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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

COMPLETE GENOMICS, INC.,
Patent Owner.

IPR2020-00079
Patent 9,222,132 B2

Before ERICA A. FRANKLIN, JON B. TORNQUIST, and JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Illumina, Inc. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–9 of U.S. Patent No. 9,222,132 B2 (Ex. 1001, “the ’132 patent”). Complete Genomics, Inc. (“Patent Owner”) filed a Preliminary Response (Paper 6, “Prelim. Resp.”).

Under 35 U.S.C. § 314(a), the Board “may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” For the reasons explained below, upon consideration of the Petition, Preliminary Response, and the evidence of record, we determine that the information presented in the Petition does not show that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the Petition. Accordingly, we do not institute an *inter partes* review.

A. *Related Proceeding*

The parties indicate that the ’132 patent is the subject of *Complete Genomics, Inc. v. Illumina, Inc.*, C.A. No. 19-cv-00970-MN (D. Del.). Pet. 82; Paper 5, 1.

B. *The Asserted Grounds of Unpatentability*

Petitioner asserts claims 1–9 of the ’132 patent (the “Challenged Claims”) are unpatentable in view of the following grounds:

Claims Challenged	35 U.S.C. §	Reference(s)
1–9	103(a)	Banerjee[1], Mathies[2]
1–9	103(a)	Chee[3]

Pet. 13. Petitioner relies on the Declaration of Floyd Romesberg, Ph.D. (Ex. 1005) in support of its contentions. Patent Owner relies on the Declaration of Michael L. Metzker, Ph.D. (Ex. 2001) in support of its Preliminary Response.

C. *The '132 Patent*

The '132 patent is directed to methods and compositions for acquiring nucleotide sequence information of target sequences. Ex. 1001, code (57). The '132 patent states that, "[i]n some embodiments, the present invention provides a method for determining an identity of a base at a position in a target nucleic acid comprising distinguishing four nucleotides from one another in a reaction using two labels." *Id.* at 2:15–18. The '132 patent further states that, "[i]n some aspects, the identity of the base in the target nucleic acid is determined by sequencing-by-synthesis . . . ." *Id.* at 2:19–21.

The '132 patent discloses that one can identify the nucleotides in a polynucleotide using sequencing-by-synthesis as follows: a first nucleotide is detected by a first fluorescent signal, a second nucleotide is detected by a second fluorescent signal, a third nucleotide is detected by both signals, and a fourth nucleotide is detected by the absence of signal.[4] Ex. 1001, 26:60–

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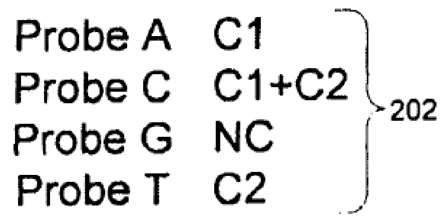
[1] Banerjee et al., WO 2007/123744 A2, published Nov. 1, 2007 (Ex. 1002, "Banerjee").
[2] Mathies et al., US 5,436,130, issued Jul. 25, 1995 (Ex. 1003, "Mathies").
[3] Chee et al., US 2005/0191698 A1, published Sept. 1, 2005 (Ex. 1004, "Chee").
[4] Patent Owner and Dr. Metzker refer to this detection by the absence of a signal as "dark state." *See* Prelim. Resp. 2; Ex. 2001 ¶ 6.

27:8. Figure 2 of the ’132 patent provides an exemplary probe set in which two labels are used to read four bases:



Id. at 26:60–27:8, Figure 2. In the example above, “the A probe is labeled with a first label (identified as C1), the T probe (or U probe, if desirable) is labeled with a second label (C2), the C probe is labeled with both the first and the second label (C1+C2), and the G probe is not labeled.” *Id.* at 26:63–67.

The ’132 patent states that the invention disclosed therein “provides methods and compositions that improve the efficiency and/or cost of identifying a base in a target sequence by distinguishing between the four possible nucleotides using fewer than four unique labels.” Ex. 1001, 9:58–62.

D. *Challenged Claims*

Claims 1 and 5, the two independent claims of the ’132 patent, are reproduced below:

> 1. A method for determining identities of nucleotides at detection positions of a plurality of different nucleic acid templates by performing sequencing-by-extension reactions, the method comprising:
>
> (a) providing an array comprising single-stranded nucleic acid templates disposed at positions on a surface;
>
> (b) for each of a plurality of said single-stranded nucleic acid templates, determining the identity of nucleotides at detection positions in the nucleic acid template in multiple cycles of a sequencing-by-extension reaction, comprising:

> i) binding a complementary nucleotide to a nucleotide at a detection position,
>
> ii) detecting, at the position on the surface occupied by the nucleic acid template, the presence or absence of fluorescent signal(s) associated with the complementary nucleotide; wherein
>
> > 1) detecting a first fluorescent signal and not a second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C;
> >
> > 2) detecting the second fluorescent signal and not the first fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotide selected in (1);
> >
> > 3) detecting both the first fluorescent signal and the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from nucleotides selected in (1) and (2); and
> >
> > 4) detecting neither the first fluorescent signal nor the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotides selected in (1), (2) and (3);
>
> iii) deducing the identity of the nucleotide at the detection position in the nucleic acid template based on the identity of the complementary nucleotide.

Ex. 1001, 49:32–50:33.

> 5. A method for determining identities of nucleotides at detection positions of a plurality of different nucleic acid templates, said method comprising:
>
> providing a plurality of nucleic acid templates each comprising an anchor site and, adjacent to the anchor site, a target nucleic acid sequence;
>
> performing sequencing reactions on the plurality of different nucleic acid templates using two distinguishable fluorescent labels by hybridizing an anchor probe to the anchor site and extending individual anchor probes by one nucleotide per cycle in one or more cycles of sequencing-by-synthesis using a set of nucleotides that comprises: (i) first nucleotides comprising a first label; (ii) second nucleotides comprising a second label; (iii) third nucleotides comprising both the first label and the second label; and (iv) fourth nucleotides comprising neither the first label nor the second label, wherein the first label and the second label are distinguishable from each other; and
>
> in each cycle of sequencing-by-synthesis, determining the identities of nucleotides at the detection positions by detecting the presence or absence of the first label and the presence or absence of the second label to determine the target nucleic acid sequences.

Id. at 50:40–63.

Claims 2–4 depend, directly or indirectly, from claim 1 and claims 6–9 depend, directly or indirectly, from claim 5.

II. ANALYSIS

A. *Principles of Law*

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. An obviousness determination requires finding "both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citation omitted); *see KSR*, 550 U.S. at 418 (for an obviousness analysis, "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"). Furthermore, an assertion of obviousness "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)); *see In re Nuvasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (a finding of a motivation to combine "must be supported by a 'reasoned explanation'" (citation omitted)).

B. *Person of Ordinary Skill in the Art*

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have been:

> a member of a team of scientists developing DNA sequencing techniques. Such teams would have included persons holding doctoral degrees in chemistry, molecular biology, physics, engineering, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience in research and development of DNA sequencing techniques, including an understanding of fluorescence spectroscopy for use in DNA sequencing.

Pet. 11.

Patent Owner contends that the person of ordinary skill in the art:

> would typically have had: (1) a Ph.D. degree in molecular biology, molecular genetics, biology or equivalent discipline,

> plus at least two years' laboratory experience working in the field of DNA sequencing technologies that include both Sanger and RCT[5], which further includes assay development and detection and analysis of labeled nucleotides; (2) a Master's degree in molecular biology, molecular genetics, biology or equivalent discipline, plus at least four years' relevant laboratory experience; or (3) a Bachelor's degree in molecular biology, molecular genetics, biology or equivalent discipline, plus at least six years' relevant laboratory experience.

Prelim. Resp. 7 (citing Ex. 2001 ¶ 30). Patent Owner further contends that "this knowledge should be possessed by an individual not a collection of individuals." *Id.* at 7–8 (citing Ex. 2001 ¶ 31).

