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Paper 20
Entered: September 18, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

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

Case IPR2018-00797
Patent 9,868,985 B2

Before JAMES A. WORTH, MICHELLE N. ANKENBRAND, and BRIAN D. RANGE, *Administrative Patent Judges.*

RANGE, *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 claims 1 and 2 of U.S. Patent No. 9,868,985 B2 (Ex. 1075, "the '985 patent"). Paper 1 ("Pet."). Petitioner relies on the Declaration of Floyd Romesberg, Ph.D. (Ex. 1078) to support its positions. The Trustees of Columbia University in the City of New York ("Patent Owner") filed a Preliminary Response. Paper 14 ("Prelim. Resp."). Patent Owner relies on the Declaration of Steven M. Menchen, Ph.D. (Ex. 2052) to support its positions.

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 claims 1 and 2, and institute review of 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 instituting 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 '985 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. 78; Paper 3, 1.

The parties further indicate that Petitioner has filed 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), IPR2018-00322 (challenging U.S. Patent No. 9,708,358), and IPR2018-00385 (challenging U.S. Patent No. 9,725,480). Pet. 77–78; Paper 3, 1.

The parties note that in Cases IPR2012-00006, IPR2012-00007, and IPR2013-00011, the Board found unpatentable the challenged claims of Patent Owner's U.S. Patent Nos. 7,713,698; 7,790,869; and 8,088,575. Pet. 78–79; Paper 3, 1; *see* Ex. 1006; Ex. 1005; Ex. 1007; Ex. 1008 (Federal Circuit decision affirming these Board decisions). In Case IPR2013-00128 and IPR2013-00266, the Board found unpatentable the challenged claims of Petitioner's U.S. Patent Nos. 7,057,026 and 8,158,346. Pet. 79; *see* Ex. 1048; Ex. 1049; Ex. 1050 (Federal Circuit decision affirming these Board decisions). In Case IPR2013-00517, the Board held that the petitioner failed to demonstrate that the challenged claims of Petitioner's U.S. Patent

No. 7,566,537 were unpatentable.[1] Pet. 79–80; *see* Ex. 1044; Ex. 1045 (Federal Circuit decision affirming this Board decision).

B. The '985 Patent

The '985 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 for the polymerase reaction, covalently linked to a solid surface such as a chip, and 4 unique nucleotides analogues." Ex. 1075, 4:25–30.

The '985 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 '985 patent discloses that "[l]ong stretches of the same bases cannot be identified unambiguously with [a] pyrosequencing method." *Id.* at 2:44–46. The '985 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 '985 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

[1] A third party also challenged the '537 patent in Cases IPR2017-02172 and IPR2017-02174, but the Board denied institution in each case. Pet. 80; Paper 10, 1.

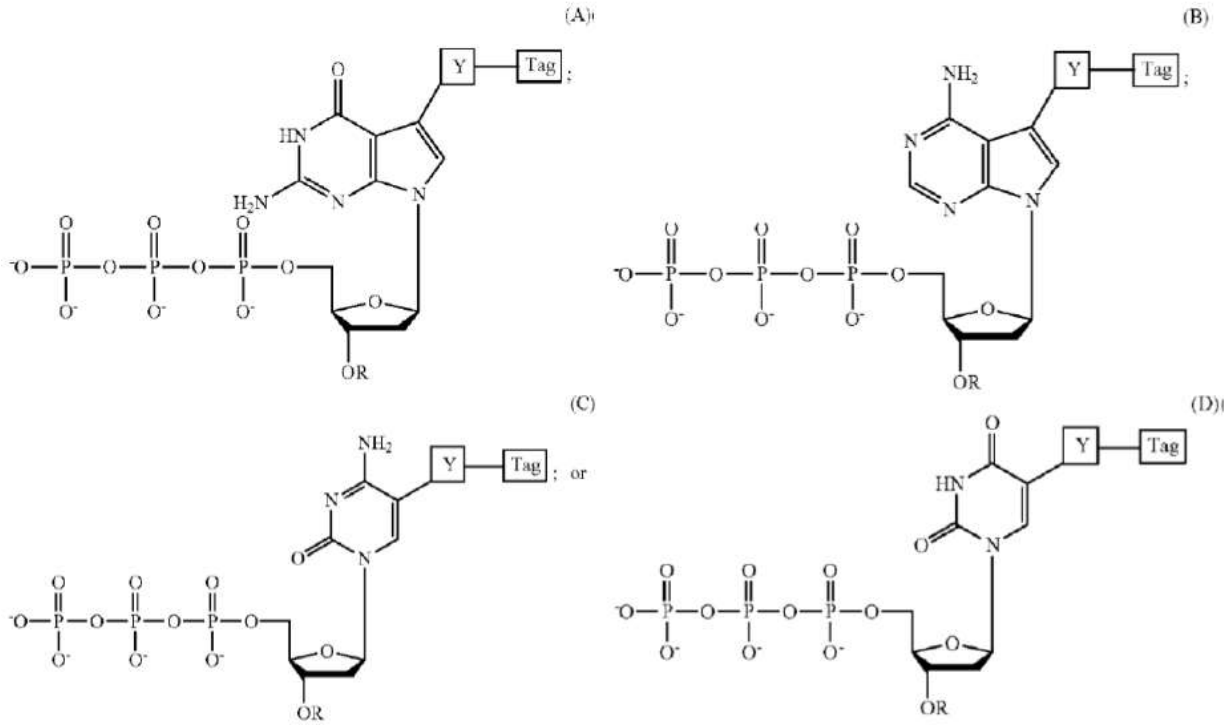
> make it nonreactive, and to incorporate the nucleotide analogues into the growing DNA strand as terminators. Detection of the unique label will yield the sequence identity of the nucleotide. Upon removing the label and the 3'-OH capping group, the polymerase reaction will proceed to incorporate the next nucleotide analogue and detect the next base.

Id. at 3:4–17; *see also id.* at 5:40–41. The approach disclosed in the '985 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 ($–CH_2OCH_3$) or an allyl group ($–CH_2CH=CH_2$), into the growing strand DNA as terminators." *Id.* at 3:44–51; *see also id.* at 5:43–44.

C. Challenged Claims

Claims 1 and 2, reproduced below (with some formatting adjusted for readability), are the challenged claims:

1. A method for sequencing a nucleic acid which comprises detecting the identity of a nucleotide analogue incorporated into the end of a growing strand of DNA in a polymerase reaction, wherein the nucleotide analogue is any of the following:



wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of tl [*sic*, 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 nucleotide 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, and iv) no longer includes a tag on the base upon cleavage of Y; and

wherein if the nucleotide analogue is: (A), it is capable of forming hydrogen bonds with cytosine or a cytosine nucleotide analogue; (B), it is capable of forming hydrogen bonds with thymine or a thymine nucleotide analogue; (C), it is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue; or (D), it is capable of forming hydrogen bonds with adenine or an adenine nucleotide analogue.

