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Paper 65
Entered: September 9, 2019

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 MICHELLE N. ANKENBRAND, *Acting Vice Chief Administrative Patent Judge*, JAMES A. WORTH and BRIAN D. RANGE, *Administrative Patent Judges.*

Opinion for the Board *per curiam.*
Opinion Dissenting filed by *Administrative Patent Judge*, WORTH.

Per curiam

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

This is a Final Written Decision addressing the *inter partes* review challenging each claim of U.S. Patent No. 9,868,985 B2 ("the '985 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Illumina, Inc. ("Petitioner" or "Illumina") demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable.

A. Procedural History

Petitioner filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of the '985 patent. We instituted trial on the following grounds:[1]

Patent	References	Basis	Claim Challenged
'985	Tsien,[2] Prober[3]	§ 103(a)	1
'985	Tsien, Prober, and Pallas[4]	§ 103(a)	2
'985	Dower,[5] Prober, Metzker[6]	§ 103(a)	1, 2

[1] *See* Paper 20.

[2] Tsien et al., WO 91/06678, May 16, 1991 ("Tsien") (Ex. 1013).

[3] James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336–41 (Oct. 16, 1987) ("Prober") (Ex. 1014).

[4] Pallas et al., WO 98/53300, pub. Nov. 26, 1998 ("Pallas") (Ex. 1080).

[5] Dower et al., U.S. 5,547,839, Aug. 20, 1996 ("Dower") (Ex. 1015).

[6] 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") (Ex. 1016).

After institution, the Trustees of Columbia University in the City of New York ("Patent Owner" or "Columbia") filed a Patent Owner Response. *See* Patent Owner's Response ("Resp."), Paper 29 (public version), Paper 32 (sealed version). Petitioner filed a Reply (Paper 43, "Reply"), and Patent Owner filed a Sur-Reply (Paper 47, "Sur-Reply"). Additionally, Petitioner filed a motion to exclude evidence (Paper 51, "Mot. Excl."), Patent Owner responded (Paper 54, "Opp. Mot. Excl."), and Petitioner provided a Reply brief (Paper 56).

We heard oral argument for this *inter partes* review (as well as for four other related *inter partes* reviews) on March 5, 2019, and a transcript of the hearing is part of the record of this proceeding. Paper 60 ("Tr."). After oral argument, we requested additional briefing regarding certain estoppel issues. Paper 59. The parties provided such briefing. Papers 61 (Patent Owner's Additional Brief ("PO Supp. Br.")), 62 (Illumina's Supplemental Brief Regarding Estoppel ("Pet. Supp. Br.")), 63 (Illumina's Supplemental Reply Regarding Estoppel ("Pet. Supp. Reply")), 64 (Patent Owner's Reply to Petitioner's Supplemental Brief ("PO Supp. Reply")).

B. 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.

Petitioner filed Petitions requesting an *inter partes* review of related U.S. Patent Nos. 9,718,852 B2 ("the '852 patent"), 9,719,139 B2 ("the '139 patent"), 9,708,358 B2 ("the '358 patent"), and 9,725,480 B2 ("the '480

patent"). We instituted trial in each matter. *See* IPR2018-00291, Paper 16 (June 25, 2018); IPR2018-00318, Paper 16 (July 3, 2018); IPR2018-00322, Paper 16 (July 3, 2018); IPR2018-00385, Paper 20 (July 27 2018). On June 21, 2019, we entered a Final Written Decision determining that Petitioner demonstrated, by a preponderance of the evidence, that each challenged claim of the four patents is unpatentable. *See, e.g.*, IPR2018-00291, Paper 67; *see also* IPR2018-00291 Paper 69 (providing minor errata).

The parties note that in 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 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 IPR2013-00517, the Board held that Intelligent Bio-Systems, Inc. failed to demonstrate that the challenged claims of Petitioner's U.S. Patent No. 7,566,537 ("the '537 patent") were unpatentable.[7] Pet. 79–80; *see* Ex. 1044; Ex. 1045 (Federal Circuit decision affirming this Board decision).

[7] 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.

C. *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 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. The '985 patent further discloses its approach as "incorporat[ing] 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.

The '985 patent presents the same polymerase efficiency incorporation requirement as the Tsien prior art reference discussed below. Ex. 1075, 20:65–21:13. The '985 patent indicates that the allyl group can be used as a cap "using well-established synthetic procedures" and cites the Metzker prior art reference. *Id.* at 26:18–21; 28:14–19.

The '985 patent does not provide data establishing good incorporation or efficiency of an allyl group. *See* Ex. 1112, 284:6–18 (Dr. Menchen testifying that he does not remember seeing in the application how allyl groups could be incorporated efficiently).