Petitioner's description is more restrictive than that of Patent Owner, by requiring the person of ordinary skill in the art to have a doctoral degree in the relevant field. Based on the current record and for the purposes of this Decision, we adopt Patent Owner's proposed description of the person of ordinary skill in the art because it also recognizes that such skilled persons may have a Master's degree or Bachelor's degree in the relevant field, along with a particular level of laboratory experience working in the field of DNA sequencing. Further, we find that the prior art of record reflects this level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Although we adopt Patent Owner's definition of a person of ordinary skill in the art, our determination regarding Petitioner's challenge does not turn on the differences between Petitioner's and Patent Owner's definitions, and we note that our conclusions would be the same under either definition.

[5] The "reversible chain termination" (RCT) method is a type of sequencing-by-synthesis method. Prelim. Resp. 3 n.2; Ex. 2001 ¶ 9.

C. *Claim Construction*

Because this *inter partes* review is based on a petition filed after November 13, 2018,[6] claim terms are construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100(b) (2019). Under this claim construction standard, claim terms are given their ordinary and customary meaning as would have been understood by one of ordinary skill in the art at the time of the invention. *See id.*; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). A patentee may define a claim term in a manner that differs from its ordinary and customary meaning; however, any special definitions must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asserts that the claim term "sequencing-by-extension" should be construed to mean "sequencing-by-synthesis" because the patent equates these two terms with each other. Pet. 11 (citing Ex. 1001, 26:40–45). Patent Owner agrees that these two terms are synonymous. Prelim. Resp. 13–14. We, therefore, adopt Petitioner's construction of this term.

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[6] On October 11, 2018, the USPTO revised its rules to harmonize the Board's claim construction standard with that used in civil actions under 35 U.S.C. § 282(b) in federal district courts. Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (now codified at 37 C.F.R. pt. 42 (2019)). This rule change applies to petitions filed on or after November 13, 2018.

D. *Asserted Obviousness of Claims 1–9 over Banerjee in View of Mathies*

Petitioner contends that claims 1–9 would have been obvious over the combined disclosures of Banerjee and Mathies. Pet. 13–60 Patent Owner disputes Petitioner's contentions. Prelim. Resp. 33–50.

1. Banerjee

Banerjee describes methodologies and devices for sequencing using the sequencing-by-synthesis method. Ex. 1002, codes (54), (57), ¶ 64. Banerjee discloses a four-label sequencing-by-synthesis system that includes an array of template nucleic acids to be sequenced, and four nucleotide analogues (A, T, G, and C) each having a removable 3'-OH protecting group. *Id.* ¶¶ 64–66, 190–195. Each of the four nucleotide analogues is labeled with a different fluorophore. *Id.* Banerjee describes a sequencing-by-synthesis system that "can image millions of nucleic acid clusters per sample (typically within a flowcell) and which can detect each of the four fluorescent dyes (one for each of the four bases)." *Id.* ¶ 190.

Banerjee's sequencing-by-synthesis method includes cycles having the following steps: (1) incorporation, (2) detection, and (3) deprotection. Ex. 1002 ¶¶ 192–195, Fig. 30. In the first step, a DNA polymerase, bound to the primed templates within each cluster, adds or incorporates one fluorescently-labeled reversibly terminating nucleotide, which is complementary to the template base. Ex. 1002 ¶¶ 192, 230–233; Ex. 2001 ¶ 44. After incorporation, the remaining unincorporated nucleotides are washed away. Ex. 1002 ¶¶ 193, 233; Ex. 2001 ¶ 44. Imaging is then performed to determine the identity of the incorporated labeled-nucleotide. Ex. 1002 ¶¶ 194, 233; Ex. 2001 ¶ 44. This imaging is followed by a deprotection or cleavage step, which removes the terminating group and the fluorescent label. Ex. 1002 ¶¶ 195, 234; Ex. 2001 ¶ 44. Additional washing is performed before starting the next incorporation step. Ex. 1002 ¶ 234; Ex. 2001 ¶ 44. The process of nucleotide incorporation, fluorescence imaging, and cleavage is repeated for as many cycles as required. Ex. 1002 ¶¶ 195, 234; Ex. 2001 ¶ 44.

2. Mathies

Mathies describes a Sanger sequencing method using single lane or channeled electrophoresis in which the "[s]equencing fragments are separated in said lane and detected using a laser-excited, confocal fluorescence scanner." Ex. 1003, code (57), 3:14–17.

Mathies teaches that existing Sanger sequencing technology used four sets of sequencing fragments that terminate in either A, G, T, or C, with each set labeled with the same fluorophore, and each set run in its own lane on a four-lane electrophoresis slab gel to separate the fragments based on mobility. Ex. 1003, 1:20–26; Ex. 2001 ¶¶ 35–38. Mathies explains that this method suffers from "lane-to-lane variations in the migration velocity of the DNA fragments [that] make it difficult to deduce the correct alignment of the bands in the four sequencing lanes." Ex. 1003, 1:38–41.

To solve this problem, Mathies describes a system in which "[e]ach set of DNA sequencing fragments is separated in the same lane and then distinguished using a binary coding scheme ***employing only two different fluorescent labels***." Ex. 1003, code (57) (emphasis added). Mathies discloses that the "DNA fragments are labeled with only two dyes which have been selected so that they have the same mobility shift during electrophoresis." *Id.* at 3:11–14. This two color DNA fragment coding method is shown in Figure 2 of Mathies:

	DYE 1	DYE 2
A	1	1
G	0	1
T	1	0
C	0	0

FIG.—2

Id. at Fig. 2. Figure 2 shows a two-color DNA fragment fluorophore coding method.

The working examples of Mathies describe two-label sequencing of fluorescently labeled nucleotide primers, but Mathies indicates that the dideoxy nucleotide ("dideoxy" or "ddNTP") terminator can also be labeled. Ex. 1003, 1:13–17, 3:5–7, 4:18–54, 5:35–40.

3. Petitioner's Position

According to Petitioner, claim 1 of the '132 patent "merely combines the admittedly well-known sequencing-by-synthesis technique with a two-label scheme that had already been used in similar polymerase-based sequencing reactions." Pet. 34. Petitioner asserts that "the supposed patentability of Claim 1 is two-labels for sequencing-by-synthesis," which is recited in limitations 1(b)(ii)(1)–(4), and is disclosed by Mathies. *Id.* at 15. Petitioner further asserts that the "remainder of the claim recites well-known aspects of sequencing-by-synthesis," which is disclosed in Banerjee.[7] *Id.* Petitioner contends that "[i]t would have been obvious to implement Mathies' two-label scheme in Banerjee's sequencing-by-synthesis method using standard and routine prior art techniques."[8] *Id.* We review limitations 1(b)(ii)(1)–(4) below:

Limitation 1(b)(ii)(1) recites: "detecting a first fluorescent signal and not a second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C." Ex. 1001, 49:49–52.

Limitation 1(b)(ii)(2) recites: "detecting the second fluorescent signal and not the first fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotide selected in (1)." Ex. 1001, 49:53–57.

Limitation 1(b)(ii)(3) recites: "detecting both the first fluorescent signal and the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from nucleotides selected in (1) and (2)." Ex. 1001, 49:58–62.

Limitation 1(b)(ii)(4) recites: "detecting neither the first fluorescent signal nor the second fluorescent signal at the position identifies the complementary nucleotide as a nucleotide selected from A, T, G and C that is different from the nucleotides selected in (1), (2) and (3)." Ex. 1001, 49:63–67.

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[7] Petitioner provides arguments on how Banerjee teaches the remaining limitations of claim 1 at pages 15–38 of the Petition.

[8] Petitioner makes similar arguments for limitations 5(b) and 5(b)(i)-(iv) of independent claim 5, which recite the use of "two distinguishable fluorescent labels." Pet. 53–55.

Petitioner asserts that "Mathies discloses a two-label scheme for polymerase-based sequencing with chain terminating nucleotide analogues (ddNTPs)." Pet. 31 (citing Ex. 1003, Fig. 2, 2:62–63, 4:18–28). Petitioner further asserts that "Mathies discloses two embodiments of two-label sequencing: (1) where labels are attached to sequencing primers ([Ex. 1003], 4:20-28), and (2) where labels are attached to chain-terminating nucleotides (*id.*, 5:35-53)." *Id.* at 32.

