

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ILLUMINA, INC.,  
Petitioner,

v.

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

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Case IPR2018-00322  
Patent 9,708,358 B2

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Before JENNIFER MEYER CHAGNON, JAMES A. WORTH, and  
MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

CHAGNON, *Administrative Patent Judge*.

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

## I. INTRODUCTION

Illumina, Inc. (“Petitioner”) filed a Petition for *inter partes* review of claim 1 of U.S. Patent No. 9,708,358 B2 (Ex. 1002, “the ’358 patent”). Paper 2 (“Pet.”). Petitioner relies on the Declaration of Floyd Romesberg, Ph.D. (Ex. 1067) to support its positions. The Trustees of Columbia University in the City of New York (“Patent Owner”) filed a Preliminary Response. Paper 9 (“Prelim. Resp.”).

We have authority to determine whether to institute *inter partes* review. *See* 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). An *inter partes* review may not be instituted “unless the Director determines . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). As discussed below, we institute an *inter partes* review of claim 1 on all grounds set forth in the Petition.

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely-filed response shall be deemed waived, even if they were presented in the Preliminary Response.

### A. *Related Proceedings*

The parties indicate that the ’358 patent is the subject of the following district court proceeding involving Petitioner and Patent Owner: *Trustees of Columbia University v. Illumina, Inc.*, Case No. 17-cv-973-GMS (D. Del.). Pet. 76; Paper 4, 1.

The parties further indicate that Petitioner has filed additional petitions for *inter partes* review of various other patents owned by Patent Owner: Cases IPR2018-00291 (challenging U.S. Patent No. 9,718,852), IPR2018-00318 (challenging U.S. Patent No. 9,719,139), IPR2018-00385 (challenging U.S. Patent No. 9,725,480), and IPR2018-00797 (challenging U.S. Patent No. 9,868,985). Pet. 75–76; Paper 3, 1; Paper 4, 1; Paper 8, 1.

The parties also note that in IPR2012-00006, IPR2012-00007, and IPR2013-00011, the Board found challenged claims of Patent Owner’s U.S. Patent Nos. 7,713,698; 7,790,869; and 8,088,575, respectively, to be unpatentable. Pet. 76–77; Paper 4, 1; *see* Ex. 1005; Ex. 1006; Ex. 1007; Ex. 1008 (Federal Circuit decision affirming these Board decisions). In IPR2013-00128 and IPR2013-00266, the Board found challenged claims of Petitioner’s U.S. Patent Nos. 7,057,026 and 8,158,346, respectively, to be unpatentable. Pet. 77; Paper 4, 2; *see* Ex. 1048; Ex. 1049; Ex. 1050 (Federal Circuit decision affirming these Board decisions). In IPR2013-00517, the Board held that challenged claims of Petitioner’s U.S. Patent No. 7,566,537 were not unpatentable.<sup>1</sup> Pet. 77–78; Paper 4, 2; *see* Ex. 1044; Ex. 1045 (Federal Circuit decision affirming this Board decision).

#### *B. The ’358 Patent*

The ’358 patent is titled “Massive Parallel Method for Decoding DNA and RNA” and relates to a “system for DNA sequencing by the synthesis approach which employs a stable DNA template, which is able to self prime

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<sup>1</sup> The ’537 patent also was challenged by a third party in IPR2017-02172 and IPR2017-02174, in each of which institution was denied. Pet. 78; Paper 13, 1.

for the polymerase reaction, covalently linked to a solid surface such as a chip, and 4 unique nucleotides analogues.” Ex. 1002, at [54], 4:26–31.

The ’358 patent discloses that electrophoresis was a bottleneck for high-throughput DNA sequencing and mutation detection projects. *Id.* at 2:16–19. It was known to perform sequencing without electrophoresis, using a chip format and laser-induced fluorescent detection for DNA sequencing. *Id.* at 2:20–27. The ’358 patent discloses that “[l]ong stretches of the same bases cannot be identified unambiguously with [a] pyrosequencing method.” *Id.* at 2:44–46. The ’358 patent also describes limited success in the prior art for the incorporation of 3'-modified nucleotides by DNA polymerase. *Id.* at 2:52–53.

The approach disclosed in the ’358 patent is

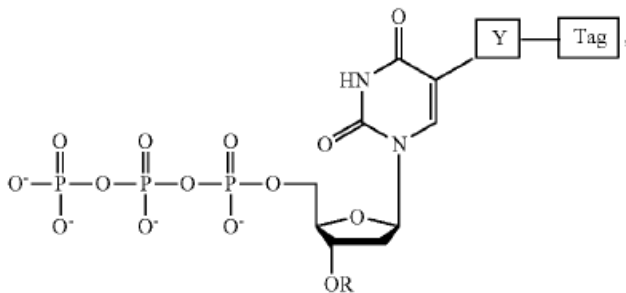
to make nucleotide analogues by linking a unique label such as a fluorescent dye or a mass tag through a cleavable linker to the nucleotide base or an analogue of the nucleotide base, such as to the 5-position of the pyrimidines (T and C) and to the 7-position of the purines (G and A), to use a small cleavable chemical moiety to cap the 3'-OH group of the deoxyribose to make it nonreactive, and to incorporate the nucleotide analogues into the growing DNA strand as terminators.

*Id.* at 3:4–13; *see also id.* at 5:40–41. The approach disclosed in the ’358 patent is further “to incorporate nucleotide analogues, which are labeled with cleavable, unique labels such as fluorescent dyes . . . and where the 3'-OH is capped with a cleavable chemical moiety, such as either a MOM group (–CH<sub>2</sub>OCH<sub>3</sub>) or an allyl group (–CH<sub>2</sub>CH=CH<sub>2</sub>), into the growing strand DNA as terminators.” *Id.* at 3:44–51; *see also id.* at 5:43–44.

*C. Illustrative Claim*

Claim 1, reproduced below, is the sole challenged claim and is illustrative of the subject matter:

1. A cytosine deoxyribonucleotide analogue having the structure:



wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue, (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase, (c) is stable during a DNA polymerase reaction, and (d) does not contain a ketone group;

wherein OR is not a methoxy group or an ester group;

wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction;

wherein tag represents a detectable fluorescent moiety;

wherein Y represents a chemically cleavable, chemical linker which (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction; and

wherein the cytosine deoxyribonucleotide analogue:

- i) is recognized as a substrate by a DNA polymerase,
- ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,

iii) produces a 3'-OH group on the deoxyribose upon cleavage of R,

iv) no longer includes a tag on the base upon cleavage of Y, and

v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue.

Ex. 1002, 34:2–35:4.

*D. The Applied References*

Petitioner relies on the following references in the asserted grounds.

Pet. 15.

Reference	Issue/Publication Date	Exhibit
WO 91/06678 (“Tsien”)	May 16, 1991	Ex. 1013
U.S. Patent No. 5,547,839 (“Dower”)	Aug. 20, 1996	Ex. 1015
Michael L. Metzker et al., <i>Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphosphates</i> , 22(20) NUCLEIC ACIDS RESEARCH 4259–67 (1994) (“Metzker”)	1994	Ex. 1016
James M. Prober et al., <i>System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides</i> , 238 SCIENCE 336–341 (Oct. 16, 1987) (“Prober”)	Oct. 16, 1987	Ex. 1014

*E. The Asserted Grounds*

Petitioner challenges claim 1 of the '358 patent as unpatentable under 35 U.S.C. § 103(a) in view of Tsien, and in view of the combination of Dower, Prober, and Metzker. Pet. 15–74.