The '985 patent does not disclose any special chemistry to, for example, provide for appropriate cleavability of an allyl group. Instead, its disclosure teaches that, according to prior art references such as Kamal, the allyl group "can be removed chemically with high yield." Ex. 1075, 26:12–31. In particular, the disclosure explains:

> [The] 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). These groups can be removed chemically with high yield as shown in FIG. **14** (Ireland, et al, 1986; Kamal et al. 1999). The chemical cleavage of the . . . allyl groups is fairly mild and specific, so as not to degrade the DNA template moiety. For example, the

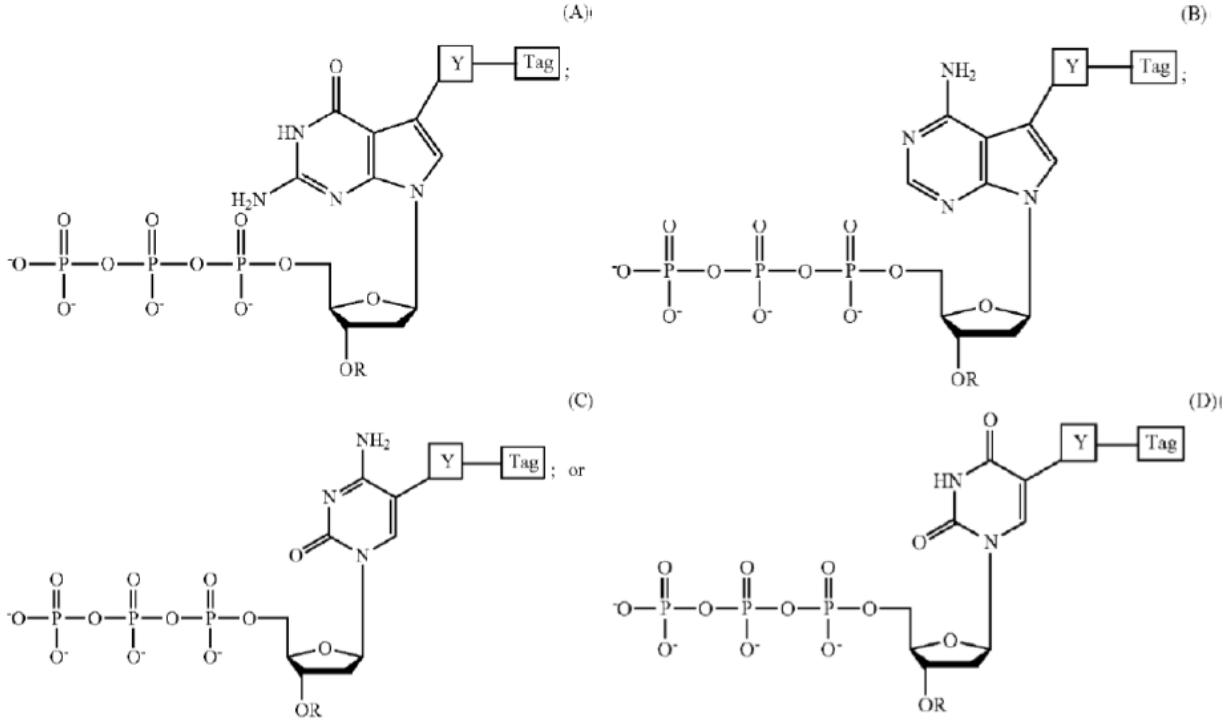
> cleavage of the allyl group takes 3 minutes with more than 93% yield (Kamal et al. 1999) . . . .

Id.

D. Challenged Claims

The ’985 patent has two claims. The two claims are reproduced below:

> 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;

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.[8]

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, 34:1–36:32.

[8] In the exhibits and briefing, the parties sometimes refer to the R group as a capping group (because it caps the molecule) and sometimes refer to it as a blocking group (because it blocks other groups from joining the molecule). We likewise use the terms capping group and blocking group interchangeably.