According to Petitioner, Mathies' two-label sequencing with labeled nucleotides meets limitations 1(b)(ii)(1)–(4)[9] as shown below:

Mathies			**'132 patent claim limitation**
	DYE 1	DYE 2	
A	1	1	1(b)(ii)(3)
G	0	1	1(b)(ii)(2)
T	1	0	1(b)(ii)(1)
C	0	0	1(b)(ii)(4)

FIG.–2

Pet. 33–34 (citing Ex. 1005 ¶ 92).

According to Petitioner, in Mathies' two-label scheme, cytidine incorporation is indicated by detecting the absence of fluorescent signals from both labels. Pet. 34 (citing Ex. 1003, Fig. 2, 4:27–28). Petitioner contends that a person of ordinary skill in the art "implementing Mathies'

[9] Although Petitioner shows how claim limitations 1(b)(ii)(1)–(4) match up with the labels disclosed in Mathies in this chart, Petitioner appears to primarily rely on Banerjee to teach limitations 1(b)(ii)(1) and 1(b)(ii)(2). *See* Pet. 26–29.

two-label scheme in Banerjee's sequencing-by-synthesis method would have followed Mathies' example and used a reversible chain terminating cytidine analogue that lacks fluorescent labels," thereby rendering obvious limitation 1(b)(ii)(4). *Id.* (citing Ex. 1005 ¶¶ 95, 98).

Similarly, Petitioner argues that a person of ordinary skill in the art "implementing Mathies' two-label scheme in Banerjee's sequencing-by-synthesis method would have used a reversible chain-terminating thymidine analogue that is identified by detecting fluorescence signals from the same labels used with both the adenosine and guanosine analogues," thereby rendering obvious limitation 1(b)(ii)(3). Pet. 35 (citing Ex. 1003, 4:20–23, Fig. 2; Ex. 1005 ¶¶ 99–100).

a. Motivation to Combine

Petitioner argues that there are several motivations to combine Banerjee and Mathies. Pet. 38. First, Petitioner asserts that Banerjee teaches the desirability of reducing image/detection time, which is an advantage provided by Mathies. *Id.* According to Petitioner, Banerjee discloses the desirability of increasing the speed and throughput of sequencing-by-synthesis by increasing the rate of fluorescence imaging during the detection step. *Id.* at 39 (citing Ex. 1002 ¶¶ 143, 203). Petitioner further asserts that two-label sequencing was known to increase detection speed. *Id.* (citing Ex. 1018, 9:5–14; Ex. 1023, 37:23–43; Ex. 1014, 549; Ex. 1036, 6348).

Petitioner also contends that "Banerjee's four-label sequencing scans each cluster four times (once per colored label) to identify each incorporated nucleotide analogue" and "[t]he four scans involve a filter-wheel that cycles between four different color filters." Pet. 39 (citing Ex. 1002 ¶¶ 143, 196, 154–155, 233–234, 240, Fig. 22B, Fig. 32). Therefore, according to Petitioner, "[m]odifying Banerjee's four-label scheme to use Mathies' two-label scheme would allow the identity of a nucleotide to be determined using two scans instead of four, thereby increasing Banerjee's detection rate by up to 50%." *Id.* (citing Ex. 1005 ¶ 105).

Second, Petitioner contends that a person of ordinary skill in the art "would have been motivated to implement Mathies' two-label scheme in Banerjee's sequencing to reduce the number of color filters from four to two, providing simplified detection instrumentation." Pet. 39. According to Petitioner, Mathies discloses that two-label sequencing simplifies instrumentation. *Id.* at 39–40 (citing Ex. 1003, 5:4–7 ("The instrument design is simplified. Since there are only two optical detection channels, the optical efficiency is increased, giving a better signal-to-noise ratio."); Ex. 1018, 9:5–14).

Third, Petitioner asserts that "Mathies emphasizes the obviousness of using the two-label scheme with nucleotide terminators for polymerase-based sequencing by stating '[i]t is obvious that the different coding methods developed with labeled primers can also be implemented using dye-labeled terminators.'" Pet. 40 (citing Ex. 1003, 5:35–40, 5:51–53; Ex. 1005 ¶¶ 106–107). Petitioner further asserts that Mathies and the '132 patent provide similar instruction to conduct two-label sequencing and contends that "[i]t is not inventive to use a known technique to improve similar methods in the same way." *Id.* (citing Ex. 1003, 5:34–53; Ex. 1001, 26:46–53; *KSR*, 550 U.S. at 401).

Fourth, according to Petitioner, a person of ordinary skill in the art "following Banerjee's disclosed desire to improve sequencing-by-synthesis throughput would have been motivated to look to prior art improvements of Sanger-sequencing methods, such as Mathies." Pet. 40. Petitioner asserts that "[r]esearchers commonly looked back on improvements developed" for Sanger-sequencing methods to improve sequencing-by-synthesis methods. *Id.* at 40–41 (citing Ex. 1002 ¶¶ 64, 146, 190; Ex. 1005 ¶¶ 104, 108; Ex. 1009, 1768; Ex. 1019 ¶¶ 214, 217; Ex. 1029, 31:13–25, 63:19–25; Ex. 1035, 25:4–12; Ex. 1037, 3:10–15, 32:22–33:23, 34:6–9, 126:4–10; Ex. 1038, 1–2; Ex. 1039, 1:28–65; Ex. 1040, 28:5–18, 29:10–31:19).

Fifth, Petitioner contends that implementing Mathies' two-label scheme would help ameliorate Banerjee's stated concern with photobleaching. Pet. 41. Petitioner asserts that, "Banerjee discloses that sequencing-by-synthesis would be benefitted by decreasing photobleaching by decreasing the amount of exposure of DNA clusters in the flowcell to laser scans during the scanning step." *Id.* (citing Ex. 1002 ¶ 153). According to Petitioner, "[u]sing Mathies' two-label scheme would expose Banerjee's clusters to half as many laser scans (two scans instead of four), which would decrease laser exposure and decrease photobleaching. *Id.* (citing Ex. 1005 ¶¶ 109–112).

Sixth, Petitioner contends that others in the field, such as Chee, had already disclosed sequencing-by-synthesis using a two-label scheme. Pet. 41, 62.

b. Expectation of Success

Petitioner asserts that a person of ordinary skill in the art would have expected that they would be able to modify the sequencing method disclosed in Banerjee with the two-label scheme disclosed in Mathies because it would involve a simplification of Banerjee's nucleotides and instrumentation. Pet.

41. Petitioner also asserts that "Banerjee and Mathies provide an expectation of success because they both demonstrated successful sequencing via polymerase-based, chain-terminating methods that use fluorescence emission to deduce the [identity] of an incorporated nucleotide." *Id.* at 41–42.

According to Petitioner, Banerjee provides an expectation of success because it discloses "a fully functional sequencing-by-synthesis system that yielded 20 cycles of sequencing with a 1% error rate." Pet. 42 (citing Ex. 1002 ¶ 240). Furthermore, Petitioner asserts that a person of ordinary skill in the art "implementing Mathies' two-label scheme in Banerjee's sequencing-by-synthesis system would select two of Banerjee's labels and corresponding filters, resulting in a simplified sequencing-by-synthesis system." *Id.* (citing Ex. 1003, 5:4–7; Ex. 1005 ¶¶ 115–116). Petitioner also contends that Banerjee detects the presence or absence of fluorescence signals and "discloses the use of waveplates that average and smooth fluorescence images so that dark locations on the flowcell surface are accurately identified." *Id.* at 43 (citing Ex. 1002 ¶¶ 109, 111, 140–141).

Petitioner further asserts that a person of ordinary skill in the art would have reasonably expected that the unlabeled nucleotide analogue (e.g., a cytidine analogue) would be "incorporated with approximately the same or better efficiency than the labeled nucleotide analogues (because the unlabeled analogue more closely resembles a natural nucleotide substrate)." Pet. 43 (citing Ex. 1005 ¶¶ 117–120). According to Petitioner, "[i]f the unlabeled nucleotide were incorporated with higher efficiency than the labeled nucleotides, a [person of ordinary skill in the art] would have known how to adjust the relative concentration of the labeled and unlabeled nucleotides based on the same type of routine concentration optimization known in the prior art for Sanger-sequencing." *Id.* (citing Ex. 1009, 1772; Ex. 1012, 4464–65).