2. A method for simultaneously sequencing a plurality of different nucleic acids which comprises simultaneously applying the method of claim 1 to the plurality of different nucleic acids.

Ex. 1075, 34:2–36:32.

D. The Applied References

Petitioner relies on the following references in the asserted grounds. Pet. 17.

Reference	**Issue/Publication Date**	**Exhibit**
U.S. Patent No. 5,547,839 ("Dower")	Aug. 20, 1996	Ex. 1015
WO 91/06678 ("Tsien")	May 16, 1991	Ex. 1013
WO 98/53300 ("Pallas")	Nov. 26, 1998	Ex. 1080
James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 Science 336–341 (Oct. 16, 1987) ("Prober")	Oct. 16, 1987	Ex. 1014
Michael L. Metzker et al., *Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphosphates*, 22(20) Nucleic Acids Research 4259–67 (1994) ("Metzker")	1994	Ex. 1016

E. The Asserted Grounds of Unpatentability

Petitioner challenges claims 1 and 2 of the '985 patent based on the alleged grounds of unpatentability set forth in the table below. Pet. 17–76.

References	Basis	Claim(s) Challenged
Tsien in view of Prober	35 U.S.C. § 103(a)	1
Tsien in view of Prober and Pallas	35 U.S.C. § 103(a)	2
Dower in view of Prober and Metzker	35 U.S.C. § 103(a)	1, 2

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 requests construction of the term "or" as recited between the nucleotide analogues (C) and (D) of claim 1. *See* Pet. 11. 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.[2] *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

[2] At this stage of the proceeding, the parties have not directed our attention to any objective evidence of non-obviousness.

> addressing DNA sequencing techniques. A POSA 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. 11. Patent Owner "agrees with [Petitioner's] criteria for defining a [person of ordinary skill in the art]." Prelim. Resp. 9. 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:

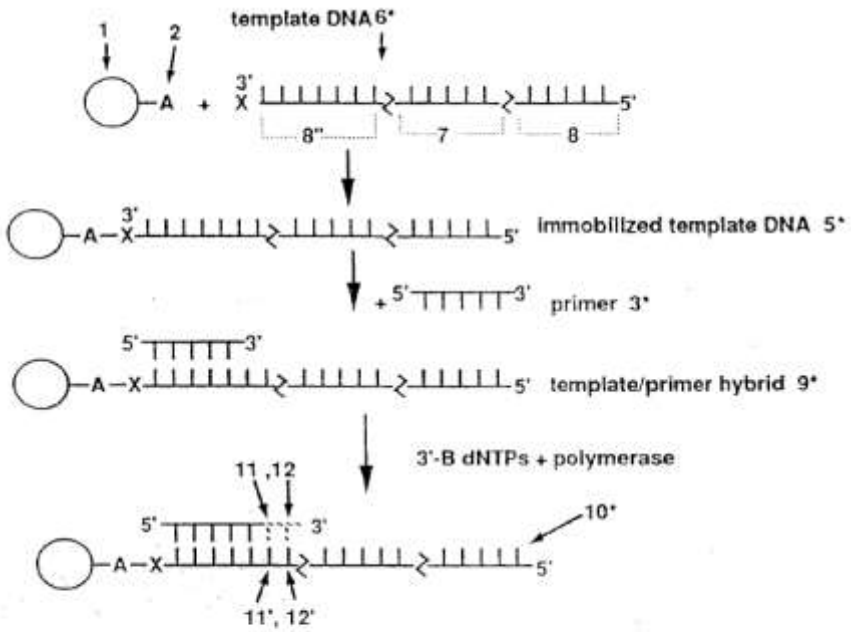


FIG. 1B

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:

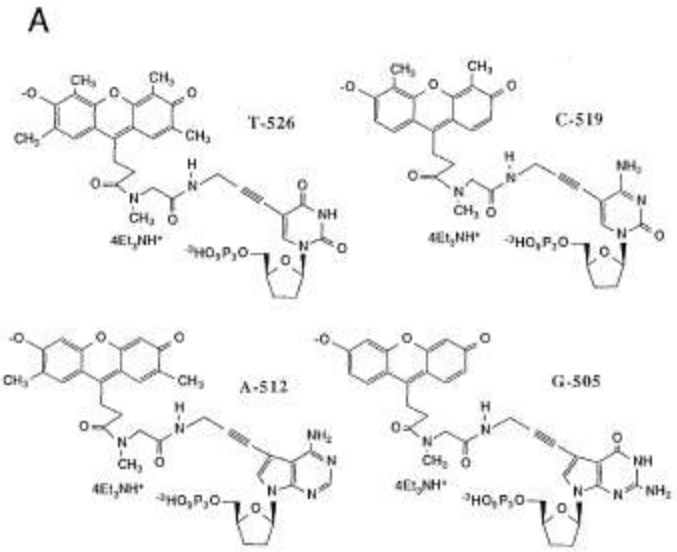


Figure 2A, above, depicts "[c]hemical structures of the reagents used in modified dideoxy reactions for DNA sequencing." *Id.* at 338. Prober discloses that succinylfluorescein is attached via a linker to a heterocyclic base, i.e., a nucleotide analogue. *See id.* at 337. In particular, the linker is

attached to the 5 position in the pyrimidines and to the 7 position in the 7-deazapurines. *Id.*

3. Pallas (Ex. 1080)

Pallas is titled "System And Apparatus For Sequential Processing Of Analytes" and relates to an apparatus and system "for simultaneously analyzing a plurality of analytes anchored to microparticles." Ex. 1080, at [54], [57]. In one embodiment, "[c]opies of each kind of polynucleotide in the population are sorted onto and anchored to one or more microparticles." *Id.* at 2:31–33. "Optical signals generated by, or produced as a result of, the interaction of processing reagents and polynucleotides on the microparticles are imaged by a detection means." *Id.* at 2:35–37.

Pallas Figure 1A discloses an exemplary system and is reproduced below.