II. PETITIONER'S MOTION TO EXCLUDE

In support of its briefing, Patent Owner provided a declaration of Dr. Stephen M. Menchen. Ex. 2114. Petitioner moves to exclude Dr. Menchen's Declaration (Ex. 2114), or in the alternative, to exclude portions thereof. Mot. Excl. 1–9. Specifically, Petitioner argues that Dr. Menchen "appeared to know very little about the very subjects on which he had opined" at his deposition, that his Declaration is not based on sufficient facts or data, and that his opinions would cause confusion. *Id.* at 1 (citing Federal Rule of Evidence ("FRE") 403, FRE 702(a); Ex. 1112, 12:8–13:6, 235:19–237:18, 239:19–240:21, 262:6–17; Ex. 1113, 363:2–14, 374:16–376:8, 379:18–380:16, 381:2–6, 383:10–20). Petitioner also argues that Patent Owner "put blinders on its testifying witness" that would call into question the credibility of the Declaration. *Id.* at 2 (citing *Braun v. Lorillard Inc.*, 84 F.3d 230, 234–35 (7th Cir. 1996)). Petitioner argues that Dr. Menchen did not form an opinion on certain topics, was unable to testify, or admitted that he did not know when asked about the meaning of the term "small," what would meet certain claim limitations, whether a 3'-capping group would be efficiently incorporated, and whether any polymerases would work to incorporate nucleotides falling in claim 1. *Id.* at 1–2 (citing Ex. 1112, 144:7–151:25, 248:13–249:14, 252:20–254:11; 171:11–177:10, 179:11–180:9, 181:10–15, 240:22–241:9, 286:15–287:17, Ex. 1112, 178:11–179:6, 239:19–240:21, 286:4–14, 242:9–245:12; Ex. 1113, 378:5–380:16, 323:2–11, 378:14–19, 394:12–397:25).

In the alternative, Petitioner seeks to strike the following portions of Dr. Menchen's Declaration based on FRE 403 or 702: paragraphs 31, 33–34, 38–39, 43, 51, 94–97, 100–106, 109. *Id.* at 2–8. Petitioner asserts that

Dr. Menchen admitted that he is not an expert in polymerases and has never worked with polymerases. *Id.* at 2–3, 5 (citing Ex. 1112, 141:21–142:5, 141:9–20, 142:21–143:18, 178:22–179:6, 193:13–18, 270:2–16, 218:13–18, 288:16–289:1; Ex. 1113, 347:9–25).

Petitioner also argues that Dr. Menchen's testimony was unsupported or contradicted by other evidence and in some cases was *ipse dixit*. *Id.* at 4–9 (citing, *e.g.*, *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997); *Delaware Valley Floral Grp., Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1381 (Fed. Cir. 2010); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1355 (Fed. Cir. 2007)). Patent Owner responds that Petitioner's motion serves as an improper merits brief. Opp. Mot. Excl. 1 (citing Office Patent Trial Practice Guide August 2018 Update, 16 ("Update"), ("[A]rguments regarding weight should appear only in the merits documents"); *Liberty Mut. Ins. v. Progressive Cas. Ins.*, CBM2012-00002, Paper 66 at 62 (Jan. 23 2014) (a motion to exclude "is not an opportunity to file a sur-reply")).

We determine that Petitioner's arguments regarding Dr. Menchen's experience go to issues of credibility, weight, and the sufficiency of the evidence rather than admissibility. *See* Update at 3 ("There is . . . no requirement of a perfect match between the expert's experience and the relevant field."), available at www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf; *see generally Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008); *Mytee Prods., Inc. v. Harris Research, Inc.*, 439 F. App'x 882, 886–87 (Fed. Cir. 2011) (non-precedential) (upholding admission of the testimony of an expert who "had experience relevant to the field of the invention," despite admission that he was not a person of ordinary skill in the art). We

determine that Dr. Menchen has relevant experience, with a Ph.D. in Organic Chemistry and over 30 years of experience developing DNA sequencing technology. *See* Ex. 2016 ¶¶ 3–5.

Similarly, we agree with Patent Owner that Petitioner's arguments about the evidentiary basis for Dr. Menchen's opinions are directed to the sufficiency rather than the admissibility of evidence and are improperly advanced in a motion to exclude. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012) (stating that a motion to exclude may not be used to challenge the sufficiency of the evidence to prove a particular fact).

Petitioner also argues that "Columbia selectively cites portions of Dr. Romesberg's deposition transcript (Exhibit 2140) in an incomplete and misleading fashion, and the selective citations should be excluded or read in fuller context under FRE 106, 401–403." Mot. Excl. 9–15. This appears to be more properly a motion to strike portions of Patent Owner's Sur-Reply rather than a motion to exclude (*see id.*), but Petitioner did not seek authorization for a motion to strike, as required. *See* 37 C.F.R. § 42.20(b) (requiring prior authorization for motions); Update at 16–17. Such a process would have allowed the Board and the parties to consider, *inter alia*, whether further briefing would have been necessary to remedy any such problem. *See* Update at 16–17. In any event, whether or not Patent Owner used incomplete citations, we have read the briefs in the context of the record, and we deny this aspect of Petitioner's motion as well.

Accordingly, Petitioner's Motion to Exclude is *denied*.