Petitioner also asserts that Mathies provides an expectation of success because it demonstrated successful two-label polymerase-based sequencing and a person of ordinary skill in the art "implementing Mathies' two-label scheme in Banerjee's sequencing method would likewise reasonably expect success." Pet. 44 (citing Ex. 1003, 4:20–23, 4:61–5:3, 5:34–53, Fig. 3; Ex. 1005 ¶ 121). In addition, according to Petitioner, "increasing Banerjee's cluster size increases the brightness of each cluster." *Id.* (citing Ex. 1005 ¶ 121).

Petitioner further contends that admissions by Patent Owner confirm that a person of ordinary skill in the art would have had a reasonable expectation of successfully implementing a two-label scheme in sequencing-by-synthesis using routine skill and knowledge in the prior art. Pet. 42. For example, Petitioner argues that the '132 patent does not explain how to implement two-label sequencing-by-synthesis but, rather, admits that the two-label scheme would be implemented in any sequencing-by-synthesis method "using standard and routine techniques by one of skill in the art." *Id.* at 45 (citing Ex. 1001, 26:40–53). According to Petitioner, "[i]f novel and nonobvious methods were needed to practice the claims, [Patent Owner] would have been obligated to disclose such methods in the specification." *Id.* at 45–46 (citing *Illumina, Inc. v. Columbia University,* IPR2018-00291, Paper 67 at 44 (P.T.A.B. 2019)).

Petitioner also argues that, during prosecution of related applications, Patent Owner relied on the general skill in the art in arguing that a person of ordinary skill in the art would expect to successfully implement two-label sequencing by synthesis. Pet. 46. In support of this argument, Petitioner cites to prosecution of U.S. Application No. 16/054,968 ("the '968 application") (Ex. 1041) and U.S. Application No. 15/359,277 ("the '277 application") (Ex. 1042), which claim priority to the same application as the '132 patent and share the same Specification as the '132 patent. Pet. 46 (citing Ex. 1001, 1:8–9; Ex. 1041, 225–226). According to Petitioner, during prosecution of the '968 application, in order to overcome an enablement rejection, Patent Owner argued that a person of ordinary skill in the art would have been able to carry out two-label sequencing by synthesis because "sequencing-by-synthesis was well known by persons of ordinary skill in the art," the level of skill in the art is "very high," and "[i]t is well established that a patent need not teach, and preferably omits, what is well known in the art." *Id.* (citing Ex. 1041, 11–16).

Petitioner also cites to prosecution of the '277 application in which Patent Owner responded to an enablement rejection by asserting that "the relative skill in the art is very high" and quoted the portion of the specification which states that a person of ordinary skill in the art would use "standard and routine techniques" to perform the claimed method. Pet. 47 (citing Ex. 1042, 31). According to Petitioner, Patent Owner "relied on the specification's instruction to simply 'replace the disclosure of labeled sequence probes with labeled dNTPs and to make other (standard and routine) variations' to implement sequencing-by-synthesis methods." *Id.* (citing Ex. 1042, 27–28).

4. Patent Owner's Position

Patent Owner asserts that the combination of Mathies and Banerjee does not raise a reasonable likelihood of unpatentability. Prelim. Resp. 33–50. According to Patent Owner, Mathies describes a method for solving a problem unique to Sanger sequencing — the problem of matching the mobility of fragments tagged with different labels so that the distances traveled by differently tagged fragments can be accurately compared. *Id.* at 35 (citing Ex. 1003, 3:11–14 (stating that "the DNA fragments are labeled with only two dyes which have been selected so that they have the **same mobility shift** during electrophoresis") (emphasis added)). Patent Owner asserts that "[t]o solve the mobility shift problem, Mathies proposed using only two dyes and a dark state because it would be easier to match the mobility shifts associated with each of those two dyes compared with four dyes." *Id.* at 34–35 (citing Ex. 1003, 2:29–37; Ex. 2001 ¶¶ 58–59).

Patent Owner contends that Mathies recognized that using two dyes and a dark state to solve the mobility shift issue created problems with accuracy in stating that "some workers might object to the binary coding since the C-fragments are not explicitly detected." Prelim. Resp. 35 (citing Ex. 1003, 5:55–58; Ex. 2001 ¶¶ 60–61, 68). According to Patent Owner, Mathies proposed certain fixes to this accuracy problem including "1) re-running the method a second time with different labels, 2) sequencing the complementary strand, and 3) labeling all four primers with different concentrations of two dyes to label each nucleotide and eliminate the dark state altogether." *Id.* (citing Ex. 1003, 5:59–6:15; Ex. 2001 ¶ 69).

Patent Owner and Dr. Metzker contend that "each of these solutions would counteract any efficiency or throughput gains achieved by using a dark state and only two colors to identify four nucleotides" in that "[t]he first two options would require running a second Sanger reaction and electrophoretic detection, thus decreasing throughput" and "the third option eliminates the dark-state altogether." Prelim. Resp. 35 (citing Ex. 2001 ¶ 70). Furthermore, according to Patent Owner, Mathies reported an error rate of 5.4% for the two-color, dark-state detection scheme. *Id.* at 35–36 (citing Ex. 1030, 2153). Patent Owner and Dr. Metzker also assert that "Mathies taught that the two-color, dark-state scheme was principally applicable to rapid screening of ***known*** sequences for mutations" and that, "if an unknown sequence is going to be determined, then one should use a method that labels all fragments and not rely on a dark-state." *Id.* at 36 (citing Ex. 2001 ¶ 54; Ex. 2017, 27). According to Patent Owner and Dr. Metzker, Mathies did not ultimately pursue the two-color dark-state Sanger scheme after issuance of the patent. *Id.* (citing Ex. 2001 ¶ 61).

Patent Owner also asserts that Mathies' working examples teach away from sequencing-by-synthesis. Prelim. Resp. 36–38. Patent Owner contends that, in general, the reagents and reactions Mathies used cannot be substituted into the methods of Banerjee. *Id.* For example, according to Patent Owner, Mathies' working examples use dye-labeled primers rather than dye-labeled nucleotides. *Id.* at 36–37 (citing Ex. 1003, 3:11–20; Ex. 2001 ¶ 64).

Patent Owner and Dr. Metzker also contend that Mathies' method of running only three terminating reactions for each template would fail in a sequencing-by-synthesis scheme because, in such a scheme, one could not run separate reactions for each chain terminating nucleotide and one could not use the non-reversible chain terminators of Mathies. Prelim. Resp. 37

(citing Ex. 2001 ¶¶ 66–67). Patent Owner also asserts that in sequencing-by-synthesis, as described in Banerjee, one could not leave out one of the chain terminating nucleotides, i.e., the dark nucleotide, as Mathies did because "[a]ll four reversible-terminating nucleotides need to be present in RCT, or the polymerase cannot continue adding nucleotides to the growing chain." *Id.* at 38 (citing Ex. 2001 ¶¶ 66–67). According to Patent Owner, "the reaction mixtures Mathies used consisting of four natural nucleotides would lead to disastrous results if used in Banerjee." *Id.* (citing Ex. 2001 ¶ 66).

a. Motivation to Combine

Patent Owner further contends that no motivation exists to combine Mathies with Banerjee's sequencing-by-synthesis method. Prelim. Resp. 38. According to Patent Owner:

> The substitution of the Mathies reaction mixture, or parts of it, into the Banerjee reaction scheme does not involve a simple substitution of parts. No part of the Mathies mixture could simply be dropped into the Banerjee mixture and result in a working system. Rather, one would have to modify portions of Mathies and substitute those modified portions into Banerjee.

Id. (citing *Black & Decker, Inc. v. Positec USA, Inc.*, 646 F. App'x 1019, 1026 (Fed. Cir. 2016) (affirming Board's finding of non-obviousness where substituted features "serve different purposes" and where there was no evidence "that a person of ordinary skill would have made the various structural changes necessary" to implement the substitution). Patent Owner concludes that "[s]uch modified substitutions are only taught through the use of hindsight." *Id.* (citing Ex. 2001 ¶¶ 95–106).