## II. ANALYSIS

### A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142–46 (2016). Petitioner does not request construction of any terms. *See* Pet. 7. Patent Owner requests construction of the terms “small” and “chemical linker.” Prelim. Resp. 9–11. Based on our review of the Petition, Preliminary Response, and both parties’ supporting evidence, we determine that no terms require express construction for the purposes of this Decision. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

### B. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) 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. *See 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 ordinary skill in the art; and (4) objective evidence of

nonobviousness.<sup>2</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). In that regard, an obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *accord In re Translogic Tech., Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007).

We analyze the asserted grounds of unpatentability in accordance with these principles to determine whether Petitioner has met its burden to establish a reasonable likelihood of success at trial.

*C. Level of Ordinary Skill in the Art*

Petitioner asserts that a person of ordinary skill in the art “would have been a member of a team of scientists developing nucleotide analogues, researching DNA polymerases, and/or addressing DNA sequencing techniques. Such a person would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience.” Pet. 8; Ex. 1067 ¶ 24. Thus, according to Petitioner, a person of ordinary skill in the art “includes a person having a doctoral degree in a field related to chemistry, and at least five years of laboratory experience directed toward the research and development of nucleotide analogues, DNA polymerases, and/or DNA sequencing.” Pet. 8; Ex. 1067 ¶ 24. Patent Owner “agrees with [Petitioner’s] criteria for defining a [person of ordinary skill in the art].”

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<sup>2</sup> At this stage of the proceeding, the parties have not directed our attention to any objective evidence of non-obviousness.



Prelim. Resp. 8. For purposes of this Decision, we adopt Petitioner’s proposal regarding the level of ordinary skill in the art.

*D. The Asserted Prior Art*

*1. Tsien (Ex. 1013)*

Tsien is titled “DNA Sequencing” and “relates to an instrument and a method to determine the nucleotide sequence in a DNA molecule without the use of a gel electrophoresis step.” Ex. 1013, at [54], [57]. Tsien discloses a method in which “an unknown primed single stranded DNA sequence . . . is immobilized . . . within a chamber with a polymerase so that the sequentially formed cDNA can be monitored at each addition of a blocked nucleotide by measurement of the presence of an innocuous marker on specified deoxyribonucleotides.” *Id.* at [57]. According to Tsien, “[b]y noting the identity of the bases present in this complementary molecule and using standard rules of DNA complementation, one can translate from the complementary molecule to the corresponding original subject molecule and thus obtain the deoxyribonucleotide sequence of the subject molecule.” *Id.* at 7:9–14.

Figure 1B of Tsien is reproduced below:

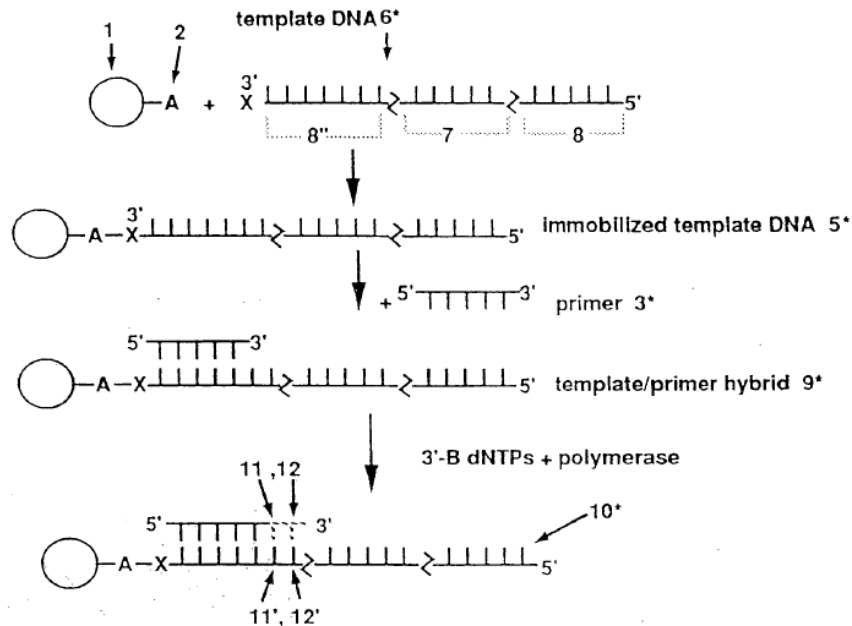


FIG. 1B

Figure 1B, above, is a schematic diagram of Tsien's process on a molecular level. *Id.* at 8:16–17.

Tsien's method "can be practiced to create the growing complementary DNA chain without interruption or it can be practiced in stages wherein a portion of the complementary chain is created and its sequence determined; this portion of the chain is then removed; a sequence corresponding to a region of the removed chain is separately synthesized and used to prime the template chain for subsequent chain growth." *Id.* at 7:34–8:5. Tsien describes that a blocking group is present on the 3'-hydroxyl position of the added dNTP to prevent inadvertent multiple additions. *Id.* at 12:27–29. The identity of this first nucleotide can be determined by detecting and identifying the label attached to it, where a different label is used for each nucleotide. *Id.* at 13:1–3. Tsien discloses adding a deblocking

solution to regenerate the 3'-hydroxyl position on the first nucleotide present. *Id.* at 13:17–22.

## 2. Prober (Ex. 1014)

Prober is titled “A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides” and relates to a “DNA sequencing system based on the use of a novel set of four chain-terminating dideoxynucleotides, each carrying a different chemically tuned succinylfluorescein dye distinguished by its fluorescent emission.”

Ex. 1014, 336. Fluorescence-tagged chain terminating reagents are depicted in Figure 2A of Prober, reproduced below:

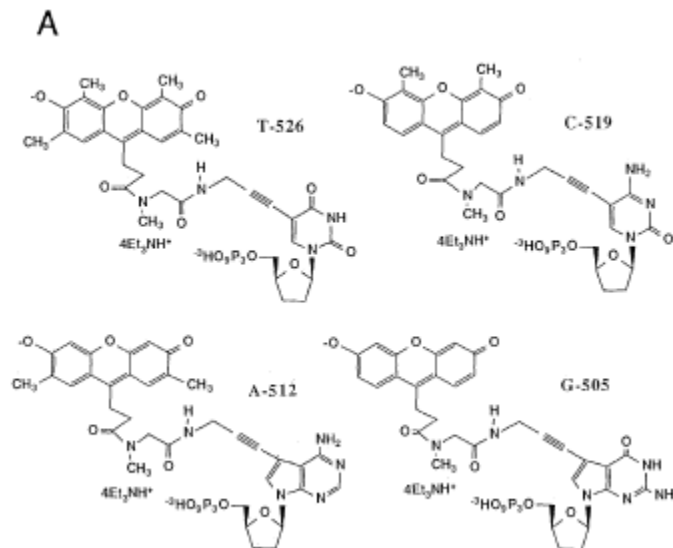


Figure 2A, above, depicts “[c]hemical structures of the reagents used in modified dideoxy reactions for DNA sequencing.” *Id.* at 338. Prober discloses that succinylfluorescein is attached via a linker to a heterocyclic base, i.e., a nucleotide analogue. *See id.* at 337. In particular, the linker is attached to the 5 position in the pyrimidines and to the 7 position in the 7-deazapurines. *Id.*

3. Dower (Ex. 1015)

Dower is titled “Sequencing Of Surface Immobilized Polymers Utilizing Microfluorescence Detection” and “relates to the determination of the sequences of polymers immobilized to a substrate.” Ex. 1015, at [54], 1:21–22. In particular, one embodiment “provides a method and apparatus for sequencing many nucleic acid sequences immobilized at distinct locations on a matrix surface.” *Id.* at 1:22–25. Dower describes a problem with prior art methods, i.e., that certain methods required “isolation and purification of the nucleic acid to be sequenced and separation of nucleic acid molecules differing in length by single nucleotides.” *Id.* at 2:35–39. According to Dower, prior art methods also “suffer[ed] from the requirement to isolate and work with distinct homogeneous molecules in each determination.” *Id.* at 2:43–44.