III. DISCUSSION OF UNPATENTABILITY CHALLENGES

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain how Petitioner has met its burden with respect to the challenged claims.

A. Principles of Law

Obviousness is a question of law based on underlying determinations of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The underlying factual determinations include: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham*, 383 U.S. at 17–18. Subsumed within the *Graham* factors are the requirements that all claim limitations be found in the prior art references and that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) (citations omitted).

Moreover, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

B. Priority Date

U.S. Patent Application No. 09/684,670 was filed on October 6, 2000. *See* Ex. 1075. The '985 patent claims priority to the specification of this application. The parties agree that the priority date for the '985 patent is October 6, 2000. Paper 60, 24:21–24 ("Tr.").

C. Level of Ordinary Skill in the Art

We consider each asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner proposes a definition of the level of skill in the art (Pet. 11), and Patent Owner does not dispute this definition (Resp. 3). Petitioner's proposal is consistent with the evidence before us. *See* Findings of Fact, *infra*. We, therefore, adopt Petitioner's proposal and find 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 techniques. A person of ordinary skill in the art would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and would have had at least five years of practical academic or industrial laboratory experience.

D. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2017)[9]; *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would have been understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Here, Petitioner addresses claim 1's recitation of "or" between the claim's recitation of the four nucleotide analogues. Pet. 11. Patent Owner requests construction of "small" and "chemical linker." Resp. 9–10. Additionally, the parties address claim 1's recitation of "[a] method for sequencing a nucleic acid." *Id.* at 11; Reply 3–5. We address these four issues below.

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[9] The Office recently changed the claim construction standard applicable to an *inter partes* review. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018). The rule changing the claim construction standard, however, does not apply to this proceeding because Petitioner filed its Petition before the effective date of the final rule, i.e., November 13, 2018. *Id.* at 51,340 (rule effective date and applicability date), 51,344 (explaining how the Office will implement the rule).

"*or*"

Petitioner argues that in reciting "or," claim 1 requires use of any one of the four recited nucleotide analogues. Pet. 11. Patent Owner's Response does not address this claim term. Resp. 9–11. We agree with Petitioner's interpretation because it is consistent with claim 1's recitation of "wherein the nucleotide analogue is any of the following" and the ordinary meaning of the word "or."

"*small*"

Claim 1 recites that the nucleotide capping group, R, "represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of [the] deoxyribonucleotide analogue." *See* Ex. 1075, 35:27–29. Patent Owner argues that "'small' means the group has a diameter less than 3.7 [Angstroms]." Resp. 9–10.

Here, each of Petitioner's asserted invalidity grounds relies upon the obviousness of using an allyl group. Tr., 14:2–11. The parties agree that an allyl blocking group is "small" within the context of the claims at issue. *Id.* at 15:9–11; Resp. 9. There is, therefore, no need for us to further construe "small." *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy"); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs.* when addressing an *inter partes* review proceeding on appeal).

"*chemical linker*"

Claim 1 recites that the Y on the nucleotide structure "represents a chemically cleavable, chemical linker." *See, e.g.*, Ex. 1075, 36:6–7. Patent

Owner argues that "'chemical linker' means a chemical moiety attached by covalent bonds at one end to a specified position on the base of a nucleotide and at the other end to a tag (detectable fluorescent moiety)." Resp. 10. Based on our review of the record, we determine that this term does not require construction in order to resolve the parties' controversy, and we decline to construe it. *Vivid Techs.*, 200 F.3d at 803.

"*[a] method for sequencing a nucleic acid*"

In our Decision to Institute, we invited the parties to address whether either claim of the '985 patent "necessarily requires sequencing, for example, of whole genomes." Paper 20 at 26. Patent Owner responds by contending that claim 1's recitation of "[a] method for sequencing a nucleic acid" requires multiple cycles of SBS. Resp. 11. Petitioner disagrees and emphasizes that a cycle of SBS requires many steps that are not recited in claim 1 and that those steps should not be incorporated into claim 1. Reply 3–4.

As we explain in more detail in Section III(F)(3)(i), *infra*, we find that a person having ordinary skill in the art would not have pursued the prior art's nucleotide analogues unless they had a reasonable expectation that the nucleotide analogue could be used to perform an sequencing-by-synthesis method that could approach or reach sequencing twenty base pairs or more. Similarly, to the extent claim 1 (or claim 2) requires sequencing, it does not recite that an entire DNA strand must be sequenced with the recited method. Indeed, Patent Owner does not contend that these claims require sequencing an entire DNA strand. *See* Resp. 11.