With regard to Banerjee, Patent Owner asserts that, "[w]hile Banerjee states that having significant throughput is a desirable result, he does not state that throughput remained a problem to be solved in his system" but, rather, Banerjee describes "several design aspects of his system that increased throughput." Prelim. Resp. 40 (citing Ex. 2001 ¶¶ 79–82). For example, according to Patent Owner, Banerjee describes "methods to increase the number of pixels that can be imaged in a single exposure" which "requir[es] fewer images to be taken to capture all the clusters on the flow cell" and speeds up the imaging process. *Id.* (citing Ex. 1002 ¶ 143; 2001 ¶ 80).

Patent Owner further contends that Banerjee also teaches that one could increase the number of cameras for imaging and simultaneously use two cameras, each having two filters, or four cameras each detecting a single color, rather than using one camera with four different filters. Prelim. Resp. 41 (citing Ex. 2001 ¶ 80). Furthermore, Patent Owner asserts that Banerjee teaches additional methods for increasing imaging speed such as the use of Time Delay Integration and assigning multiple flow cells to a single optical system. *Id.* (citing Ex. 1002 ¶ 203, Figs. 36, 37, 43; Ex. 2001 ¶¶ 79, 88).

According to Patent Owner, "Banerjee never suggests that his methods for improving speed are inadequate and there is a further need to increase the speed or throughput of the system." Prelim. Resp. 41 (citing Ex. 2001 ¶ 82). Patent Owner concludes that, "[g]iven these facts and all the problems associated with the accuracy of Mathies' two-label dark-state Sanger method, there would have been no motivation for a [person of ordinary skill in the art] to combine Mathies with Banerjee to arrive at the inventions of the '132 patent." *Id.*

Patent Owner and Dr. Metzker also argue that none of Petitioner's proposed motivations to combine Banerjee with Mathies are supported by evidence. Prelim. Resp. 41–47.

b. Expectation of Success

Patent Owner also asserts that there would have been no expectation of success in combining Mathies' Sanger sequencing solution with Banerjee's RCT sequencing. Prelim. Resp. 47–50. According to Patent Owner, "[t]here is no dispute that Sanger sequencing and RCT are two different sequencing technologies that involve different reagents and methodology." *Id.* at 47. Patent Owner argues that "[t]he combination of Mathies with Banerjee does not involve the simple substitution of one element for another" and provides arguments as to why this is the case. *Id.* at 47–50.

Patent Owner also contends that "Petitioner has presented no evidence that these are simple modifications that a [person of ordinary skill in the art] would expect to work" and that, "[o]n the contrary, a [person of ordinary skill in the art] would have understood, as explained previously, that even Mathies could not get his system, for which his two-label, dark-state scheme was designed, to work in an acceptable fashion." Prelim. Resp. 48 (citing Ex. 2001 ¶ 61). Patent Owner further contends that "[t]he fixes Mathies suggested to solve the accuracy problems, *e.g.*, multiple rounds of sequencing, were also not standard in all sequencing techniques." *Id.* (citing Ex. 2001 ¶¶ 69–70).

Patent Owner also asserts that the teachings of Mathies refute Petitioner's claims regarding a reasonable expectation of success because Mathies states that the two-label dark-state scheme "was useful primarily for rapid screening of a known sequence; for determining an unknown sequence, the use of four colors was preferred." Prelim. Resp. 48 (citing Ex. 2001 ¶ 95). According to Patent Owner, "[n]othing demonstrates that Mathies' method, which produced error rates of 5.4%, would be expected to work in the Banerjee system, where the error rates were less than 1%." *Id.* (citing Ex. 2001 ¶ 60).

Patent Owner also contends that Petitioner is incorrect in its assertion that one of skill in the art would know that adjusting the cluster size in Banerjee would compensate for the lack of intensity that would result if Mathies two-label, dark-state scheme was incorporated into Banerjee. Prelim. Resp. 49 (citing Ex. 1005 ¶ 121). According to Patent Owner and Dr. Metzker, "[i]ncreasing cluster size will result in overlap between clusters, unless fewer clusters are placed on each array—and reducing the number of clusters per array will decrease throughput and counteract some of the purported benefits Dr. Romesberg identifies of applying the two-label scheme to Banerjee's methods." *Id.* at 49–50 (citing Ex. 2001 ¶ 103; Ex. 1002 ¶¶ 197, 201, Fig. 31). Patent Owner also asserts that "Banerjee teaches away from making fewer, larger clusters by presenting evidence that a 'higher cluster density' coupled with a faster imaging rate can achieve higher throughput." *Id.* at 50 (citing Ex. 1002 ¶ 143, Fig. 29; Ex. 2001 ¶ 103).

c. Illumina's Prosecution History

Patent Owner also asserts that this Petition should be denied based on statements made by Petitioner during prosecution of Petitioner's U.S. Patent

No. 9,453,258 ("the Kain patent")[10] regarding the non-obviousness of two-label, dark-state sequencing-by synthesis. Prelim. Resp. 14–28, 50.[11]

5. Analysis

For the reasons explained below, upon consideration of the Petition, Preliminary Response, and the evidence of record, we are not persuaded that Petitioner has provided sufficient argument and supporting evidence to demonstrate a reasonable likelihood that challenged claims 1–9 would have been obvious over the combined teachings of Banerjee and Mathies.

a. Motivation to Combine

We agree with Patent Owner that Petitioner has not presented sufficient information to show that one of ordinary skill in the art would have been motivated to combine the two-labeling scheme disclosed in Mathies with the sequencing-by-synthesis method disclosed in Banerjee. *See InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) ("A party seeking to invalidate a patent on obviousness grounds must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.") (citations and internal quotations omitted).

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[10] Kain et al., US 9,453,258 B2, issued Sept. 27, 2016 (Ex. 2004, "Kain patent").

[11] Patent Owner also asserts that Petitioner should be judicially estopped from making its arguments in Grounds 1 and 2 given the allegedly inconsistent positions it took during prosecution of the Kain patent and in the Petition. *See* Prelim. Resp. 29–32. Because we determine that Petitioner has not demonstrated a reasonable likelihood that claims 1–9 of the '132 patent would have been obvious, we do not need to decide the estoppel issue for purposes of this Decision.

First, Mathies is directed to the problem, specific to Sanger sequencing, in which use of four dyes led to different electrophoretic shifts leading to the necessity of "perform[ing] complicated shift corrections before the sequence can be read." Ex. 1003, 2:10–14. To solve this problem, Mathies proposed the use of two dyes "having substantially the same mobility shift." *Id.* at 2:29–36. Because sequencing-by-synthesis does not involve the migration of nucleotides on a gel, the problem identified by Mathies did not exist in Banerjee's sequencing-by-synthesis technique and Petitioner has not sufficiently shown why the proposed solution disclosed in Mathies is applicable to sequencing-by-synthesis. Ex. 2001 ¶ 72.

Second, Mathies' published error rate for the two-label approach in Sanger sequencing was 5.4%. Ex. 1030, 2153. Petitioner has not sufficiently explained why one of ordinary skill in the art would have been motivated to use such a method despite this high error rate or why this error rate would not persist in Banerjee's sequencing-by-synthesis system. *See* Ex. 1009, 1768 (stating that an error rate of 1% "serves as the commodity standard throughout the sequencing community"); *see also* Ex. 1002 ¶ 240 (disclosing an error rate of less than 1% for the first 20 cycles of the experiment).

Indeed, in order to overcome an obviousness rejection during prosecution of the Kain patent, Petitioner submitted evidence showing doubts of experts in the field that a sequencing-by-synthesis method with two dye labels would produce acceptable error rates in the context of the January 2014 launch of Petitioner's NextSeq 500 instrument. Ex. 2008, 12–15. These arguments were made years after the priority date of the '132 patent, which has a non-provisional application filing date in 2009. Ex. 1001, code (63).