In one embodiment for the synthesis of nucleotides, Dower discloses that a polymerase is used to extend a primer complementary to a target template, where the primer is elongated one nucleotide at a time by using a particular modified nucleotide analogue to which a blocking agent is added and which prevents further elongation. *Id.* at 14:48–53. Dower discloses that, in certain embodiments, the blockage is reversible. *Id.* at 14:53–56. The analogue also is labeled with a removable moiety, e.g., a fluorescent label so that a scanning system can detect the particular nucleotide. *Id.* at 14:56–58. Figure 8A of Dower is reproduced below:



*E. Obviousness of Claim 1 in view of Tsien*

Petitioner asserts that claim 1 is unpatentable under 35 U.S.C. § 103 as obvious in view of Tsien. Pet. 16–38. Patent Owner opposes. Prelim. Resp. 16–50. We address the parties’ contentions below. We emphasize that the following determinations regarding the sufficiency of the Petition are preliminary in nature at this stage of the proceeding.

*1. “A cytosine deoxyribonucleotide analogue having the structure” as depicted in claim 1*

Petitioner asserts, *inter alia*, that Tsien discloses a 3'-blocked cytosine analogue. Pet. 19 (citing, e.g., Ex. 1013, 9:30–10:15, 12:22–27, Fig. 2; Ex. 1067 ¶ 55).<sup>3</sup> Patent Owner does not appear to dispute this limitation. *See generally* Prelim. Resp. 19–50. On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Figure 2 of Tsien discloses “3'-BLOCKED dC"TP.” Ex. 1013, Fig. 2; *see also id.* at 12:22–27.

Petitioner asserts that Tsien further discloses 5-substituted pyrimidines, and in particular “a cytosine deoxyribose nucleotide having a fluorescent label attached through a linker to the 5-position of the base,” as depicted in claim 1. Pet. 20 (citing Ex. 1013, 30 (Fig. B); Ex. 1067 ¶ 57). On this record, we are persuaded that Petitioner has made an adequate showing.

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<sup>3</sup> The parties are instructed to use spaces rather than dashes where appropriate so as not to circumvent word count limits in future filings, i.e., to use “Ex. 1013” rather than “Ex-1013” or “Ex. 2029” rather than “Ex.-2029.”

2. “wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue”; “wherein R . . . (d) does not contain a ketone group”; and “wherein OR is not a methoxy group or an ester group”

Petitioner asserts, *inter alia*, that Tsien discloses a cytosine deoxyribonucleotide analogue having a blocking group capping the 3'-oxygen of the deoxyribose and that an O-allyl ether group is an advantageous blocking group. *See* Pet. 22–24 (citing Ex. 1013, 12:27–29, 24:25–25:3, Fig. 2; Ex. 1067 ¶ 61); *id.* at 26–27 (citing Ex. 1013, 24:5–7, 24:24–25:3; Ex. 1067 ¶ 70). Petitioner contends that Tsien discloses the same allyl capping group that the patent applicant “admitted . . . would have been recognized as small.” *Id.* at 23 (citing Ex. 1066 ¶ 22a; Ex. 1065, 21); Ex. 1066 ¶ 19. Petitioner also relies on experiments using allyl groups disclosed in Metzker, which we discuss in further detail with respect to other claim limitations. Pet. 23 (citing Ex. 1016, 4263); *see* Section II.E.3., *infra*.

Patent Owner counters that Petitioner has not established that Tsien discloses a “small” capping group not containing a ketone and not forming an ester or a methoxy group with the 3'-oxygen of the nucleotide analogue.<sup>4</sup> Prelim. Resp. 19–47. We address Patent Owner’s arguments as follows.

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<sup>4</sup> Patent Owner further contends that Petitioner has not shown “‘small’ capping groups, like the allyl capping group, ‘were desirable.’” Prelim. Resp. 40–43. However, on this record, we are persuaded that Petitioner has made an adequate showing that the allyl capping group of Tsien is “small” within the meaning of the claim. *See, e.g.*, Pet. 23 (citing Ex. 1066 ¶ 22a; Ex. 1065, 21). We, thus, do not further address Patent Owner’s arguments in this regard for purpose of this Decision, but focus instead on Patent Owner’s arguments that a person of ordinary skill in the art would not have been motivated to select the allyl group of Tsien.

Efficiency and mildness arguments

Patent Owner argues that Tsien requires mild conditions for cleaving and argues that Petitioner has failed to show that Tsien's allyl capping group could be cleaved quantitatively under mild conditions, or that a person of ordinary skill in the art would have had a reasonable expectation of success in using an allyl group. Prelim. Resp. 33 (citing Ex. 1013, 20–21), 43. Patent Owner argues that Petitioner has failed to demonstrate that allyl capping can be conducted under mild conditions because the references on which Petitioner relies to support that teaching disclose conditions that are “*not mild*.” *Id.* at 33–34. Specifically, Patent Owner asserts that Qian<sup>5</sup> uses methanol, which was known to denature DNA, Boss<sup>6</sup> uses heat, and both Qian and Boss use PdCl<sub>2</sub>, which was not necessarily known to be compatible with DNA. *Id.* (citing Ex. 1036, 2185; Ex. 2007 ¶¶ 47, 55; Ex. 1035, 558–559). Patent Owner also asserts that Qian required 2 hours for cleavage and Boss required “a few hours.” *Id.* at 34 (citing Ex. 1036, 2185; Ex. 1035, 558–559). Patent Owner has not adduced testimonial evidence interpreting these references at this stage of the proceeding.

Patent Owner further argues that Petitioner has not established a reason one of ordinary skill in the art would have selected Tsien's allyl capping group. Prelim. Resp. 23–37. Patent Owner argues that Tsien also discloses ester capping groups that offer the advantage of preventing

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<sup>5</sup> Xiangping Qian et al., *Unexpected Enzymatic Fucosylation of the Hindered Tertiary Alcohol of 3-C-Methyl-N-Acetylglucosamine Produces a Novel Analogue of the LeX-Trisaccharide*, 120 J. AM. CHEM. SOC. 2184–84 (1998) (Ex. 1036).

<sup>6</sup> Roland Boss & Rolf Scheffold, *Cleavage of Allyl Ethers with Pd/C*, 15 ANGEW. CHEM. INT. ED. ENGL. 558–59 (1976) (Ex. 1035).



significant premature deblocking and identifies groups suitable for photochemical and enzymatic removal. *Id.* at 24 (citing Ex. 1013, 24–25). Patent Owner asserts that “Tsien discloses no preference or requirement regarding the size of the blocking group, and provides no other disclosures that would [have led] a [person of ordinary skill in the art] to use the allyl capping group.” *Id.* at 25; *see also id.* at 27–30.

Petitioner asserts that Qian discloses “quantitative” allyl cleavage. Pet. 22, 33 (citing Ex. 1036, 2184). Petitioner also asserts that Patent Owner has admitted that it was known that an allyl group could be cleaved with high yield. Pet. 23 (quoting Ex. 1002, 3:41–44 (“[i]t is known that ... allyl (-CH<sub>2</sub>CH=CH<sub>2</sub>) groups can be used to cap an -OH group, and can be cleaved chemically with high yield (Ireland et al. 1986; Kamal et al. 1999.”); citing Ex. 1002, 26:22–25 (“The MOM (-CH<sub>2</sub>OCH<sub>3</sub>) or allyl (-CH<sub>2</sub>CH=CH<sub>2</sub>) group is used to cap the 3'-OH group using well-established synthetic procedures (FIG. 13) (Fuji et al. 1975, Metzker et al. 1994).”)).

