenge based on Stemple II and Anazawa. Illumina has not provided evidence that they would be more likely to prevail on the combination with Stemple II and Prober I or Hobbs than Stemple II combined with Anazawa. The rejections appear to be duplicative. *See* 37 C.F.R. § 42.108(a) and discussion above about duplicative rejections. We will not authorize inter partes review on either of these grounds.

I. Patentability challenge based on Stemple III

Illumina challenges the patentability of claims 15 and 16 based on Stemple III in combination with Anazawa, Prober I or Hobbs. As discussed above, Stemple III is the National Stage application of the PCT application that published as Stemple II. Illumina relies on substantially the same disclosure in Stemple II as they did for Stemple II. The evidence does not show that Stemple III in combination with Anazawa, Prober I or Hobbs would be more likely than Stemple II in combination with the same publications to render claims 15 and 16 obvious. The rejections appear to be duplicative. Accordingly, we shall not authorize an inter partes review at this time for the grounds based on Stemple III in combination with Anazawa, Prober I or Hobbs. *See* 37 C.F.R. § 42.108(a) and discussion above about duplicative rejections.

SUMMARY

I. Inter partes review is authorized for claims 12, 13, 17, 20-26, 28, 29, 31, and 33 under 35 U.S.C. § 102(b) as anticipated by Tsien.

II. Inter partes review is authorized for claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Tsien and Prober I.

III. Inter partes review is authorized for claims 12, 13, 17, 20-23, 25, 26, 28, 29, and 31 under 35 U.S.C. § 102(a) as anticipated by Stemple I

IV. Inter partes review is authorized for Claims 15 and 16 under 35 U.S.C. § 103(a) as obvious in view of Stemple II and Anazawa.

Inter partes review is not authorized for any patentability challenge or ground not specified in I, II, III, and IV.

It is ORDERED that an initial conference call with the Board is scheduled for April 16, 2013 at 2:00 pm EST; the parties are directed to the Office Trial Practice Guide, 77 Fed. Reg. 48756, 48765-66 (Aug. 14, 2012) for guidance in preparing for the initial conference call, and should come prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

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U.S. Patent 7,790,869

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