Because, as explained below, we find that a person of ordinary skill in the art would have pursued the method of claim 1 to achieve some

sequencing, it is not necessary for us to further construe this claim term. *Vivid Techs.*, 200 F.3d at 803.

E. Fact Findings

The fact findings below focus on issues that must be resolved in order to assess Petitioner's obviousness challenges. *Graham*, 383 U.S. at 17–18. Each finding is based upon consideration of the record as a whole and is supported by the preponderance of the evidence.

1. Technology Overview

Deoxyribonucleotides make up the building blocks of DNA, and the chemical formula, nomenclature, and uses of deoxyribonucleotides were generally known before October 6, 2000. Ex. 1011, 46, 47, 58–60, 98–103. A strand of DNA consists of deoxyribonucleotides where the 5'-phosphate of one nucleotide is attached to the 3´-oxygen of the adjacent nucleotide. Ex. 1078 ¶¶ 33–36; Pet. 12–13.

Before October 6, 2000, persons having ordinary skill in the art would have been aware of several methods for determining the sequence of DNA, including Sanger sequencing and sequencing-by-synthesis ("SBS"). Ex. 1078 ¶ 38 (citing as examples of Sanger sequencing Ex. 1014 (Prober) and Ex. 1018 (Sanger); citing as examples of SBS Ex. 1013 (Tsien), Ex. 1015 (Dower), Ex. 1016 (Metzker), and Ex. 1020 (Cheeseman)).

The sequencing method of primary focus in this IPR is SBS. Ex. 1078 ¶ 38; Pet. 14. SBS incorporates modified nucleotides ("nucleotide analogs") having a detectable label into a growing strand of DNA. Ex. 1078 ¶ 38. The label on the incorporated nucleotide analogue is detected to determine the DNA sequence. *Id.*

SBS may be distinguished from Sanger sequencing. Sanger sequencing was the favored DNA sequencing method in the 1990s. Ex. 2114 ¶ 11. Sanger sequencing had certain limitations to "both the number of DNA segments that can be sequenced in parallel, and the number of operations which may be carried out in sequence." Ex. 2099,[10] 1:29–45.

2. The Asserted Prior Art References

i. Dower (December 1990)

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, [54], 1:21–22. The Dower patent application was filed Dec. 6, 1990, and issued Aug. 20, 1996.

One Dower 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.

Dower describes SBS methods. Resp. 4; Ex. 2114 ¶ 12. In one embodiment for the synthesis of nucleotides, Dower discloses that a polymerase is used to extend a primer complementary to a target template,

[10] Jones, U.S. 5,858,671, Jan. 12, 1999.

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. Ex. 1015, 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:

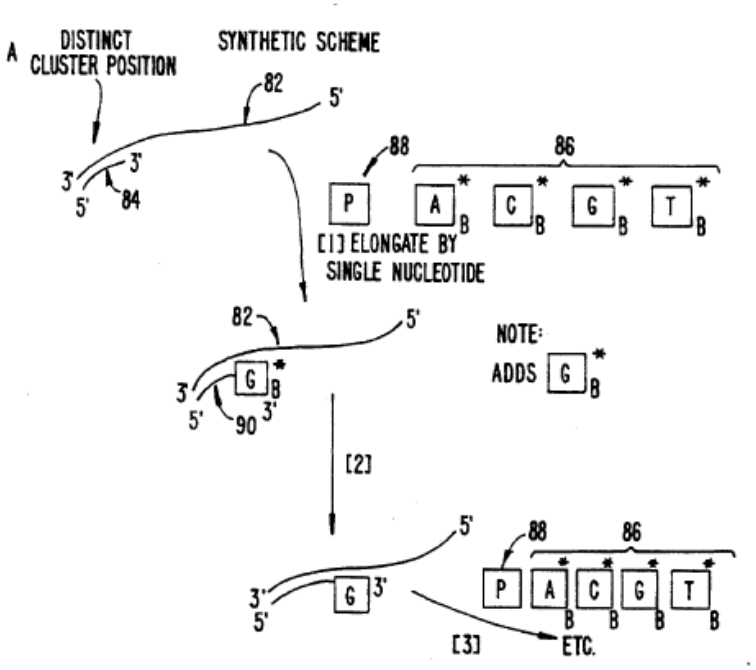

Figure 8A, above, illustrates schematically, at a molecular level, the sequence of events which occur during a particular sequencing cycle. *Id.* at 5:30–32.

Dower suggests that choosing an appropriate terminator that is easily removed is not difficult:

> A second, unlabeled and reversible, set of terminators is also required. Examples of these compounds are deoxynucleotide triphosphates with small blocking groups such as acetyl, tBOC,

> NBOC and NVOC on the 3'OH. These groups are easily and efficiently removed under conditions of high or low pH, exposure to light or heat, etc.