In particular, during prosecution of the Kain patent, Petitioner cited to an article published on the Opiniomics weblog entitled "7 reasons why NextSeq 500 is a strange choice," in which the authors state that having a mixture of dyes identifying A and no dye measuring G, "are causing most *concern*. I've little doubt that this new system will introduce *bias*." Ex. 2008, 12. Petitioner also cited to a statement by Paul T. Morrison, the Director of Molecular Biology Core Facilities at Harvard's Dana-Farber Cancer Institute, in which he stated, "[t]wo dye could be evolutionary it may only cut run times in half but the inherent simplicity of doing half the work, half the plumbing . . . could really be huge *if they keep error rates in hand*." *Id.* at 13.

Similarly, during prosecution of the Kain patent, Petitioner also cited to Dr. Keith Robinson of the Omics! Weblog, which commented about Illumina's new instrument, "there is trepidation in the bioinformatics community as to *error rates* given the unusual dye scheme, which only large datasets can allay (or lead to recalibration of various models)." Ex. 2008, 13. Petitioner also referred to the quote below from the Core Genomics weblog article as a "logical/scientific truism":

> So Illumina must be 100% sure the label-less G will 100% incorporate and the 3'prime protecting group be fully removed in every cycle… even in difficult GC rich regions. *This can't be possible*. Suffice to say, *it's fundamental scientific methodology that the absence of a result is not at all the same and can't be assumed to be a positive result*.

Id.

Petitioner contends that the statements made during prosecution of the Kain patent do not apply to the present Petition because different prior art was cited by the Examiner in that case. Pet. 47–49. However, we agree with Patent Owner that, while certain arguments made by Petitioner in the Kain prosecution may have been specific to the particular references cited in that prosecution, the evidence and arguments discussed herein were broadly directed to the use of two labels in a sequencing-by-synthesis method, which is relevant to the issues in this matter. *See* Prelim. Resp. 26.

In summary, despite Petitioner's arguments during prosecution of the Kain patent regarding the potential for error in a two-label system, and despite the problems and error rate disclosed by Mathies discussed *supra*, Petitioner fails to sufficiently address why one of ordinary skill in the art would have expected the combined system of Mathies and Banerjee to have an acceptable error rate. Thus, we are not persuaded that Petitioner has sufficiently explained why one of ordinary skill in the art would have sought to implement Mathies' high-error rate method in Banerjee's sequencing by synthesis method.

Next, although Mathies states that its two label system "utilizing only two optical detection channels" provides for a simplified instrument design, increased "optical efficiency," and a "better signal-to-noise ratio," Petitioner has not presented sufficient evidence to show that the instrument design for Banerjee's sequencing-by-synthesis method could similarly be simplified or that the overall system would be more efficient given the potential issues identified by Mathies. Ex. 1003, 5:4–7.

Mathies acknowledges that, with the use of only two labels, "some workers might object to the binary coding since the C-fragments are not explicitly detected" and proposes some solutions to this problem that could negate any potential efficiency that might be gained with using only two color filters. Ex. 1003, 5:55–6:15. For example, Mathies states that a second sequencing run can be done on the same DNA strand where the binary coding is permuted, the complementary strand can be sequenced, or all four primers can be labeled with two labels but with different amounts to alter their fluorescent intensity. *Id.* Petitioner has not sufficiently shown that use of these solutions would still result in reduced sequencing/imaging time in a sequencing-by-synthesis method. Ex. 2001 ¶¶ 70, 84.

Petitioner also argues that Mathies teaches that its two label scheme provides advantages over a four label scheme. Pet. 38. However, as discussed above, Mathies teaches potential advantages of a two label scheme in the context of fixing the problem of varying electrophoresis mobility shifts of four dyes during Sanger sequencing. Ex. 1003, 2:34–37, 3:11–14; Ex. 2001 ¶¶ 57–59. Furthermore, as discussed above, Mathies also identifies a potential issue with a two-label scheme in which the C-fragments are not explicitly detected and lists proposed solutions to this issue. Ex. 1003, 5:55–6:15. Although Petitioner mentions these proposed solutions (Pet. 44–45), Petitioner fails to sufficiently explain why the proposed solutions of Mathies (e.g., resequencing the same strand with different coding or sequencing the complementary strand) would not have reduced any potential gained efficiencies by using two labels. Nor does Petitioner adequately explain why these modifications could reduce the error rate of the combined system to an adequate level.

Therefore, we are not persuaded by Petitioner's arguments that Banerjee's alleged disclosure of desiring to reduce imaging/detection time or

Mathies' teachings of the advantages of its two label scheme would have motivated one of ordinary skill in the art to use the two-label scheme disclosed in Mathies with the sequencing-by-synthesis method disclosed in Banerjee.

We also agree with Patent Owner that the substitution of the reaction mixture disclosed in Mathies into the Banerjee reaction scheme does not involve a simple substitution of parts. Petitioner argues that Mathies states that "[i]t is obvious that the different coding methods developed with labeled primers can also be implemented using dye-labeled terminators." Pet. 40 (citing Ex. 1003, 5:35–40, 5:51–53; Ex. 1005 ¶¶ 106–107). However, even though Mathies discloses the potential labeling of dye-labeled ddNTP terminators, the ddNTPs disclosed in Mathies are non-reversible in contrast to the reversible terminators used in Banerjee's sequencing-by-synthesis method. Petitioner has not provided sufficient evidence to show why one of ordinary skill in the art would have been motivated to use Mathies' method to fix a problem associated with Sanger sequencing and apply it to non-reversible terminators, which are nowhere described in Mathies.

Along these lines, Petitioner also asserts that researchers typically looked to Sanger-sequencing methods to improve sequencing-by-synthesis given the similarities between the two sequencing methods. Pet. 38. In support of this argument, Petitioner cites to several exhibits. *See id.* at 40–41 (citing Ex. 1002 ¶¶ 64, 146, 190; Ex. 1005 ¶¶ 104, 108; Ex. 1009, 1768; Ex. 1019 ¶¶ 214, 217; Ex. 1029, 31:13–25, 63:19–25; Ex. 1035, 25:4–12; Ex. 1037, 3:10–15, 32:22–33:23, 34:6–9, 126:4–10; Ex. 1038, 1–2; Ex. 1039, 1:28–65; Ex. 1040, 28:5–18, 29:10–31:19). However, we do not find that these exhibits support Petitioner's position. For example, Exhibits 1029 and 1037 discuss the opposite—the use of reversible terminators developed for sequencing-by-synthesis in Sanger sequencing. Ex. 1029, 30:28–36; Ex. 1037, 32:22–30; Ex. 2001 ¶ 105. Exhibits 1009 and 1040 refer to Prober[12] for the attachment of the dye to the base in a ddNTP, which is a non-reversible terminator used in Sanger sequencing. Ex. 1009, 1768; Ex. 1040, 28:5–18; 29:10–31:19; Ex. 1035, 25:4–12; Ex. 2001 ¶ 105. The other cited exhibits describe methods specific to Sanger sequencing (e.g., discussion of eliminating gel electrophoresis) that do not appear to be transferable to the sequencing-by-synthesis method disclosed in Banerjee. *See* Ex. 1019 ¶¶ 215, 217; Ex. 1038, 1–2; Ex. 1039, 1:28–65; Ex. 2001 ¶ 105. Therefore, Petitioner and Dr. Romesberg have not sufficiently shown how their cited exhibits demonstrate the use of Sanger sequencing techniques in a sequencing-by-synthesis method as taught by Banerjee.

Petitioner also asserts that using Mathies' two-label scheme in Banerjee's sequencing-by-synthesis method would decrease photobleaching. Pet. 41. Similar to the discussion above, Banerjee itself already describes ways to deal with any potential photobleaching problem. For example, Banerjee describes a technique called Time Delay Integration which decreases the scanning time and other ways to reduce exposure time, for example, by narrowing the area that is illuminated to only those spots that are being imaged. Ex. 2001 ¶ 88; Ex. 1002 ¶¶ 125, 134, 145, 153, 203. In view of these improvements, Petitioner does not sufficiently explain why

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[12] Prober et al., A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides, Science, Vol. 238, 336–341 (1987) (Ex. 1011, "Prober").

Banerjee's system would still require or benefit from additional methods of reducing photobleaching.

Petitioner further argues that one of ordinary skill in the art would have been motivated to combine the teachings of Mathies and Banerjee because others in the field, such as Chee, had already disclosed sequencing-by-synthesis and binary coding to identify four nucleotides. Pet. 41. However, as discussed below, Chee does not disclose a two-label detection scheme in a sequencing-by-synthesis method. Accordingly, this argument also fails.