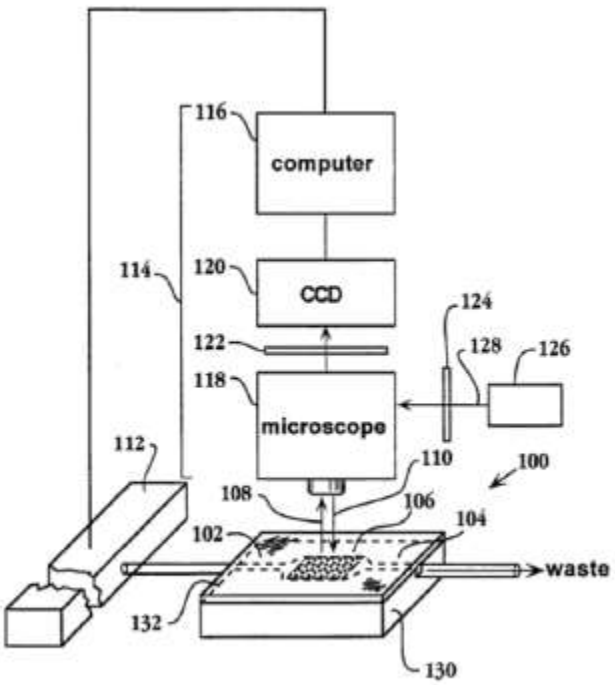


Fig. 1A

Figure 1A "is a schematic representation of a flow chamber and fluidics and detection systems for observing a planar array of microparticles loaded with analyte molecules, such as cDNA molecules for sequencing." *Id.* at 3:5–7.

4. Dower (Ex. 1015)

Dower is titled "Sequencing Of Surface Immobilized Polymers Utilizing Microflourescence 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:

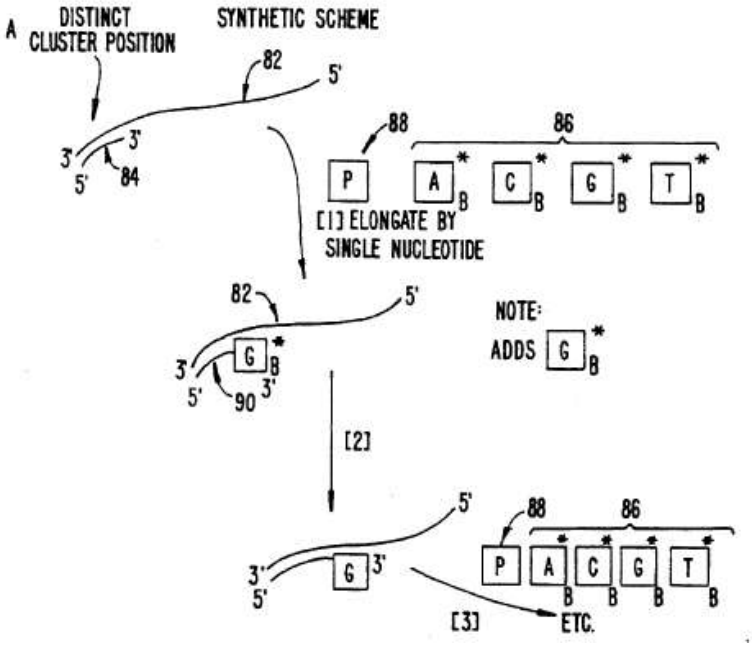


Figure 8A, above, illustrates schematically, at a molecular level, the sequence of events which occur during a particular sequencing cycle. *Id.* at 5:30–32.

5. Metzker (Ex. 1016)

Metzker is titled "Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphosphates" and is directed to a gel-free method for DNA sequencing. Ex. 1016, 4259. Metzker reports on experiments in which "eight 3'-modified dNTPs were synthesized and examined for their ability to terminate DNA synthesis mediated by a variety of polymerases." *Id.* Metzker reports that there are differences among the eight species in the manner of enzymatic incorporation. *Id.* at 4265. According to Metzker, 3'-O-allyl-modified dNTP was incorporated by at least one polymerase, e.g., $Vent_R$(exo-) DNA polymerase. *Id.* at 4263 & Table 2, 4265.

E. Ground 1: Obviousness of Claim 1 over Tsien in view of Prober

Petitioner asserts that claim 1 is unpatentable under 35 U.S.C. § 103 as obvious over Tsien in view of Prober. 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 method for sequencing a nucleic acid"

Petitioner asserts that Tsien discloses "a method to determine the nucleotide sequence in a DNA molecule." Pet. 18 (citing, e.g., Ex. 1013, Abstract). Patent Owner does not appear to dispute this recitation at this time.

On this record, we are persuaded that Petitioner has made a sufficient showing. *See* Section II.D.1, *supra*.

2. "which comprises detecting the identity of a molecule nucleotide analogue incorporated into the end of a growing strand of DNA in a polymerase reaction"

Petitioner asserts that Tsien discloses the detecting step in Figure 2 and its description. Pet. 19–21 (citing, e.g., Ex. 1013 Fig. 2, 11:27–13:35, 8:15–26). Patent Owner does not appear to dispute this recitation at this time.

On this record, we are persuaded that Petitioner has made a sufficient showing. *See* Section II.D.1, *supra*.

3. "wherein the nucleotide analogue is any of the following" as depicted in claim 1 with the four depictions (A)–(D) being connected with "or"

Petitioner asserts that Tsien teaches the thyamine and cytosine deoxyribose nucleotides having a fluorescent label attached through a linker

to the 5-position of the base and having a 3'-blocking group (i.e., respectively corresponding to nucleotide analogues (D) and (C) of claim 1). Pet. 21–26. Patent Owner does not presently appear to dispute Petitioner's position in this regard.

On this record, we are persuaded that Petitioner has made a sufficient showing. In particular, Tsien Figure 2 (reproduced below) discloses exemplary deoxyribonucleotide triphosphate analogues:

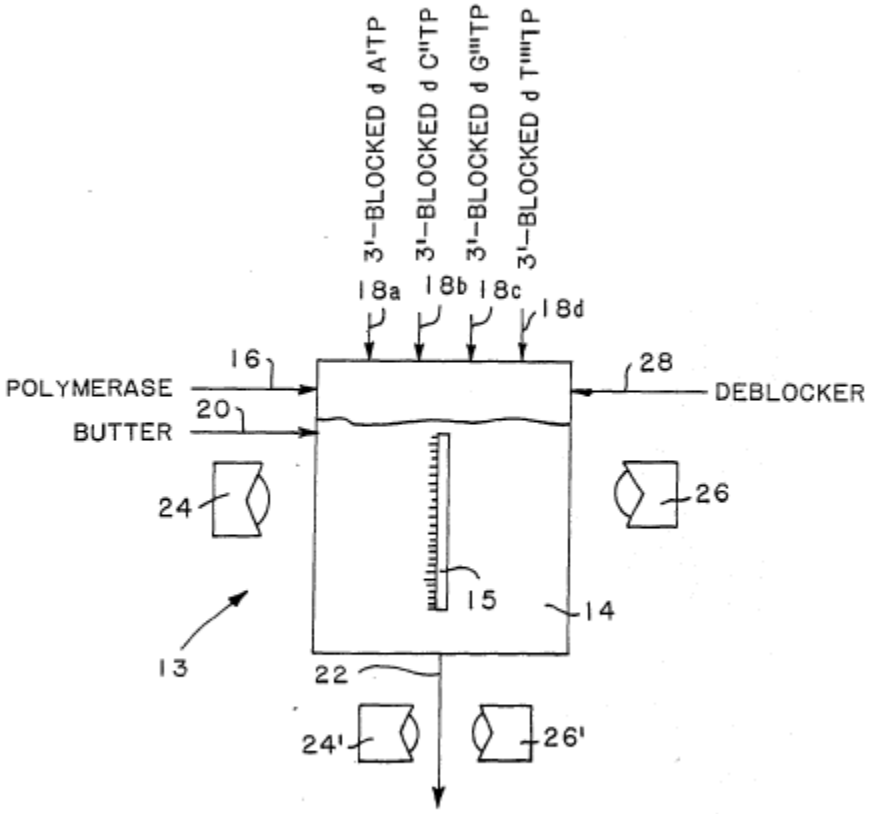


FIG. 2

Tsien Figure 2 depicts device 13 for carrying out Tsien's alleged invention schematically. Ex. 1013, 11:28–33. Tsien discloses, in particular, a 5-substituted thymine analogue and 5-substituted cytosine analogue. Ex. 1013, 29:10–30.

Petitioner also asserts that Prober discloses nucleotides with a deaza-adenine or deaza-guanine base having a label attached through a linker at the 7-position (corresponding to nucleotide analogues (B) and (A) of claim 1, respectively). Pet. 42 (citing Ex. 1014, 337–38, Fig. 2A). Patent Owner does not presently appear to dispute Petitioner's position in this regard. On this record, we are persuaded that Petitioner has made an adequate showing. *See* Section II.D.2, *supra*.

Petitioner further asserts that Tsien recommends using Prober's nucleotides and that "[t]he Board previously determined that a POSA was motivated to combine Tsien and Prober with a reasonable expectation of success of making and using 3'-capped 7-substituted deaza-adenine and deaza-guanine nucleotide analogues with a cleavable linker." Pet. 42 (citing Ex. 1005, 28–29).

On this record, we are persuaded that Petitioner has made an adequate showing that a person of ordinary skill would have modified Tsien's chain termination method with Prober's fluorescently labeled ddNTPs (i.e., dideoxynucleotides (Ex. 1013, 2:6–18)) by reason of express invitation and with reasonable expectation of success. For example, Tsien discloses, by way of background, that there is an automated system (e.g., Prober's system) that uses fluorescently labeled ddNTPs to terminate the reaction instead of fluorescent primers. Ex. 1013, 2:23–27. Tsien also includes Prober in the list of alternatives showing "enzymatic competence," stating that Prober shows enzymatic incorporation of ddNTPs by reverse transcriptase and Sequenase. *Id.* at 28:5–18.

4. *"wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of tl [sic, the] deoxyribonucleotide analogue"; "wherein R . . . (d) does not contain a ketone group"; and "wherein OR is not a methoxy 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. 26–28 (citing, e.g., Ex. 1013, 12:27–29, 24:25–25:3, Fig. 2; Ex. 1078 ¶ 74); *id.* at 30 (citing Ex. 1013, 24:5–7, 24:24–25:3; Ex. 1078 ¶ 83). Petitioner contends that Tsien discloses the same allyl capping group that the patent applicant "admitted . . . would have been recognized as . . . 'small.'" *Id.* at 27 (citing Ex. 1076, 18; Ex. 1077 ¶¶ 11–16, 19, 22a). Petitioner also relies on experiments using allyl groups disclosed in Metzker. Pet. 27–28 (citing Ex. 1016, 4263); *see also* Section II.E.5, *infra* (further addressing Metzker).

Patent Owner counters that Petitioner fails to establish that Tsien or Prober 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. Prelim. Resp. 18–50. Patent Owner also argues that Petitioner has not established that a person having ordinary skill in the art would have had a reason to select a small capping group or reasonable expectation of success in doing so. *Id.* We address Patent Owner's arguments as follows.

Argument that Tsien and Prober do not disclose the recited "small" capping group

Patent Owner contends that Petitioner has not shown that Tsien or Prober discloses a small capping group having the characteristics that claim 1 requires. Prelim. Resp. 18–23; *see also id.* at 13–14 (arguing Tsien sets forth a wide variety of prophetic embodiments for a 3'-OH blocking group), 24–27 (arguing that Tsien does not provide motivation to select an allyl capping group). Patent Owner also contends that Petitioner does not establish that "'small' capping groups, like the allyl capping group, 'were desirable.'" *Id.* at 45–46. On this record, however, we are persuaded that Petitioner has made an adequate showing that a person of ordinary skill in the art would have known to select a "small" allyl capping group within the broader teaching of Tsien. *See, e.g.*, Pet. 26–28 (citing Ex. 1013, 20:24–25:34 (in particular citing 24:29–30); Ex. 1021, 1897–98, 1903; Ex. 1075, 2:63–3:3; Ex. 1077 ¶¶ 11–16, 19, 22a, 31–33). For example, Petitioner presents evidence that a person of ordinary skill would have understood that "the active site [of the crystal structure of DNA polymerase] is spatially constrained where it binds to the 3'-group of a nucleotide substrate." Pet. 26 (citing Ex. 1021 at 1897–98, 1903). Petitioner also cites the 1994 Metzker paper as demonstrating that a 3'-O-allyl group is compatible with polymerase. *Id.* at 27–28 (citing Ex. 1016, 4263).

Patent Owner also contends that Petitioner previously "admitted that Tsien does not teach or suggest a nucleotide analogue with the three-carbon allyl capping group." Prelim. Resp. 20–23, 25–27. Patent Owner argues that, during reexamination of Petitioner's U.S. Patent No. 6,232,465

(Ex. 2038), Petitioner overcame obviousness and novelty rejections by admitting that "Tsien ***does not*** disclose a nucleotide analogue with the allyl capping group." *Id.* at 20. Patent Owner argues that judicial estoppel should prevent Petitioner from taking an inconsistent position now. *Id.* at 22–23.