On this record, we determine that Petitioner has demonstrated a reason for using, and a reasonable expectation of success in using, an allyl group as a blocking group to cap the 3'-hydroxyl group of a nucleotide analogue based on the teachings of Tsien, Kamal<sup>7</sup>, Qian, and the admission in the '358 patent as to what was well known in the art. Ex. 1013, 24; Ex. 1037, 371–72; Ex. 1036, 2184; Ex. 1002, 3:41–44, 26:22–25; *see also* Ex. 1035, 559. On the current record at this stage of the proceeding, Qian

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<sup>7</sup> Ahmed Kamal et al., *A Mild and Rapid Regeneration of Alcohols from their Allylic Ethers by Chlorotrimethylsilane/Sodium Iodide*, 40 TETRAHEDRON LETTERS 371–72 (1999) (Ex. 1037).

reports “quantitative” yield using PdCl<sub>2</sub> to remove the O-allyl group. Ex. 1036, 2184. Further, whether or not Qian’s technique for deblocking allyl groups is sufficiently mild, other techniques were known. We note that Tsien’s teaching to deblock allyl ethers using Hg immediately follows the statement that care must be taken not to denature the DNA. Ex. 1013, 24. Further, the patentee has admitted that allyl capping was well known and effective, referring to Kamal. Ex. 1002, 3:41–44 (“[i]t is known that . . . allyl . . . groups . . . can be cleaved chemically with high yield”), 26:22–25 (using “well-established synthetic procedures”). Based on the evidence at this stage of the proceeding, we are persuaded that Petitioner has made a sufficient showing that a person of ordinary skill would have combined the teachings of Tsien to use the allyl group that Tsien discloses to be an advantageous blocking group, to block the 3'-oxygen, as elsewhere disclosed in Tsien’s method. *See* Ex. 1013, 12:27–29, 24:5–25:3. We invite further briefing on this issue at trial, including whether it was appreciated in the art that sufficiently mild conditions were known for cleaving allyl groups when working with nucleotide analogues.

*Estoppel arguments*

Patent Owner also argues that Kamal (Ex. 1037) establishes that cleavage was 93% and argues that such a cleavage rate (as a percent) is inconsistent with the requirements of Tsien’s methods that Petitioner has argued for, or that the Federal Circuit has required, in previous proceedings involving Petitioner (and another party):

Illumina cites Kamal (Ex-1037) as evidence the allyl capping group could be cleaved under mild conditions, but Kamal’s conditions do not result in what Illumina terms quantitative cleavage, resulting instead in 93% cleavage.

Ex-1037 at 372, Entry 8 (reporting 93% cleavage of allyl on sugar). Illumina previously asserted 93% cleavage is **not enough** to practice Tsien's methods, and that anything less than quantitative cleavage is insufficient. *See* Ex-2029<sup>[8]</sup> at 45 ("One skilled in the art would not have been motivated to combine the prior art references for SBS [sequencing by synthesis] unless there was a reasonable expectation that the combination would provide a 3'-protecting group that cleaves with nearly 100% efficiency."), 28 ("[O]ver 97% . . . is required."); Ex-2030<sup>[9]</sup> at 1 ("[T]he [cleavage] efficiency needed to be >97%."); Ex-1045<sup>[10]</sup> at 6 (Federal Circuit finding that: "In order for the deblocking (i.e., the removal of the protecting group) to be quantitative, it must take place at 100% or near-100% efficiency.").

Prelim. Resp. 34–35.

We do not find that Petitioner's position in this proceeding is necessarily inconsistent with the cited papers, based on the current record—even under Patent Owner's argument that Kamal resulted in 93% cleavage, Patent Owner has not persuaded us on this record that 93% is not sufficiently close to 100% cleavage for purposes of the experiments at issue here.<sup>11</sup> To the extent that Petitioner has previously argued to the Board that over 97% cleavage is required, the full quotation from Exhibit 2029 is "The experts for

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<sup>8</sup> *Illumina Cambridge Ltd. v. Intelligent Biosystems, Inc.*, Case No. 2015-1123 (Brief of Patent-Owner-Appellant Illumina Cambridge Ltd.) (filed Mar. 10, 2015) (Ex. 2029).

<sup>9</sup> *Illumina Cambridge Ltd. v. Intelligent Biosystems, Inc.*, Case IPR2013-00266 (Patent Owner Illumina's Reply to Petitioner's Opposition to Illumina's Motion To Amend) (filed Mar. 21, 2014) (Ex. 2030).

<sup>10</sup> *Intelligent Biosystems, Inc. v. Illumina Cambridge Ltd.*, Case No. 2015-1693, slip op. (Fed. Cir. May 9, 2016) (Ex. 1045).

<sup>11</sup> Although the burden for proving estoppel against Petitioner rests with Patent Owner, we are mindful that the ultimate burden for establishing reasonable likelihood of success on the merits remains with Petitioner.

both parties agreed that SBS requires that the 3'-protecting group of the nucleotides be removed with greater than 90% efficiency. The evidence showed that over 97%, and preferably nearly 100%, removal efficiency of the 3'-protecting group is required.” Ex. 2029, 28. It is possible that Petitioner’s argument is simply characterizing the evidence from a different proceeding, and Patent Owner has not necessarily established the same requirement based on the evidence of record in this proceeding.

Patent Owner also contends that Petitioner has previously taken an inconsistent position in a reexamination proceeding, when it argued that Tsien describes an allyl group as part of a general description of blocking methods, but does not disclose a removable allyl group at the 3'-carbon. Prelim. Resp. 20–21 (quoting Ex. 2022<sup>12</sup>, 10–11). Patent Owner argues that Petitioner breached its obligations by failing to disclose this inconsistent position. *See id.* at 22 (citing 37 C.F.R. § 42.11(a); 37 C.F.R. § 42.51(b)(1)(iii)).

At this stage of the proceeding, we are unpersuaded by Patent Owner’s contention that Petitioner has previously taken an inconsistent position because the asserted ground is based on obviousness, whereas the subject of the arguments in the previous reexamination to which Patent Owner refers were based on anticipation. *See* Ex. 2022, 10. Accordingly, on the present record, Petitioner’s arguments are not “clearly inconsistent” with those made in the reexamination and, for at least this reason, do not give rise to a judicial estoppel. *See Fitness Quest, Inc. v. Monti*, 330 Fed. Appx. 904 (Fed. Cir. 2009) (discussing *New Hampshire v. Maine*, 532 U.S.

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<sup>12</sup> *In re Hiatt*, Reexamination Application No. 90/008,152, Remarks (Apr. 30, 2007) (Ex. 2022).

742, 750–51 (2001) (several factors inform the decision whether to apply the doctrine of judicial estoppel, including whether a party’s later position is “clearly inconsistent” with its earlier position)). Further, Tsien suggests an allyl group as a blocking group in the very context of an application for a method of DNA sequencing. *See* Ex. 1013, 24–25.

Patent Owner also contends that Petitioner has admitted that there was “no concrete embodiment of the successful cleavage of a 3'-allyl group under DNA compatible conditions.” Prelim. Resp. 36 (citing Ex. 2015<sup>13</sup>, 2:60–65). However, Patent Owner has not established that this type of statement, in an unrelated issued patent, is binding as an admission against Petitioner in this *inter partes* review proceeding. Further, this statement appears to be, at most, a statement that there is no anticipatory reference, and does not preclude a determination of obviousness. *See* Ex. 2015, 2:60–65

3. “wherein R . . . (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase”

Petitioner asserts, *inter alia*, that Tsien discloses that “criteria for successful use of 3'-blocking groups include[s] . . . the ability of a polymerase enzyme to accurately and effectively incorporate the dNTPs carrying the 3'-blocking groups into the cDNA chain.” Pet. 24 (quoting Ex. 1013, 20:28–32; citing *id.* at 12:11–18, 19:4–18, 24:1–2). Petitioner further asserts that a person of ordinary skill in the art would have known that Tsien’s 3'-O-allyl group does not interfere with recognition by a DNA polymerase because Metzker demonstrated polymerase recognition in 1994. *Id.* (citing Ex. 1016, 4263; Ex. 1067 ¶¶ 63, 66).