Therefore, for the reasons set forth above, we agree with Patent Owner that neither Petitioner nor Dr. Romesberg explains persuasively why one of ordinary skill in the art, absent resort to hindsight and/or use of the '132 patent as a roadmap, would have sought to combine the two-label teaching of Mathies with the sequencing-by-synthesis method of Banerjee. *See KSR*, 550 U.S. at 418 ("[A] patent ... is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.").

b. Expectation of Success

We also find that Petitioner has not presented sufficient evidence that one of skill in the art would have had a reasonable expectation of success in using the two-label technique disclosed in Mathies for Sanger sequencing in the sequencing-by-synthesis method disclosed in Banerjee. As discussed above, Mathies' two-label technique resulted in a 5.4% error rate and neither Petitioner nor Dr. Romesberg provide sufficient evidence that one of ordinary skill in the art would have expected a better outcome using the two-label approach in the sequencing-by-synthesis method.[13] *See* Ex. 1030, 2153.

Furthermore, we agree with Patent Owner and Dr. Metzker that Sanger sequencing and sequencing-by-synthesis are two different sequencing technologies with different reagents and methodologies. *See* Ex. 2001 ¶ 100. As described by Dr. Metzker, the combination of Mathies with Banerjee does not involve the simple substitution of one element for another and Petitioner has not sufficiently shown that one of ordinary skill in the art would have had a reasonable expectation of success in using the two-label technique of Mathies in the sequencing-by-synthesis method of Banerjee. *See* Ex. 2001 ¶ 100.

For example, combining Mathies with Banerjee would require taking Mathies' disclosure of irreversible chain terminating nucleotides (that may or may not be labeled), and modifying them to be reversible and labeled. *See* Ex. 2001 ¶¶ 64–67, 100. Such a combination would also require modifying Mathies' disclosure of using only three irreversible chain terminating nucleotides, by adding a fourth, dark-state nucleotide, which would also need to be reversibly terminating, to be used in the sequencing-by-synthesis method of Banerjee. *See* Ex. 2001 ¶¶ 64–67. Petitioner has not sufficiently shown that one of ordinary skill in the art would have had a reasonable expectation of success in making these modifications.

[13] Petitioner asserts that "the relevant expectation of success is performing at least two cycles of sequencing-by-synthesis and making a deduction as to the identity of the incorporated nucleotide." Pet. 49–50. Regardless of whether or not this is true, Petitioner still has not sufficiently shown why one of ordinary skill in the art would have had a reasonable expectation of success given the high error rates of Mathies' two-label system.

In addition, Petitioner and Dr. Romesberg have not sufficiently shown that one of skill in the art would have known how to modify the Sanger sequencing reagents Mathies used to produce acceptable results in the sequencing method of Banerjee. Petitioner and Dr. Romesberg assert that a person of ordinary skill in the art "would have known how to adjust the relative concentration of the labeled and unlabeled nucleotides based on the same type of routine concentration optimization known in the prior art for Sanger-sequencing." Pet. 43 (citing Ex. 1005 ¶¶ 117–120). However, neither Petitioner nor Dr. Romesberg sufficiently account for the fact that there is a difference in adjusting the concentrations of natural and terminating nucleotides in a mixture in Sanger sequencing compared to adjusting concentrations of labeled reversible terminators relative to unlabeled reversible terminators. *See* Ex. 2001 ¶ 97.

We are not persuaded by Petitioner's assertion that the waveplates disclosed in Banerjee allow for dark locations on the flowcell surface to be accurately identified. *See* Pet. 43. Banerjee describes rotation of waveplates which "results in spatial redistribution of the dark and bright regions;" however, neither Petitioner nor Dr. Romesberg have presented sufficient evidence to show how use of such waveplates could potentially solve the issues with a dark state as described in Mathies. Ex. 1002 ¶ 140; Ex. 2001 ¶ 99.

Similarly, we are not persuaded by Petitioner's argument that increasing Banerjee's cluster size increases the brightness of each cluster as evidence that one of skill in the art would have had a reasonable expectation of success in combining Mathies and Banerjee. *See* Prelim. Resp. 49 (citing Ex. 1005 ¶ 121). Petitioner does not provide sufficient information to show

how this increase in cluster size could ameliorate the problems with the dark-state as discussed in Mathies.

With regard to Petitioner's arguments regarding statements made by Patent Owner during prosecution of related patents as evidence of a reasonable expectation of success in combining the disclosures of Mathies and Banerjee, we are similarly not persuaded. *See* Pet. 46–47. For example, the arguments made by Patent Owner during prosecution of the '277 application were made in the context of using techniques from sequencing-by-ligation in a sequencing-by-synthesis method rather than applying Sanger sequencing techniques in Banerjee's sequencing-by-synthesis method. *See* Ex. 1042, 27–28.[14] Furthermore, with regard to the '968 application, Petitioner has not sufficiently described how statements made by Patent Owner regarding the level of skill in the art and certain disclosures in the Specification are probative of a reasonable expectation of success in combining Mathies and Banerjee. *See* Ex. 1041, 12, 14.[15]

We are similarly not persuaded by Petitioner's argument that, because all of the examples in the '132 patent are prophetic, this provides evidence that one of ordinary skill in the art would have had a reasonable expectation of success. *See* Pet. 45–46. Petitioner has not provided sufficient evidence that the asserted lack of disclosure in the '132 patent results in a reasonable expectation of success to one of skill in the art in combining the teachings of Mathies and Banerjee.

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[14] The cited page number in Exhibit 1042 refer to the numbers added by Petitioner in the bottom-right corner of the page.
[15] The cited page number in Exhibit 1041 refer to the numbers added by Petitioner in the bottom-right corner of the page.

In view of the foregoing, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that the subject matter of challenged claims 1–9 would have been obvious over the combined disclosures of Banerjee and Mathies.

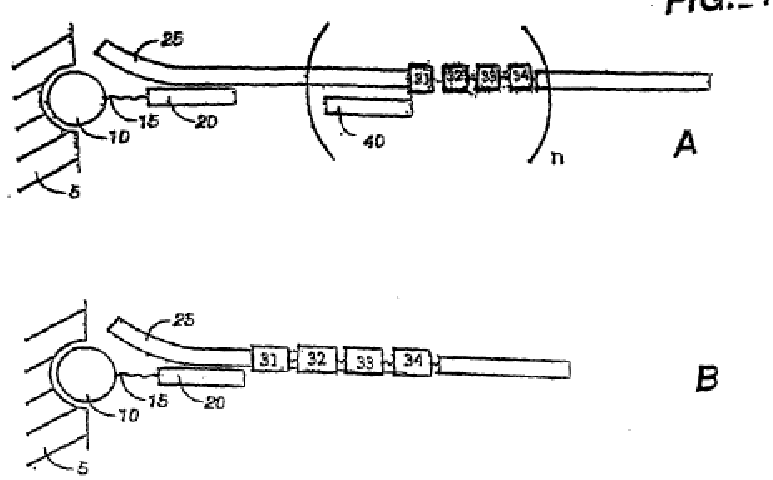
E. *Asserted Obviousness of Claims 1–9 over Chee*

Petitioner asserts that claims 1–9 would have been obvious over the disclosure of Chee. Pet. 60–81. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 51–62.

1. Chee

Chee discloses a sequencing method using microsphere arrays, which are comprised of an array of microspheres or beads. Ex. 1004, code (57). Chee teaches that each bead has multiple copies of a single type of nucleic acid capture probe attached to its surface. *Id.* ¶¶ 87, 119, 127. The capture probes "capture" target nucleic acids onto the array via hybridization. *Id.* ¶¶ 25, 84, 119–120. Figures 1A and 1B of Chee illustrate the beads 10, nucleic acid capture probes 20, and hybridized target nucleic acids 25:

FIG._1



Ex. 1004, Figs. 1A–1B. Figures 1A and 1B depict a substrate 5 with a capture probe 20.