Judicial estoppel "is an equitable doctrine invoked by a court at its discretion." *New Hampshire v. Maine*, 532 U.S. 742, 750 (2001). "The circumstances under which judicial estoppel may appropriately be invoked are probably not reducible to any general formulation of principle." *Id.* (citation omitted). Patent Owner addresses (Prelim. Resp. 22–23) three factors that the Supreme Court states "typically inform the decision." *New Hampshire*, 532 U.S. at 750. Here, we decline to exercise our discretion to invoke judicial estoppel at this time. We invite the parties to further address whether judicial estoppel is applicable to this *inter partes* review proceeding. *See Athena Automation Ltd. v. Husky Injection Molding Sys. Ltd.*, Case IPR2013-00290, slip op. at 13 (PTAB Oct. 25, 2013) (Paper 18) (precedential) (pointing out that statutory framework for *inter partes* review includes no counterpart to 19 U.S.C. § 1337(c) wherein Congress provided

that "[a]ll legal and equitable defenses may be presented" in International Trade Commission (ITC) investigations involving patent disputes).

Efficiency and mildness arguments

Patent Owner argues that Petitioner has not established a reason one of ordinary skill in the art would have selected Tsien's allyl capping group or would have had a reasonable expectation of success in doing so. Prelim. Resp. 24–51. Patent Owner argues that Tsien also discloses ester capping groups that offer the advantage of preventing significant premature deblocking and identifies groups suitable for photochemical and enzymatic removal. *Id.* at 24–25 (citing Ex. 1013, 21, 24–25).

Patent Owner also argues that the Metzker reference teaches that the allyl capping group would "plague" any SBS (sequencing by synthesis) method. Prelim. Resp. 27–33; *see also id.* at 1–3 (introduction), 48–51 (arguing that person having ordinary skill would not have had reasonable expectation of success in using allyl capping group). Patent Owner's declarant, Dr. Menchen, testifies that a person having ordinary skill in the art would not have had a reason to select an allyl capping group because Metzker indicates that the termination of the allyl capping group was incomplete and because efficient incorporation is essential to SBS in order to maintain synchronization. *Id.* at 28–29 (citing Ex. 1016, 4263; Ex. 2052 ¶¶ 16–33). Patent Owner refers to the Stemple reference[3] as teaching that SBS techniques were "plagued by any inefficiencies of incorporation and

[3] Stemple et al., WO 00/53805, published Sept. 14, 2000 ("Stemple") (Ex. 2013).

deprotection." *Id.* at 29–30 (emphasis omitted) (citing Ex. 2013, 2–3). Patent Owner cites additional references as confirming Metzker's incomplete incorporation (*id.* at 30–32) and further argues that adding a label to the analogue would have resulted in even worse incorporation (*id.* at 32 (citing Ex. 2052 ¶ 28)).

Patent Owner further argues that: (1) Tsien requires mild conditions for cleaving, (2) Petitioner has failed to show that Tsien's allyl capping group could be cleaved quantitatively under mild conditions, and (3) Petitioner has failed to show that a person of ordinary skill in the art would have had a reasonable expectation of success in using an allyl group. Prelim. Resp. 36–37 (citing Ex. 1013, 20–21). 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 37–39. Specifically, Patent Owner asserts that Qian[4] uses methanol, which was known to denature DNA, Boss[5] uses heat, and both Qian and Boss use $PdCl_2$, which was not necessarily known to be compatible with DNA. *Id.* (citing Ex. 1036, 2185; Ex. 2007 ¶¶ 47, 55; Ex. 1035, 558–59). Patent Owner also asserts that Qian required 2 hours for cleavage and Boss required "a few hours." *Id.* at 36 (citing Ex. 1036, 2185; Ex. 1035, 558–59).

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[4] Xiangping Qian et al., *Unexpected Enzymatic Fucosylation of the Hindered Tertiary Alcohol of 3-C-Methyl-N-Acetyllactosamine Produces a Novel Analogue of the LeX-Trisaccharide,* 120 J. AM. CHEM. SOC. 2184–85 (1998) (Ex. 1036).

[5] Roland Boss & Rolf Scheffold, *Cleavage of Allyl Ethers with Pd/C*, 15 ANGEW. CHEM. INT. ED. ENGL. 558–559 (1976) (Ex. 1035).

Patent Owner further supports its positions with Dr. Menchen's testimony. *Id.* at 36–39 (citing Ex. 2052 ¶¶ 59–68).

Petitioner asserts that Qian discloses "quantitative" allyl cleavage. Pet. 35, 33 (citing Ex. 1036, 2184). Petitioner also asserts that Patent Owner admitted that it was known that an allyl group could be cleaved with high yield. Pet. 35 (quoting Ex. 1075, 3:39–44 ("It is known that . . . allyl (-$CH_2CH=CH_2$) 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. 1075, 26:19–33 ("The MOM (-CH_2OCH_3) or allyl (-$CH_2CH=CH_2$) 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 the current 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,[6] Qian, and the admission in the '985 patent as to what was well known in the art. Ex. 1013, 24; Ex. 1037, 371–72; Ex. 1036, 2184; Ex. 1075, 3:39–44, 26:19–33; *see also* Ex. 1035, 559. On the current record, Qian reports "quantitative" yield using $PdCl_2$ 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

[6] 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).

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. 1075, 3:39–44, 26:22–25.

With respect to Patent Owner's arguments that rely on Dr. Menchen's testimony (*see*, *e.g.*, Prelim. Resp. 2–3, 27–33), Petitioner's declarant, Dr. Romesberg, states that a person having ordinary skill in the art would have recognized that Tsien's allyl group is advantageous. Ex. 1078 ¶¶ 73–77. Dr. Romesberg's statements are supported by citations to, for example, Tsien, Metzker, and Pelletier. *Id.* Dr. Romesberg's and Dr. Mechen's testimony is not, in general, conclusory as to the suitability of the allyl group; rather, each declarant supports his position with citations to evidence. The conflicting testimony of Dr. Romesberg and Dr. Menchen creates a genuine issue of material fact regarding whether or not a person of ordinary skill in the art would have considered an allyl blocking group acceptable in the context of the challenged claims. For purposes of deciding whether to institute an *inter partes* review, we must view any issues of material fact that testimonial evidence creates in the light most favorable to Petitioner. *See* 37 C.F.R. § 42.108(c). Thus, for purposes of this Decision, we must resolve the dispute between Dr. Romesberg and Dr. Menchen regarding acceptability of allyl blocking groups in Petitioner's favor.

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. We also invite briefing on (1) whether or not the parties take the position that either challenged claim necessarily requires sequencing, for example, of whole genomes as Dr. Menchen discusses and (2) whether or not the claims otherwise require that recited steps be repeated. Ex. 2052 ¶¶ 17–21; *see also, e.g.*, Prelim. Resp. 30–32.

Allegedly inconsistent positions

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, or that the Federal Circuit has required, in previous proceedings involving Petitioner (and another party):

> 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 has previously admitted that a POSA reading Tsien understood that greater than 97% cleavage is required to practice Tsien's method . . . .