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<sup>13</sup> U.S. Patent No. 7,541,444 B2, assigned to Illumina Cambridge Limited (Ex. 2015).

Patent Owner alleges that Metzker indicates that O-allyl-dATPs achieved termination in a non-specific manner when it reports that certain other nucleotide analogues were specific. Prelim. Resp. 27–28 (citing Ex. 1016, 4263). Although Metzker reports that three other capping groups resulted in specific termination, Metzker does not state that 3'-O-allyl-dATPs were non-specific and Patent Owner's assertion appears to be based on an inference that is not necessarily justified. On the contrary, the legend to Table 2 of Metzker states that the label "Inhibition" is used to refer to nonspecific DNA synthesis. Metzker instead uses the "Termination\*" label for O-allyl-nucleotides, where Termination "means that the termination bands mimic ddNTP termination bands." Ex. 1016, 4263 (Table 2).

Patent Owner further argues that Metzker indicates that termination was incomplete at a final concentration of 250  $\mu$ M of 3'-O-allyl-dATPs. Prelim. Resp. 27–29 (citing, e.g., Ex. 1016, 4263; Ex. 1017, 6348). Patent Owner asserts that Metzker reported that only three compounds "proved to be interesting DNA synthesis terminators," i.e., 3'-O-(2-nitrobenzyl)-dATP, 3'-O-methyl-dATP, and 3'-O-methyl-dTTP. *Id.* at 28 (citing Ex. 1016, 4265). Patent Owner argues that a person of ordinary skill would not have been interested in allyl capping groups because Tsien sets forth a requirement that a polymerase enzyme "accurately and efficiently" incorporate the 3'-modified dNTPs. Prelim. Resp. 30–32 (citing, e.g., Ex. 1013, 20–21).

As Patent Owner observes, Metzker reports that three other capping groups resulted in specific termination, and that the termination effect for the O-allyl capping group was incomplete at the studied concentration. *See* Ex. 1016, 4263 ("Termination\*" where "\*" means the activity was

incomplete at a final concentration of 250  $\mu\text{M}$ "); Ex. 1067 ¶ 63. A different reference, Wu<sup>14</sup>, further relates as follows:

The novel RT, N<sup>6</sup>-(2-nitrobenzyl)-dATP **IIIc**, provides favorable enzymatic properties with a variety of wild-type and mutant DNA polymerases. This is unlike the situation for 3'-modified nucleotides, which typically act as poor substrates for DNA polymerases. For example, screening 3'-O-allyl-dATP with eight different DNA polymerases revealed limited activity at high micromolar concentrations with only Vent(exo-) DNA polymerase (8). The highly related 9°N(exo-) DNA polymerase (30), containing the A485L and Y409V amino acid variants (Terminator II), has been shown to incorporate 3'-O-allyl-dNTPs, however, efficient incorporation requires up to 50 min per single base addition, highlighting the difficulty of incorporating these analogs (7,10).

Ex. 1017, 6348 (referring to Ex. 1016, as "(8)"). Wu, thus, states that an allyl-modified nucleotide "typically act[s]" as a "poor substrate" because it only had activity with one DNA polymerase, and does so with limited activity at high micromolar concentrations. *See id.*

Nevertheless, Petitioner's Declarant testifies that a person of ordinary skill reading Metzker would have understood that DNA polymerase recognizes nucleotides with O-allyl blocking groups. Ex. 1067 ¶ 63. Patent Owner has not adduced any expert testimony at this stage of the proceeding with respect to the proper interpretation of Metzker or Wu.

We determine, on this record, that Petitioner has made an adequate showing that a person of ordinary skill would have selected O-allyl to be a blocking group inasmuch as Tsien discloses that O-allyl ethers are

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<sup>14</sup> Weidong Wu et al., *Termination of DNA synthesis by N<sup>6</sup>-alkylated, not 3'-O-alkylated, photocleavable 2'-deoxyadenosine triphosphates*, 35 NUCLEIC ACIDS RESEARCH 6339–6349 (Sept. 18, 2007) (Ex. 1017).

exemplary blocking groups because they are cleaved selectively and minimize premature deblocking. Ex. 1013, 24–25; Ex. 1067 ¶ 64. This passage in Tsien represents at least a suggestion to try capping a nucleotide with O-allyl at the 3'-OH group. It is not clear from the documentary evidence at this stage of the proceeding that the caveats in Metzker and Wu regarding the limited activity of an O-allyl-modified nucleotide would have discouraged a person of ordinary skill in the art from using an O-allyl-nucleotide, particularly in view of the teachings in Tsien regarding the benefits of an allyl group as a cleavable blocking group.

We are mindful that this is a situation in which a person of ordinary skill would have been weighing the disadvantages of a compound against its benefits. *See, e.g., Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1327 (Fed. Cir. 2017) (“ . . . prior art must be considered as a whole and the disadvantages of a reference must be considered in addition to the benefits . . .”) (citations omitted). As Patent Owner notes, Tsien itself sets forth three requirements for a blocking group: accurate and effective incorporation by a polymerase, availability of mild conditions for rapid and quantitative deblocking, and ability of a polymerase to reinitiate cDNA synthesis. Prelim. Resp. 30–31; Ex. 1013, 20–21. These considerations were, therefore, known to a person of ordinary skill and would have been considered both individually and as a whole.

The above determinations are preliminary in nature and based on the record at this stage of the proceeding. The parties are encouraged to develop these arguments further at trial, e.g., whether the limitations of an O-allyl blocking group noted in Metzker and Wu would have discouraged a person of ordinary skill from using such a group for DNA polymerization



reactions.<sup>15,16</sup> On this record, we are persuaded that a person of ordinary skill would have understood that an allyl ether blocking group meets the limitation, i.e., does not interfere with DNA polymerase, in view of the data

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<sup>15</sup> Petitioner argues that a “lead compound” analysis is not necessary because independent claim 1 is functionally claimed, but that if it were, Tsien provides 3'-O-allyl dCTP as a lead compound or provides 3'-O-acetyl dTTP as a lead compound that is modifiable to 3'-O-allyl dCTP. Pet. 39–47. Patent Owner argues that Metzker would have discouraged the skilled artisan from using 3'-O-allyl dCTP. Prelim. Resp. 47–48. Above, we review the evidence at this stage of the proceeding as to whether Metzker would have discouraged the use of 3'-O-allyl dCTP in the context of obviousness. However, Patent Owner does not substantively respond to Petitioner’s argument that it is unnecessary to conduct a “lead compound” analysis as such, i.e., by identifying a lead compound for study or modification. Given the lack of argument, we do not engage in a “lead compound” analysis at this time, and instead analyze whether the teachings of the prior art as a whole would have rendered the compound of claim 1 obvious. Patent Owner is free to argue at trial as to whether our obviousness analysis should begin with a lead compound, and if so, whether Petitioner’s arguments are sufficient to establish 3'-O-allyl dCTP or 3'-O-acetyl dTTP as a lead compound, e.g., based on the teachings in Tsien regarding an allyl group’s ability to serve as a cleavable blocking group.