Chee discloses the target nucleic acid sequence 25 comprises "target positions" 31, 32, 33 and 34 for which sequence information is desired. Ex. 1004 ¶¶ 15, 16, 25, 59. The identification of a plurality of target positions in a target nucleotide results in the determination of the sequence of the target nucleotide. *Id.* ¶ 25.

Chee's microsphere arrays have many beads that are randomly distributed within wells on the surface of a substrate. Ex. 1004 ¶¶ 108, 131–132, 159. These microsphere arrays "are constructed such that information about the identity of the capture probe is built into the array, such that the random deposition of the beads in the fiber wells can be 'decoded' to allow identification of the capture probe at all positions" on the surface of the substrate. *Id.* ¶ 159. The capture probes may serve as bead identifiers to decode the beads in the array. *Id.* ¶¶ 132, 135, 159–160.

The identity of the capture probes is determined by "identifier binding ligands" ("IBLs"), which can encompass a variety of compounds and will bind to a capture probe. Ex. 1004 ¶ 135. The IBL compound "is a molecule whose color or luminescence properties change in the presence of a selectively-binding DBL." *Id.* ¶ 137. The use of IBLs is described in Chee as follows:

> Alternatively, the combination of different IBLs can be used to elucidate the sequence of the nucleic acid. Thus, for example, using two different IBLs (IBL1 and IBL2), the first position of a nucleic acid can be elucidated: for example, adenosine can be represented by the presence of both IBL1 and IBL2; thymidine can be represented by the presence of IBL1 but not IBL2, cytosine can be represented by the presence of

> IBL2 but not IBL1, and guanosine can be represented by the absence of both. The second position of the nucleic acid can be done in a similar manner using IBL3 and IBL4; thus, the presence of IBL1, IBL2, IBL3 and IBL4 gives a sequence of AA; IBL1, IBL2, and IBL3 shows the sequence AT; IBL1, IBL3 and IBL4 gives the sequence TA, etc. The third position utilizes IBL5 and IBL6, etc. In this way, the use of 20 different identifiers can yield a unique code for every possible 10-mer.
>
> In this way, a sort of "bar code" for each sequence can be constructed; the presence or absence of each distinct IBL will allow the identification of each capture probe.

Id. ¶¶ 146–147.

2. Petitioner's Position

Petitioner asserts that Chee renders the claims of the '132 patent obvious based on its disclosure of a "two-label array decoding scheme" and "the more general disclosure in Chee to use sequencing-by-synthesis as an array decoding scheme for arrays of capture probes." Pet. 72. With respect to limitations 1(b)(ii)(1)–(4) of claim 1, which recite the two-label approach, Petitioner asserts that Chee discloses these limitations when it "discloses a combination of two IBLs as a binary coding scheme for the purpose of elucidating the [sequence of] nucleic acids to decode an array." *Id.* at 70. Specifically, Petitioner cites to the following excerpt from Chee:

> [T]he combination of different IBLs can be used to elucidate the sequence of the nucleic acid. Thus, for example, using two different IBLs (IBL1 and IBL2), the first position of a nucleic acid can be elucidated: for example, adenosine can be represented by the presence of both IBL1 and IBL2; thymidine can be represented by the presence of IBL1 but not IBL2, cytosine can be represented by the presence of IBL2 but not IBL1, and guanosine can be represented by the absence of both.

Id. (citing Ex. 1004 ¶ 146). According to Petitioner, "Chee's two-label IBL approach (e.g. two fluorescent labels) for sequencing-based decoding 'allow[s] the identification of each capture probe.'" *Id.* (citing Ex. 1004 ¶ 147).

Petitioner argues that "Chee suggests decoding the sequence of capture probes using sequencing-by-synthesis by implementing Chee's preferred reversible chain termination nucleotides with Chee's two-label decoding scheme to identify incorporated nucleotides" and, therefore, "renders obvious limitations 1(b)(ii)(1)-(4)." Pet. 71 (citing Ex. 1005 ¶ 196). Petitioner further contends that a person of ordinary skill in the art "would have been motivated to implement Chee's two-label method in Chee's preferred reversible chain termination sequencing-by-synthesis for the purpose of decoding the sequence of capture probes." *Id.* at 74 (citing Ex. 1005 ¶¶ 199–203).

3. Patent Owner's Position

Patent Owner argues, *inter alia*, that "Chee actually discloses a scheme to identify a known capture probe using two unique labels ***at each nucleotide position*** of the capture probe." Prelim. Resp. 51. Therefore, according to Patent Owner, "rather than teaching the use of ***two*** labels, Chee actually teaches the use of ***2n*** labels, where ***n*** is the number of nucleotides to be decoded." *Id.* Patent Owner further asserts:

> Chee does not even teach a decoding method using just two labels, let alone a sequencing or [sequencing-by-synthesis] method using just two labels. Instead, Chee teaches a decoding method that uses ***a different set of two identifying labels for each nucleotide*** in the capture probe to be decoded. So, if one were determining what nucleotide was present at each position in an oligonucleotide comprised of ten nucleotides, known as a

> "10 mer," Chee teaches that one would need ***twenty*** different unique identifiers or labels.

Id. at 52 (citing Ex. 2001 ¶ 116). Therefore, Patent Owner asserts that Petitioner's argument that Chee renders claims of the '132 patent obvious fails. *Id.* at 51.

4. Analysis

For the reasons explained below, upon consideration of the Petition, Preliminary Response, and the evidence of record, we are not persuaded that Petitioner has provided sufficient argument and supporting evidence to demonstrate a reasonable likelihood that challenged claims 1–9 would have been obvious over Chee.

Petitioner has not presented sufficient evidence to show that Chee renders obvious limitations 1(b)(ii)(1)–(4) of claim 1. Petitioner cites to a portion of paragraph 146 of Chee, which describes the use of two IBLs (IBL1 and IBL2) to elucidate the sequence of a capture probe (Pet. 70); however, Petitioner fails to cite the remainder of this paragraph, which describes using two different labels (IBL3 and IBL4) to elucidate the second position of the sequence and still two different labels (IBL5 and IBL6) to elucidate the third position as shown below:

> Alternatively, the combination of different IBLs can be used to elucidate the sequence of the nucleic acid. Thus, for example, using two different IBLs (IBL1 and IBL2), the first position of a nucleic acid can be elucidated: for example, adenosine can be represented by the presence of both IBL1 and IBL2; thymidine can be represented by the presence of IBL1 but not IBL2, cytosine can be represented by the presence of IBL2 but not IBL1, and guanosine can be represented by the absence of both. **The second position of the nucleic acid can be done in a similar manner using IBL3 and IBL4; thus, the**

> **presence of IBL1, IBL2, IBL3 and IBL4 gives a sequence of AA; IBL1, IBL2, and IBL3 shows the sequence AT; IBL1, IBL3 and IBL4 gives the sequence TA, etc. The third position utilizes IBL5 and IBL6, etc. In this way, the use of 20 different identifiers can yield a unique code for every possible 10-mer.**

Ex. 1004 ¶ 146 (emphasis added).

Therefore, we agree with Patent Owner and Dr. Metzker that Chee actually teaches the use of 2n labels, where n is the number of nucleotides to be decoded. *See* Prelim. Resp. 51; Ex. 2001 ¶ 122. For example, as stated in Chee, to decode an oligonucleotide that is ten nucleotides long, one would need twenty different labels. Ex. 1004 ¶ 146.

Accordingly, Petitioner has not sufficiently shown that limitations 1(b)(ii)(1)–(4) of claim 1 would have been obvious to one of ordinary skill in the art based on the disclosure of Chee. Similarly, Petitioner has not sufficiently shown that Chee would have rendered obvious the limitations of claim 5 that require the use of "two distinguishable fluorescent labels" in steps (i) through (iv). Ex. 1001, 50:47–58.

In view of the foregoing, we are not persuaded that Petitioner has demonstrated a reasonable likelihood that the subject matter of challenged claims 1–9 would have been obvious over the disclosure of Chee.

III. CONCLUSION

For the reasons set forth above, Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to challenged claims 1–9 of the ’132 patent. Thus, we do not institute an *inter partes* review with respect to the challenged claims.

IV. ORDER

It is

ORDERED that the Petition is *denied* and no *inter partes* review is instituted.

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