Prelim. Resp. 39 (citing Ex. 2030, 1; 2029, 28).

We do not find that Petitioner's position in this proceeding is necessarily inconsistent with the cited papers, based on the current record. As explained above, Petitioner sufficiently establishes sufficiently quantitative cleavage. 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 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 characterizes 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 proceedings, when, for example, 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. 17–18; *see also id.* at 2 (citing Ex. 2009, Ex. 2065), 12 (citing Ex. 2007, 2008, 2042), 21 (quoting Ex. 2065), 26–27. Patent Owner argues that Petitioner breached its obligations by failing to disclose this inconsistent position. *See id.* at 16–18 (citing 37 C.F.R. § 42.11(a); 37 C.F.R. § 42.51(b)(1)(iii)). Although Petitioner's statements may ultimately affect a weighing of credibility at trial, we decline to address the alleged violation of the duty of candor or of discovery obligations based on arguments presented in the context of a Preliminary Response.

Patent Owner contends that Illumina claims to have invented the same nucleotide analogues at issue now in 2002 (Prelim. Resp. 17–18 (citing Ex. 2015, Ex. 2016) and also contends that Petitioner has admitted that there was as of 2002 "no concrete embodiment of the successful cleavage of a 3'-allyl group under DNA compatible conditions" (Prelim. Resp. 41 (emphasis omitted) (quoting Ex. 2015,[7] 2:60–65)). To the extent Petitioner has taken

[7] U.S. Patent No. 7,541,444 B2, assigned to Illumina Cambridge Limited (Ex. 2015).

inconsistent positions, this may have bearing on credibility issues at trial. Moreover, this statement appears to be, at most, a statement that there is no anticipatory reference and does not preclude an obviousness determination. *See* Ex. 2015, 2:60–65.

5. *"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 "a successful 3'-blocking group has the ability to be accurately and effectively incorporated by a polymerase enzyme." Pet. 28 (citing Ex. 1013, 12:11–18, 19:4–18, 20:28–32, 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. 1078 ¶¶ 76, 79).

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 exemplary blocking groups because they are cleaved selectively and minimize premature deblocking. Ex. 1013, 24–25; Ex. 1078 ¶¶ 76, 79. This passage in Tsien represents at least suggests capping a nucleotide with O-allyl at the 3'-OH 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, 1328 (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").

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 arguments further at trial, e.g., whether the limitations of an O-allyl blocking group noted in Metzker would have discouraged a person of ordinary skill from using such a group for DNA polymerization reactions.[8,9] On this

[8] Petitioner argues that a "lead compound" analysis is not necessary because similar claims have been analyzed based on a *Graham*-based analysis and because claims 1 and 2 include the "R," Y," and "Tag" functional groups. Pet. 43–44. Petitioner also argues that if a lead compound analysis were applied, Tsien nucleotide analogues that are a natural starting place for development efforts and that there was motivation to modify starting compounds to reach claim 1. *Id.* at 45–51. Patent Owner does not substantively respond to Petitioner's argument that it is unnecessary to conduct a "lead compound" analysis. 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.

[9] Petitioner asserts that a person of ordinary skill would have recognized that Tsien's allyl group is advantageous for an additional reason. Petitioner

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

6. "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. 29–30 (citing Ex. 1013, 12:11–13:13, 19:4–18, 23:28–32, 24:24–25:3; Ex. 1078 ¶ 81).

Patent Owner argues that Petitioner has not established that polymerase could reinitiate DNA synthesis after the allyl capping group was deblocked. Prelim. Resp. 41–42. 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, e.g., "detecting the identity of a nucleotide analogue incorporated into the

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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. 15, 27 (citing, e.g., Ex. 1021, 1897, 1903; Ex. 1076, 18; Ex. 1077 ¶¶ 11–16, 31–33). 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 does further support that an allyl group as disclosed in Tsien is, in fact, "small" within the meaning of the claim. *See* Section II.E.4, *supra*.

end of a growing strand of DNA in a polymerase reaction," it is not clear that claim 1 necessarily requires reinitiation of DNA synthesis. This argument may further weigh against a reason to choose an allyl blocking group, but, as explained above, Petitioner has adequately explained why a person of skill in the art would have chosen an allyl blocking group for the present purposes.

In any event, we are persuaded on 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.

7. "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. 30–31 (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.

8. "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. 31 (citing, e.g., Ex. 1013, 28:5–8, 28:19–29). 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.

9. "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 that Tsien discusses polymerase incorporation of 5-substituted cytosine analogues. Pet. 31 (citing, e.g., Ex. 1013, 28:16–18, 28:31–35, 29:12–16, 30; Ex. 1014, 337, 340; Ex. 1040,[10] 3228, 3230; Ex. 1041,[11] 4832–33; Ex. 1078 ¶ 90). Petitioner further asserts that Tsien's teaching of "removal of the fluorescent group from the nucleotide analogue *after* incorporation and *before* the addition of [the] next nucleotide indicates the linker is stable during the polymerase reaction." *Id.* at 33 (citing Ex. 1013, 28:19–25, 28:31–35; Ex. 1078 ¶ 92). Patent Owner does not separately dispute this limitation at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

[10] Hong Yu et al., *Cyanine dye dUTP analogs for enzymatic labeling of DNA probes*, 22 NUCLEIC ACIDS RESEARCH 3226–32 (1994) (Ex. 1040).

[11] 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).

10. "wherein the nucleotide 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. 33–35 (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. 1078 ¶ 95). As described in Tsien, nucleotide analogues are added at the end of the growing chain. *Id.* at 34–35 (citing, e.g., Ex. 1013, Fig. 1B, 12:22–13:29; Ex. 1078 ¶¶ 97–98). Patent Owner does not separately argue these limitations at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

11. "wherein the nucleotide 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. 35 (citing, e.g., 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.

12. "wherein the nucleotide 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. 35 (quoting 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.

13. "wherein if the nucleotide analogue is: (A) ...; (B) ...; (C) ...; or (D) ...."

Petitioner asserts, *inter alia*, that Tsien discloses that each nucleotide analogue should pair with its complementary nucleotide. Pet. 36 (citing Ex. 1013, 7:19–24, 12:22–27, 28:31–35; Ex. 1011, 99; Ex. 1042, 966; Ex. 1078 ¶ 105). Petitioner further asserts that Prober discloses that "DNA polymerase maintains fidelity during incorporation of 5-labeled pyrimidine analogues" and that this indicates that the 5-labeled cytosine analogue (claim 1 analogue C) forms hydrogen bonds with guanine and that the 5-labeled thymine analogue (claim 1 analogue D) forms hydrogens bonds with adenine. Pet. 36–37 (citing Ex. 1013, 29:12–16, 28:16–18; Ex. 1014, 337, 340; Ex. 1078 ¶ 104). 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 teaches, for example, that the key to its nucleotides is direct identification "as they are incorporated into the growing complementary DNA chain." Ex. 1013 7:19–24; *see also id.* at 28:31–35

("Long tethers may be used so that the large fluorescent groups . . . do not interfere . . . with [the] proper base pairing during complementary chain growth."). Dr. Romesberg testifies that "[a] person of ordinary skill in the art would recognize that Prober's statement that DNA polymerase maintains 'fidelity' means that during a DNA polymerase reaction Prober's nucleoside trisphosphate analogues base pair with their complementary nucleotide according to standard Watson-Crick base pairing." Ex. 1078 ¶ 104.