<sup>16</sup> Petitioner asserts that a person of ordinary skill would have recognized that Tsien’s allyl group is advantageous for an additional reason. Petitioner asserts that it was known from the crystal structure of DNA polymerase that the active site is spatially constrained where it binds to the 3'-group of a nucleotide substrate and that an allyl group would have been recognized as one of a limited number of geometrically compatible capping groups because it is small, citing a declaration from the inventor during prosecution. *See* Pet. 22–23 (citing, e.g., Ex. 1021, 1897, 1903 n.101; Ex. 1065, 16, 21; Ex. 1066 ¶¶ 11–16, 19). We do not rely on this particular argument as a reason to use Tsien’s allyl group, at this stage of the proceeding, because reliance on the inventor’s testimony would have to be differentiated from hindsight. However, this evidence is probative that an allyl group as disclosed in Tsien is, in fact, “small” within the meaning of the claim. *See supra* Section II.E.2.

reported in Table 2 of Metzker. Ex. 1016, 4263 & Table 2; *see also* Ex. 1013, 20:28–32.

4. “wherein R . . . (c) is stable during a DNA polymerase reaction” and “wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction”

Petitioner asserts, *inter alia*, that Tsien discloses that the 3'-O-allyl capping group is stable. Pet. 26 (citing Ex. 1013, 12:11–13:13, 19:4–18, 23:28–32, 24:24–25:3; Ex. 1067 ¶ 68).

Patent Owner argues that Petitioner has not established that polymerase could reinitiate DNA synthesis after the allyl capping group was deblocked. Prelim. Resp. 37. Patent Owner asserts that Tsien lists as a requirement that the polymerase be able to reinitiate DNA synthesis subsequent to deblocking the 3'-OH group. *Id.* Although claim 1 requires a cleavable blocking group, it is not clear that claim 1 necessarily requires reinitiation of DNA synthesis.

In any event, we are persuaded on the basis of the current record that Tsien discloses that the allyl capping group is stable, as recited. In particular, Tsien discloses deblocking of the allyl capping group occurs only when the specific deblocking reagent is present and premature deblocking is minimized. Ex. 1013, 24:24–25:3.

5. “wherein tag represents a detectable fluorescent moiety”

Petitioner asserts, *inter alia*, that Tsien discloses an exemplary cytosine analogue, 3'-blocked dC''TP, where the apostrophes indicate a fluorescent tag. Pet. 27 (citing, e.g., Ex. 1013, 10:4–15, Fig. 2). Patent Owner does not dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Tsien discloses that each of the nucleotides is tagged or labeled with different reporters, such as different fluorescent groups. Ex. 1013, 10:7–10.

6. “wherein Y represents a chemically cleavable, chemical linker”

Petitioner asserts, *inter alia*, that Tsien discloses “cleavable tethers” that link the fluorescent tag to the base moiety. Pet. 28 (citing, e.g., Ex. 1013, 28:5–8, 28:23–29). Patent Owner does not dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Tsien discloses that the tag may be chemically cleaved. Ex. 1013, 28:5–8.

7. “wherein Y . . . (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction”

Petitioner asserts, *inter alia*, that Tsien discloses that the exemplary tethers do not interfere with the binding of the dNTP to the polymerase, and also discusses polymerase incorporation of 5-substituted cytosine analogues. Pet. 29 (citing Ex. 1013, 28:16–18, 28:31–35, 29:12–16, 30; Ex. 1014, 337, 340; Ex. 1040<sup>17</sup>, 3228, 3230; Ex. 1041<sup>18</sup>, 4832–33; Ex. 1067 ¶¶ 76–77). Petitioner further asserts that Tsien’s teaching of “removal of the fluorescent

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<sup>17</sup> Hong Yu et al., *Cyanine dye dUTP analogs for enzymatic labeling of DNA probes*, 22 NUCLEIC ACIDS RESEARCH 3226–32 (1994) (Ex. 1040).

<sup>18</sup> K. J. Livak et al., *Detection of single base differences using biotinylated nucleotides with very long linker arms*, 20 NUCLEIC ACIDS RESEARCH 4831–37 (1992) (Ex. 1041).

group from the nucleotide *after* incorporation and *before* the addition of the next nucleotide indicates the linker is stable during the polymerase reaction.” *Id.* at 30 (citing Ex. 1013, 28:19–25, 28:31–35; Ex. 1067 ¶ 79). Patent Owner does not separately dispute this limitation at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

8. “wherein the cytosine deoxyribonucleotide analogue: i) is recognized as a substrate by a DNA polymerase, [and] ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction”

Petitioner asserts, *inter alia*, that Tsien discloses that a 3'-blocked dC"TP is added to a reaction zone with a polymerase, where the nucleotide has a 3'-OH capping group and a detectable tag. Pet. 30–31 (citing Ex. 1013, 12:22–27, 19:4–18, 20:28–32, Fig. 2). Petitioner states that it was known that Vent polymerase incorporates 3'-O-allyl nucleotide analogues, as well as 5-substituted cytosine nucleotide analogues. *Id.* at 31 (citing Ex. 1016, 4263; Ex. 1040, 3228, 3230; Ex. 1041, 4832–33; Ex. 1059, 632; Ex. 1067 ¶ 82). As described in Tsien, nucleotide analogues are added at the end of the growing chain. *Id.* at 32 (citing Ex. 1031, 12:22–13:29; Ex. 1067 ¶¶ 84–85). Patent Owner does not separately argue these limitations at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

9. “wherein the cytosine deoxyribonucleotide analogue . . . iii) produces a 3'-OH group on the deoxyribose upon cleavage of R”

Petitioner asserts, *inter alia*, that Tsien discloses that 3'-blocking group removal “generates an active 3' hydroxyl.” Pet. 32 (citing Ex. 1013,

13:14–22). Patent Owner does not separately dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made an adequate showing. For example, Tsien discloses that a deblocking solution removes the blocking group and regenerates an active 3'-hydroxyl. Ex. 1013, 13:17–22.

10. “wherein the cytosine deoxyribonucleotide analogue . . . iv) no longer includes a tag on the base upon cleavage of Y”

Petitioner asserts, *inter alia*, that Tsien discloses that “[t]he tether can be cleavable if desired to release the fluorophore or other label on demand.” Pet. 33 (citing Ex. 1013, 28:19–23). Patent Owner does not dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Tsien discloses that the tether can be cleavable to permit removing the fluorophore on demand. Ex. 1013, 28:19–25.

11. “wherein the cytosine deoxyribonucleotide analogue . . . v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue”

Petitioner asserts, *inter alia*, that Tsien discloses 5-labeled cytosine analogues, which would have been understood to be complementary with guanine. Pet. 33–34 (citing, e.g., Ex. 1013, 30 (Structure B); Ex. 1067 ¶ 91). Patent Owner does not dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Tsien discloses complementary binding of nucleotides and, Prober discloses 5-labeled cytosine analogues, and Petitioner’s declarant explains that a cytosine analogue would have formed

hydrogen bonds with guanine. Ex. 1013, 7:19–24, 11:5–10, 30  
(Structure B); Ex. 1067 ¶ 91.

## 12. Conclusion

For the preceding reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its contentions that Tsien would have rendered obvious the subject matter of independent claim 1.

### *F. Obviousness of Claim 1 in view of Dower, Prober and Metzker*

Petitioner asserts that claim 1 is unpatentable under 35 U.S.C. § 103 as obvious in view of Dower, Prober, and Metzker. Pet. 55–74. Patent Owner opposes. Prelim. Resp. 51–64. We address the parties’ contentions below. We emphasize that the following determinations regarding the sufficiency of the Petition are preliminary in nature at this stage of the proceeding.