Id. at 25:47–53.

Dower does not describe any actual experiments or provide data. Resp. 5 (citing Ex. 2116 ¶ 13). While attempting to obtain its own patent claims that stood rejected over Dower, Petitioner argued that undue experimentation would be required to successfully choose one of Dower's blocking groups:

> Undue experimentation would be required to determine which of the multitude of potential blocking groups would be expected to be removable blocking moieties that also protect the 3' position of said mononucleoside 5'-triphosphates, [as required by the instant claims].

Ex. 2009, 17 (March 2011, Response to Office Action).

ii. Tsien (May 1991)

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 published on May 16, 1991, has an October 26, 1990, international filing date, and claims priority to an October 26, 1989, United States patent application. *Id.*

Tsien describes an SBS method. Ex. 1078 ¶ 38; Ex. 2114 ¶ 12; Resp. 4. In particular, Tsien describes determining the sequence of a single stranded DNA molecule by synthesizing the complementary DNA molecule. Ex. 1013, 6:28–7:14. Tsien explains that deoxyribonucleotide triphosphates (dNTP) are used to build up numerous copies of the complementary molecule and that, as each dNTP is added, it is identified by a label. *Id.*

Tsien suggests employing 3' hydroxyl-blocked dNTPs to prevent inadvertent extra additions. *Id.* at 20:24–21:19.

Figure 1B of Tsien is reproduced below:

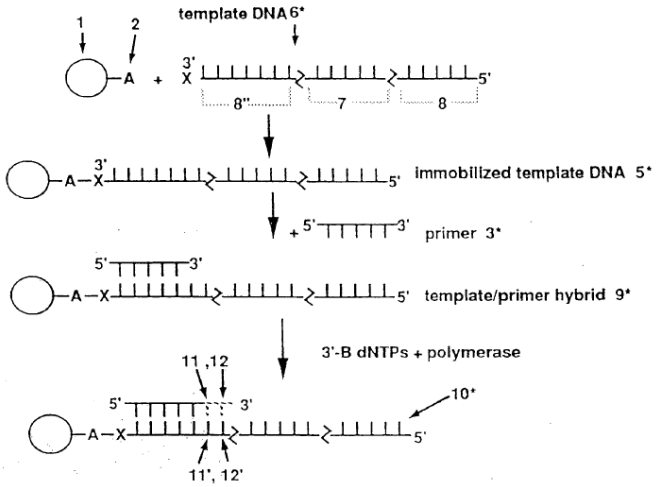

FIG. 1B

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

Tsien indicates that its method can assemble "25 to 300, or more" nucleotides. *Id.* at 17:34–18:2. Tsien explains that its method can be useful even if only creating a portion of a DNA chain at one time:

> [the 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.

Tsien provides criteria for successful use of a 3' hydroxyl-blocked dNTP:

> (1) the ability of a polymerase enzyme to accurately and efficiently incorporate the dNTPs carrying the 3´-blocking groups into the cDNA chain,
> (2) the availability of mild conditions for rapid and quantitative deblocking, and
> (3) the ability of a polymerase enzyme to reinitiate the cDNA synthesis subsequent to the deblocking stage.

Id. at 20:24–21:3. With respect to incorporation, Tsien explains that even 98% incorporation can lead to low yield after numerous additions. *Id.* at 16:21–30. Tsien, however, also teaches that periodically halting DNA molecule growth and recreating the molecule for renewed DNA fabrication can alleviate this limitation. *Id.* at 16:31–35.

Tsien explains that after incorporation, the sequencing scheme requires removing the blocking group. Tsien sets forth criteria for a successful deblocking method:

> (a) proceed rapidly,
> (b) yield a viable 3´-OH function in high yield, and
> (c) not interfere with future enzyme function or denature the DNA strand.

Id. at 23:27–24:5.

Tsien identifies many possible blocking groups. For example, Tsien states that the blocking groups can be esters and ethers, or may include other

modifications to the 3'-hydroxyl position. *Id.* at 21:9–31. Tsien explains that ester blocking groups can be achieved by base hydrolysis. *Id.* at 24:3–23. Important to the issues at hand, Tsien teaches the use of an allyl ether as a blocking group:

> A wide variety of hydroxyl blocking groups are cleaved selectively using chemical procedures other than base hydrolysis. 2,4-Dintrobenzenesulfenyl groups are cleaved rapidly by treatment with nucleophiles . . . . **Allyl ethers are cleaved by treatment with Hg(II) in acetone/water (Gigg and Warren, 1968)**. . . . Tetrahydrothiofuranyl ethers are removed under neutral conditions using . . . . These protecting groups, which are stable to the conditions used in the synthesis of dNTP analogues and in the sequence incorporation steps, have some advantages over groups cleavable by base hydrolysis – deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized.