Summary

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

F. Ground 2: Obviousness of Claim 2 over Tsien in view of Prober and Pallas

Petitioner asserts that claim 2 is unpatentable under 35 U.S.C. § 103 as obvious over Tsien in view of Prober and Pallas. Pet. 51. Patent Owner opposes but does not separately dispute the recitations of claim 2 at this time. Prelim. Resp. 54. We emphasize that the following determinations regarding the sufficiency of the Petition are preliminary in nature at this stage of the proceeding.

Claim 2 recites: "A method for simultaneously sequencing a plurality of different nucleic acids which comprises simultaneously applying the method of claim 1 to the plurality of different nucleic acids." Ex. 1075, 36:29–32. Petitioner asserts, *inter alia*, that Pallas discloses "a system for simultaneously analyzing the nucleotide sequences of a population of

polynucleotides." Pet. 51 (quoting Ex. 1080, 2:30–31, 2:31–33, 2:35–37; citing *id.* at Fig. 1A, 5:19–21, 10:36–11:19, Figs. 6A–6B; citing Ex. 1078 ¶¶ 143–144). Petitioner asserts that Pallas provides an express motivation to combine its teachings with Tsien. *Id.* at 52–53 (quoting Ex. 1080, 16:26–33, citing Ex. 1078 ¶¶ 145–146). Patent Owner does not challenge Petitioner's position regarding this ground at this time. Prelim. Resp. 54.

On this record, we are persuaded that Petitioner has made an adequate showing. In particular, Pallas teaches simultaneously sequencing different nucleic acids. *See, e.g.*, Ex. 1080, 2:30–37. Pallas encourages use of its simultaneous sequencing combined with Tsien's approach. *Id.* at 16:26–33. Petitioner's declarant provides support for Petitioner's position. Ex. 1078 ¶¶ 145–146.

Summary

For the preceding reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its contentions that the combination of Tsien in view of Prober and Pallas would have rendered obvious the subject matter of independent claim 2.

G. Ground 3: Obviousness of Claims 1 and 2 over Dower in view of Prober and Metzker

Petitioner asserts that claims 1 and 2 are unpatentable under 35 U.S.C. § 103 as obvious over Dower in view of Prober and Metzker. Pet. 56–76. Patent Owner opposes. Prelim. Resp. 54–65. 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 method for sequencing a nucleic acid"

Petitioner asserts that Dower discloses "a method and apparatus for sequencing many nucleic acid sequences." Pet. 56 (citing, e.g., Ex. 1015, Abstract, 1:23–25, 4:10–21, 14:38–59). Patent Owner does not appear to dispute this recitation at this time.

On this record, we are persuaded that Petitioner has made a sufficient showing. *See* Section II.D.4, *supra*.

2. "which comprises detecting the identity of a molecule nucleotide analogue incorporated into the end of a growing strand of DNA in a polymerase reaction"

Petitioner asserts that Dower discloses the detecting step in Figure 8A and its description. Pet. 57–58 (citing, e.g., Ex. 1015, Fig. 8A, 14:41–59, 15:1–10, 15:35–40, 25:4–12; Ex. 1078 ¶ 155). Patent Owner does not appear to dispute this recitation at this time.

On this record, we are persuaded that Petitioner has made a sufficient showing. *See* Section II.D.4, *supra*.

3. "wherein the nucleotide analogue is any of the following" as depicted in claim 1 with the four depictions (A)–(D) being connected with "or"

Petitioner asserts, *inter alia*, that Dower teaches cytosine and thymidine analogues (i.e., respectively corresponding to nucleotide analogues (C) and (D) of claim 1). Pet. 59–61. Petitioner cites Figure 8A of Dower, for example, as illustrating the cytosine and thymidine analogues wherein the asterisk (*) represents a fluorescent label and B represents a 3' blocking group. Pet. 59–60 (citing, e.g., Ex. 1015, Fig 8A, 15:1–3, 15:35–40). Petitioner further asserts that Dower cites to Prober for its disclosure of labeled nucleotide analogues (Pet. 60 (citing Ex. 1015, 17:35–36, 20:39–42,

23:16–26, 25:4–12, 25:44–47, 28:6–17)) and asserts that Prober discloses nucelotides with succinylfluorescein attached via linker "to the 5 position in the pyrimidines" (*id.* (citing Ex. 1014, 337, 338, Fig. 2A)). Petitioner concludes that "Dower in view of Prober therefore renders obvious a cytosine or thymidine deoxyribonucleotide having a 3'-OH capping group and a tag attached through a cleavable linker at the 5-position, which are the pyrimidine nucleotides (C) and (D) depicted in claim 1." Pet. 60–61. Patent Owner does not presently appear to dispute Petitioner's position in this regard.

On this record, we are persuaded that Petitioner has made a sufficient showing.[12] In particular, Dower discloses adding a blocking agent onto the 3'-hydroxyl group of the nucleotide (*see, e.g.*, Ex. 1015, Fig. 8A, 15:1–3, 15:35–40), 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, 25:4–12, 25:44–47, 20:39–42, 23:16–26, 28:6–17. 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 Prober teaches, e.g., based on the express disclosure of Dower. *See, e.g.*, Ex. 1015, 25:4–12.

[12] We reach this determination by applying the ordinary meaning of "or" to the word "or" as recited in claim 1. If the construction of "or" is in dispute, we invite the parties to further address this issue in trial.

4. *"wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of tl [sic, the] deoxyribomucleotide 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 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. 61–62 (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)). Petitioner also asserts that Dower teaches that the label and blocking group are selected so that they "are selected to be compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension." Pet. 62–63 (quoting Ex. 1015, 26:6–9) (citing Ex. 1015, 15:62–65, 18:14–16, 24:61–25:22; Ex. 1007, 13; Ex. 1008, 33; Ex. 1078 ¶¶ 171–172).