#### 1. “A cytosine deoxyribonucleotide analogue having the structure” as depicted in claim 1

Petitioner asserts, *inter alia*, that Dower discloses sequencing using deoxyribonucleotide triphosphate analogues, which includes the following cytosine analogue (depicted in Figure 8A of Dower):



A detail portion from Figure 8A, above, relied on by Petitioner, illustrates a cytosine analogue, where the asterisk (\*) represents a fluorescent label and B

represents a 3'-blocking group. Pet. 56–59 (citing, e.g., Ex. 1015, 5:35–40, 14:41–47, 15:1–3, 15:35–40, 18:64–19:10, Fig. 8A, Fig. 9; Ex. 1007, 10, 11; Ex. 1008, 13–14.). Petitioner further asserts that Prober discloses nucleotides to which succinylfluorescein has been attached via a linker to the heterocyclic base, where the linker is attached to the 5 position of pyrimidines. *Id.* at 58 (citing Ex. 1014, 337, 338). Petitioner argues that Dower cites to Prober for its disclosure of labeled nucleotide analogues of dATP, dCTP, dGTP, and dTTP. *Id.* (citing Ex. 1015, 25:4–12; also citing *id.* at 17:35–36, 20:39–42, 23:16–26, 25:4–12, 25:44–47, 28:6–17).

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Dower discloses adding a blocking agent onto the 3'-hydroxyl group of the nucleotide (Ex. 1015, 18:1–18), and Prober discloses attaching a fluorescent label to the 5 position of 5-substituted pyrimidines (Ex. 1014, 337). Further, Dower refers to the label described in Prober. Ex. 1015, 20:38–41. At this stage of the proceeding, Petitioner has made an adequate showing that a person of ordinary skill performing the method of Dower would have incorporated the label taught by Prober, e.g., based on the express teaching of Dower. Ex. 1015, 25:4–12.

2. “wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue”; “wherein R . . . (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase”; “wherein R . . . (d) does not contain a ketone group”; and “wherein OR is not a methoxy group or an ester group”

Petitioner asserts, *inter alia*, that Dower discloses deoxynucleotide triphosphates with small, cleavable blocking groups on the 3'-OH capping group, as the Board found previously and the Federal Circuit affirmed.

Pet. 59 (citing, e.g., Ex. 1015, 25:48–51, 25:15–18; Ex. 1007, 10 (prior Board decision, determining “Dower describes nucleotides with a label attached to the base and a small removable chemical moiety capping the 3'-OH group”); Ex. 1008, 33 (Federal Circuit affirming Board decision)); *see also* Pet. 61–62 (citing Ex. 1015, 15:62–65, 18:14–16, 24:61–25:22, 26:6–9; Ex. 1007, 13; Ex. 1008, 33; Ex. 1067 ¶¶ 133–135).

Petitioner further asserts that Dower discloses the following blocking groups: “acetyl, tBOC, NBOC, and NVOC.” Pet. 59 (citing Ex. 1015, 25:48–51). Petitioner asserts that Metzker discloses 3'-ether capping groups—including 3'-O-allyl-ether capping groups—for use in sequencing DNA, and that Metzker reports that 3'-O-ethers are advantageous because they are incorporated by polymerases. *Id.* at 60 (citing, e.g., Ex. 1016, 4261, 4265); *see also id.* at 62 (citing Ex. 1016, 4265; Ex. 1002, 3:26–30), 63 (citing Ex. 1016, 4261). Petitioner argues that a person of ordinary skill would have used a 3'-O-allyl substituted nucleotide, as Metzker teaches, because (1) it was shown to be incorporated by a polymerase, and (2) it is removable. *Id.* at 60 (citing Ex. 1067 ¶¶ 129–131).

Patent Owner asserts that Petitioner has not established a reason to use an allyl capping group, for similar reasons as for the ground of unpatentability based on Tsien, i.e., that Metzker taught that an allyl capping group was a non-specific and incomplete terminator. Prelim. Resp. 54–56 (citing, e.g., Ex. 1016, 4263, 4265; Ex. 1017, 6348). Patent Owner also argues that Petitioner has not established that an allyl group was capable of being deblocked (cleaved) with suitable yield. *Id.* at 56–57.

On this record, we are persuaded that Petitioner has made a sufficient showing. For example, Dower discloses blocking the 3'-hydroxyl group



(Ex. 1015, 25:18–22), and Metzker indicates that 3'-O-allyl ethers are recognized by Vent DNA polymerase (*see* Ex. 1016, 4263 & Table 2); Ex. 1067 ¶¶ 129–131. Further, the '358 patent indicates that there were “well-established synthetic procedures” for using allyl blocking groups. Ex. 1002, 26:22–25, 3:41–44.

3. “wherein R . . . (c) is stable during a DNA polymerase reaction” and “wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction”

Petitioner asserts, *inter alia*, that the 3'-blocking group prevents polymerase extension until the 3'-OH is made available by appropriate treatment. Pet. 62–63 (citing Ex. 1015, 25:4–22; Ex. 1067 ¶ 137). Petitioner further asserts that Metzker describes that the 3'-O-allyl nucleotide was incorporated by polymerase and terminated the growing strand. *Id.* at 63 (citing, e.g., Ex. 1016, 4263, 4265; Ex. 1067 ¶ 138). Patent Owner does not separately dispute this limitation at this time.

On this record, we are persuaded that Petitioner has made a sufficient showing. In particular, Metzker discloses that 3'-O-allyl-modified dATP results in termination activity. Ex. 1016, 4263 & Table 2. Further, Dower discloses that the blocked 3'-OH of the terminating base must be made available for chain extension in the next round of polymerization. *Id.* at 24:24–25:3.

4. “wherein tag represents a detectable fluorescent moiety” and “wherein Y represents a chemically cleavable, chemical linker”

Petitioner asserts, *inter alia*, that Dower discloses a fluorescent label as a removable moiety (e.g., “chemical[ly]”), and that Prober discloses succinylfluorescein attached via linker to the heterocyclic base, where the

linker is attached to the 5 position in pyrimidines. Pet. 64–65 (citing, e.g., Ex. 1015, 14:46–59, 15:52–53, 20:50–53, 21:32–40, 23:16–26; Ex. 1014, 337–338, Fig. 2A; Ex. 1067 ¶¶ 143–144, 146).

Patent Owner asserts that Dower describes attaching a label directly to the nucleotide base with no cleavable linker, and that the Board has previously found that Dower does not “expressly” identify a cleavable linker. Prelim. Resp. 51–53 (citing, e.g., Ex. 2036, 14–15). Patent Owner is referring to a non-instituted ground of unpatentability in which it was asserted that Dower was anticipatory. *See* Ex. 2036, 14–15. However, here, Petitioner asserts obviousness based on Dower in combination with other references.

Whether or not Dower discloses an anticipatory embodiment, we agree with Petitioner, on this record, that Dower suggests that it is desirable for a fluorescent label to be removable. *See* Ex. 1015, 15:52–53. We are persuaded that Petitioner has made an adequate showing. Prober discloses a fluorescent label attached via a linker to the 5 position in pyrimidines. *Id.* at 14:56–59; 15:52–53; Ex. 1014, 337.

Patent Owner argues that there would not have been a reason to combine the teachings of Dower and Prober. Prelim. Resp. 61–63. Patent Owner asserts that the Board previously considered these disclosures in Dower and found that “Illumina did not identify a teaching in Dower where Dower describes using Prober [] to modify Dower’s nucleotides[.]” *Id.* at 61 (quoting Ex. 1007, 14). However, Patent Owner is referring to a non-instituted ground based on anticipation by Dower in which the Board found that Dower did not incorporate by reference Prober’s structures. Ex. 1007, 14. Petitioner here argues a ground based on obviousness. We determine,

on this record, that Petitioner has made an adequate showing that a person of ordinary skill would have looked to the fluorescent label Prober teaches, based on the teachings of Dower. *See, e.g.*, Ex. 1015, 24:46–59.