Id. at 24:24–25:3 (emphasis added).

Tsien does not provide any data supporting whether or not an allyl blocking group would meet Tsien's stated criteria for a successful blocking group. Petitioner has previously taken the position that Tsien is a "purely prophetic disclosure." Ex. 2009, 15 (March 2011, Response to Office Action).

When attempting to obtain its own patent claims that stood rejected over Tsien, Petitioner argued that undue experimentation would have been required to successfully choose one of Tsien's blocking groups:

> Undue experimentation would be required to determine which of the multitude of potential blocking groups would be expected to be <u>removable</u> blocking moieties that also <u>protect</u> the 3' position of said mononucleoside 5'-triphosphates, as required by the instant claims.

Id. (emphases original). Similarly, a third party PCT application filed in 1995 describes Tsien (referencing Tsien by its patent number) and several other prior art references as deficient as follows:

> [T]he necessary 3'-blocking groups are either not described in any detail, or are not accepted by the required enzyme, or do not permit desired rapid deblocking of the growing template copy strand after each polymerization event.

Ex. 2110 at 3.

iii. Metzker (July 1994)

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 describes a Base Addition Sequencing Scheme equivalent to SBS. *Id.* Similar to Tsien, Metzker states that its scheme has "stringent requirements" that are "formidable obstacles" in designing analogs:

> The complete scheme demands nucleotide analogs that are tolerated by polymerases, spectroscopically distinct for each base, stable during the polymerization phase, and deprotected efficiently under mild conditions in aqueous solution.

Id.

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 (species [1] to [8]) 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; *see*

also id. at Table 2, 4265 (reporting that compound [3] was "incorporated by some of the polymerases"). Metzker's table reporting the activity of the O-allyl group (*id.* at 4263) is reproduced here:

Table 2. Activity matrix of RP-HPLC purified 3′-protecting dNTPs challenged against commercially available polymerases

3′-modified-dATP (except compound [8])	AMV-RT	M-MuLV-RT	Klenow fragment	Sequenase®	*Bst* DNA polymerase	AmpliTaq® DNA polymerase	Vent$_R$(exo$^-$)® DNA polymerase	*rTth* DNA polymerase
[1] *O*-methyl	Termination	Termination*	-	-	-	-	Inhibition	Inhibition*
[2] *O*-acyl	-	-	-	-	-	-	Inhibition	-
[3] *O*-allyl	-	-	-	-	-	-	Termination*	-
[4] *O*-tetrahydropyran	-	-	-	-	-	-	-	-
[5] *O*-(4-nitrobenzoyl)	-	-	-	-	-	-	-	-
[6] *O*-(2-aminobenzoyl)	-	-	-	-	-	-	-	-
[7] *O*-(2-nitrobenzyl)	-	-	-	Inhibition	Termination	Termination*	Termination*	-
[8] 3′-*O*-methyl-dTTP	-	Inhibition	-	Inhibition	Termination	Termination	Termination	Termination

All compounds were assayed at a final concentration of 250 μM according to the conditions specified in Table 1. '−' means no activity was detected, 'Termination' means that the termination bands mimic ddNTP termination bands, and 'Inhibition' means the rate of DNA synthesis is reduced in a nonspecific manner. '*' means the activity was incomplete at a final concentration of 250 μM .

Metzker's Table 2 summarizes data from enzymatic screening of compounds [1]–[8]. *Id.* at 4263. Metzker indicates that the O-allyl group showed "Termination*" with respect to one commercial polymerase. Metzker states that the * "means the activity was incomplete at a final concentration of 250 μM." *Id.*[11, 12] Metzker reports that "Compounds [1], [8], and [7] showed specific termination and were further evaluated with respect to their concentration dependent effects." *Id.*

[11] The unit "μM" is a measure of molarity—micro moles per liter.

[12] Tsien discusses methods at smaller μM concentrations. *See, e.g.*, Ex. 1013 at 35–36. Tsien, however, also teaches that using "substantial excesses (over stoichiometry)" may be helpful. *Id.* at 20:17–22.

In a 2007 paper, Dr. Metzker explained that his 1994 publication taught that 3'-O-allyl-dATP was a "poor substrate[]" with "limited activity." Ex. 1017 at 6348. In particular, the 2007 paper states:

> This is unlike the situation for 3'O-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).