Petitioner further asserts that Dower discloses the desirability of "small" blocking groups, and Dower refers to "acetyl, tBOC, NBOC, and NVOC." Pet. 60 (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 62 (citing, e.g., Ex. 1016, 4261, 4265); *see also id.* at 63 (citing Ex. 1016, 4265), 64 (citing Ex. 1016, 4263, 4265). 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 62 (citing Ex. 1078 ¶¶ 166–168).

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. 56–59 (citing, e.g., Ex. 1016, 4263, 4265; Ex. 1017, 6348). Patent Owner also argues that Petitioner has not established that an allyl group was suitably "chemically cleavable" as recited in claim 1. *Id.* at 54–56. Patent Owner also argues that a person having ordinary skill in the art would not have had a reasonable expectation of success in meeting the recitations of the challenged claims. Prelim. Resp. 64–65.

Patent Owner's argument regarding suitability of an allyl group is addressed in detail above with respect to Ground 1. *See, e.g.*, Section II.E.4., *supra*. Metzker, for example, provides some indication that allyl groups would have been appropriate (Ex. 1016, 4263) although the parties dispute the importance of Metzker's statement that "activity was incomplete" (Ex. 1016, 4263). Dr. Romesberg and Dr. Menchen present conflicting testimony regarding suitability of the allyl group, and, procedurally, we must view issues of material fact created by testimonial evidence in Petitioner's favor at this stage. *See* 37 C.F.R. § 42.108(c).

We determine, on this record, that Petitioner has made an adequate showing. Petitioner has adequately established, for example, that a person of skill in the art would have had a reasonable expectation of success in using an allyl blocking group and would have a reasonable expectation of

success in that group being chemically cleavable. 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. 1078 ¶¶ 166–168). Further, the '985 patent indicates that there were "well-established synthetic procedures" for using allyl blocking groups. Ex. 1075, 26:18–29, 3:41–44.

5. *"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. 63–64 (citing Ex. 1015, 25:4–22; Ex. 1078 ¶ 174). 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, 4259, 4263, 4265; Ex. 1078 ¶ 175). 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 24:24–25:22.

6. *"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. 65 (citing, e.g., Ex. 1015, 14:46–59, 15:52–53, 20:50–53, 21:32–40, 23:16–26; 25:35–40; Fig. 9; Ex. 1014, 337–338, Fig. 2A; Ex. 1078 ¶¶ 183).

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. 54–56 (citing, e.g., Ex. 2036, 14–15; Ex. 2052 ¶¶ 69–75). Patent Owner is referring to a non-instituted ground of unpatentability in another proceeding in which the petitioner asserted Dower as an anticipatory reference. *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. 62–64. 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 (alterations in original) (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, 20:38–44.

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 that Dower discloses that the linked label "does not interfere with the nucleotide-specific chemistry or enzymology" (quoting Ex. 1015, 20:47–49) and is "compatible with appropriate polymerization" by DNA polymerase (quoting *id.* at 15:56–59, 15:3–14, Fig. 8). Pet. 66; Ex. 1078 ¶¶ 185–186. 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. 66 (citing Ex. 1014, 336–37; Ex. 1078 ¶ 187). Patent Owner asserts that none of the references discloses the functional features for the claimed cytosine nucleotide. Prelim. Resp. 56. On this record, we are persuaded that Petitioner has made an adequate showing. *See* Section II.G.6., *supra*.

8. "wherein the nucleotide 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. 66–67 (citing, e.g., 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. 1078 ¶ 190), 68 (citing Ex. 1078 ¶ 194). Petitioner further asserts that Metzker discloses that a 3'-O-allyl nucleotide analogue was incorporated by polymerase. *Id.* at 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. 1078 ¶ 90 (discussing Ex. 1041).

9. "wherein the nucleotide 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 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, 25:15–22; Ex. 1037, 371–72; Ex. 1035, 559; Ex. 1036, 2184; Ex. 1078 ¶ 198). 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, 25:15–22.

10. "wherein the nucleotide 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. 1078 ¶ 200). 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.

11. "wherein if the nucleotide analogue is: (A) ...; (B) ...; (C) ...; or (D) ...."

Petitioner asserts, *inter alia*, that Dower discloses nucleotide analogues and that a person of ordinary skill would have understood that dCTP analogues form hydrogen bonds with guanine and dTTP analogues form hydrogen bonds with adenine. Pet. 69–71 (citing, e.g., Ex. 1015, 14:44–53, 15:1–10, 25:4–11, Fig. 8; Ex. 1014, 337, 340; Ex. 1078 ¶¶ 202). Patent Owner does not dispute this limitation at this time. On this record, we are persuaded that Petitioner has made an adequate showing.

12. Claim 2: "A method for simultaneously sequencing a plurality of different nucleic acids which comprises simultaneously applying the method of claim 1 to the plurality of different nucleic acids."

Petitioner asserts, *inter alia*, that Dower teaches "simultaneous parallel sequence analysis of a large number of biological polymer macromolecules." Pet. 75 (quoting Ex. 1015, Abstract). Petitioner asserts that Dower discloses methods for concurrently obtaining sequence information using parallel detection devices. *Id.* at 75–76 (citing, e.g., Ex. 1015, 1:23–25, 2:66–3:2, 3:58–4:43, 12:47–49, 14:41–59, 15:1–13, 15:35–40, 22:53–55, Fig 8A; Ex. 1078 ¶¶ 217–218). Patent Owner does not dispute this limitation at this time. On this record, we are persuaded that Petitioner has made an adequate showing. *See, e.g.*, Ex. 1015, Abstract, 1:23–25.

Summary

For the preceding reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its contentions that Dower in view of Prober and Metzker would have rendered obvious the subject matter of independent claim 1 and dependent claim 2.

H. 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 and Prober were considered during prosecution of the '985 patent." Prelim. Resp. 52. 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 Petitioner

prevailing on its assertions with respect to both grounds, we decline to exercise our discretion under § 325(d) not to institute.

I. Other Arguments

Petitioner requests that Patent Owner "be barred from participating in the present proceeding under the Board's patent owner estoppel regulation." Pet. 9–10 (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 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 '985 patent is is not patentably distinct from a claim canceled in any previous final written decision of the Board. Petitioner has not accounted for or evaluated the differences between the claims challenged in this proceeding and those canceled in the previous proceedings. *See, e.g.*, Prelim. Resp. 5–8 (claim charts). Instead, Petitioner points to a terminal disclaimer the patentee filed during prosecution as evidence that the claims are patentably indistinct. Pet. 10. However, as Patent Owner correctly observes, the filing of a terminal disclaimer does not constitute an admission of a rejection or of double patenting. MPEP § 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 claims 1 and 2 of the '985 patent are unpatentable.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1 and 2 of U.S. Patent No. 9,868,985 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 '985 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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