5. “wherein Y . . . (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction”

Petitioner asserts that Dower discloses that the linked label “does not interfere with the nucleotide specific chemistry or enzymology” (citing Ex. 1015, 20:47–49) and is “compatible with appropriate polymerization” by DNA polymerase (citing *id.* at 15:56–59, 15:3–14, Fig. 8). Pet. 65; Ex. 1067 ¶¶ 148–149. Petitioner further asserts that Prober demonstrated that DNA polymerase recognized and incorporated a cytosine nucleotide analogue having a stable linker at the 5-position. Pet. 65 (citing Ex. 1014, 336–37; Ex. 1067 ¶ 150). Patent Owner asserts that none of the references discloses the functional features for the claimed cytosine nucleotide. Prelim. Resp. 54. On this record, we are persuaded that Petitioner has made an adequate showing.

6. “wherein the cytosine deoxyribonucleotide analogue: i) is recognized as a substrate by a DNA polymerase, [and] ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,”

Petitioner asserts, *inter alia*, that Dower discloses that a fluorescently labeled dCTP analogue with 3'-OH blocking group is “incorporated” by DNA polymerase. Pet. 66 (citing Ex. 1015, 24:61–25:22; Ex. 1007, 13). Petitioner reasons that a person of ordinary skill would have understood that polymerase incorporation and compatibility for Dower’s nucleotide analogues involves recognition by the polymerase, and that polymerase

incorporates a nucleotide at the end of a growing strand of DNA. *Id.* (citing Ex. 1067 ¶ 153), 68 (citing Ex. 1067 ¶ 158). Petitioner further asserts that Metzker discloses that a 3'-O-allyl nucleotide analogue was incorporated by polymerase. *Id.* at 66–67 (citing, e.g., Ex. 1016, 4263, 4265; Ex. 1041, 4832–33).

Patent Owner does not separately dispute these limitations. On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Metzker discloses that Vent polymerase incorporates 3'-O-allyl nucleotide analogues and other studies show that Vent polymerase [Tli DNA polymerase] incorporates 5-substituted pyrimidine nucleotide analogues. Ex. 1016, 4263; Ex. 1041, 4283–33; Ex. 1067 ¶ 77 (discussing Ex. 1041).

7. “wherein the cytosine deoxyribonucleotide analogue . . .  
iii) produces a 3'-OH group on the deoxyribose upon cleavage  
of R”

Petitioner asserts, *inter alia*, that Dower discloses that 3'-blocking groups are cleaved by treatment with pH and other chemical reagents, and that Metzker's 3'-O-allyl capping group was known to be chemically cleaved in high yield to produce a 3'-OH group. Pet. 69 (citing, e.g., Ex. 1015, 25:15–18; Ex. 1037, 371–72; Ex. 1035, 559; Ex. 1036, 2184; Ex. 1067 ¶ 161). Patent Owner does not separately dispute this limitation.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Dower discloses that 3'-blocking groups are cleavable, making the 3'-OH group available for the next round of polymerization. Ex. 1015, 25:20–21:2; *see also* Ex. 1002, 16:22–25.

8. “wherein the cytosine deoxyribonucleotide analogue . . . iv) no longer includes a tag on the base upon cleavage of Y”

Petitioner asserts, *inter alia*, that Dower discloses that it is important that the fluorescent label is removable, and preferably under mild conditions. Pet. 69 (citing Ex. 1015, 15:52–56, 21:32–40; Ex. 1067 ¶ 163). Patent Owner does not separately dispute this limitation.

On this record, we are persuaded that Petitioner has made an adequate showing. As Petitioner notes, Dower discloses that one important functional property of the monomers is for the label to be removable. Ex. 1015, 15:52–56.

9. “wherein the cytosine deoxyribonucleotide analogue . . . v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue”

Petitioner asserts, *inter alia*, that Dower discloses cytosine analogues and that a person of ordinary skill would have understood dTTP analogues to form hydrogen bonds with guanine. Pet. 69–70 (citing, e.g., Ex. 1015, 25:4–11, Fig. 8, Ex. 1014, 337, 340; Ex. 1067 ¶¶ 165–166). Patent Owner does not dispute this limitation at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

10. Conclusion

For the preceding reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its contentions that the combination of Dower, Prober and Metzker would have rendered obvious the subject matter of independent claim 1.

*G. Discretion Under 35 U.S.C. § 325(d)*

Patent Owner states: “The Board should also exercise its discretion under 35 U.S.C. §325(d) and deny institution on Ground 1 because Tsien was considered during prosecution of the ’358 patent.” Prelim. Resp. 48–50.<sup>19</sup> Under 35 U.S.C. § 325(d), the Board may deny a petition where “the same or substantially the same prior art or arguments previously were presented to the Office.” Having found a reasonable likelihood of prevailing on its assertions with respect to both grounds, we decline to exercise our discretion under § 325(d) not to institute.

*H. Other Arguments*

Petitioner requests that Patent Owner “be barred from participating in the present proceeding under the Board’s patent owner estoppel regulation.” Pet. 7 (citing 37 C.F.R. § 42.73(d)(3)(i)). That regulation states as follows: “(3) Patent applicant or owner. A patent applicant or owner is precluded from taking action inconsistent with the adverse judgment, including obtaining in any patent: (i) A claim that is not patentably distinct from a finally refused or canceled claim.” 37 C.F.R. § 42.73(d)(3)(i). Petitioner

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<sup>19</sup> Patent Owner’s request appears limited to Ground 1; Patent Owner does not request that we deny institution of the entire proceeding based on § 325(d). Nevertheless, under law clarified after Patent Owner filed the Preliminary Response, a decision to institute is to institute the petition with respect to all challenges or to deny as to all challenges. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1358 (2018) (“SAS”); *PGS Geophysical AS v. Iancu*, Case Nos. 2016-2470, 2016-2472, 2016-2474, 2018 WL 2727663 (Fed. Cir. June 7, 2018); *see also Guidance on the impact of SAS on AIA trial proceedings* (USPTO Apr. 26, 2018), available at <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial>.

does not direct us to any authority to support its argument that the rule applies to existing claims challenged in an *inter partes* review proceeding and, as a result, we do not determine the applicability of this rule.

Nevertheless, even assuming that Rule 42.73(d)(3)(i) applies, Petitioner has not adequately established that claim 1 of the '358 patent is patentably indistinct from claims canceled in any previous final written decision of the Board. Petitioner has not accounted for or evaluated the differences between the claim challenged in this proceeding and those canceled in the previous proceedings. *See, e.g.*, Prelim. Resp. 5–7 (claim charts). Instead, Petitioner points to a terminal disclaimer the patentee filed during prosecution as evidence that the claims are patentably indistinct. Pet. 7, 52. However, as Patent Owner correctly observes, the filing of a terminal disclaimer does not constitute an admission of a rejection or of double patenting. M.P.E.P. § 804.02; *Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 874 (Fed. Cir. 1991) (“Thus, a terminal disclaimer is of circumscribed availability and effect. It is not an admission of obviousness of the later-filed claimed invention in light of the earlier-filed disclosure, for that is not the basis of the disclaimer.”); *see* Prelim. Resp. 65–66. Thus, Patent Owner is not barred from participating in this proceeding.

### III. CONCLUSION

We conclude that Petitioner has demonstrated a reasonable likelihood of prevailing on its assertion that claim 1 of the '358 patent is unpatentable.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claim 1 of U.S. Patent No. 9,708,358 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '358 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.



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Patent 9,708,358 B2

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