Ex. 1017 at 6348. The "(8)" in the quote above is an endnote reference to the 1994 Metzker paper.

iv. Prober (1987)

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, reproduced below:

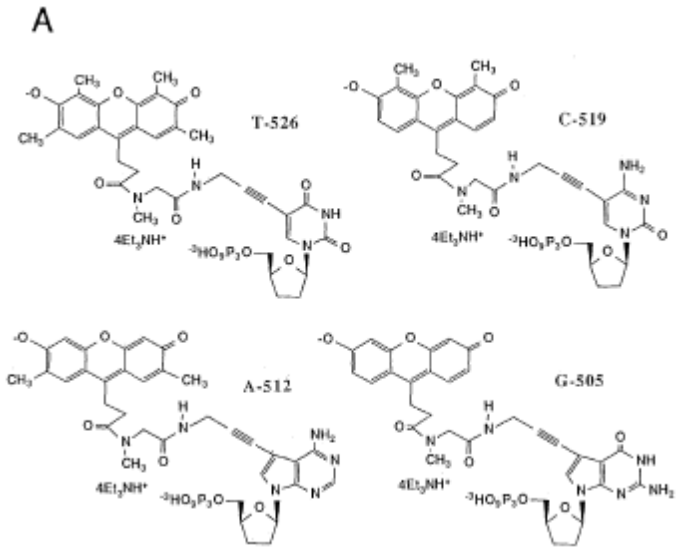

Figure 2A depicts "[c]hemical structures of the reagents used in modified dideoxy reactions for DNA sequencing." *Id.* at 338. Prober discloses that succinylfluorescein is attached via a linker to a heterocyclic base, i.e., a nucleotide analogue. *See id.* at 337. In particular, the linker is attached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

v. Pallas (1998)

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.

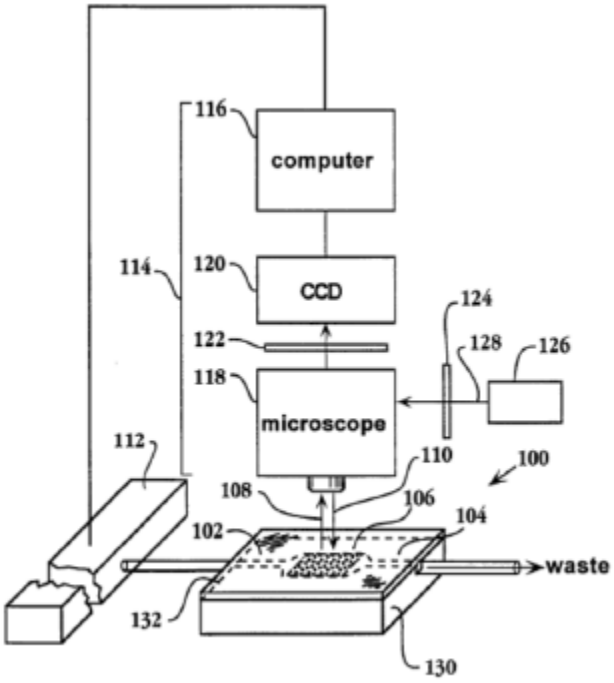

Fig. 1A

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.

3. Other Record Evidence Regarding the State of the Art

In the 1990's various groups attempted using different blocking groups with sequencing methodologies with varying reported success. Ex. 1020, 4:50–63 (patent filed in 1991 suggests O-succinyl protecting group); Ex. 2031, 3 (1994 paper indicates incomplete blocking under some conditions); Ex. 2109, 2:15–21 (PCT application with 1995 priority reports on other references as suggesting that 90% removal protecting groups after ten minutes of treatment will be unacceptably low).

Hiatt,[13] a patent filed in 1995, discloses the 3'-O-allyl blocking group for polymerase incorporation. Ex. 1106, 11:58, 12:39, 30:8. Hiatt, however, presents an immense number of possibilities for the blocking group. *See id. passim*.

Jones,[14] a patent filed in 1996, references Metzker and states "[t]echnical obstacles include a relatively low efficiency of extension and deprotection, and interference with primer extension . . . ." Ex. 2099, 2:34–36. Jones explains that even at 95% efficiency, only 75% product of interest remains after only six cycles. *Id.* at 2:43–45. Thus, inefficiency "will severely limit the ability of this method [SBS] to sequence anything but very short DNA sequences." 2:45–47.[15] Jones then, again, cites Metzker as demonstrating that "[o]nly one cycle of template-directed analog incorporation and deprotection appears to have been demonstrated so far." Ex. 2099, 2:47–52.

In 1999, researchers at Texas A&M University, Welch and Burgess,[16] described removal of the blocking group under mild conditions as a "major challenge." Ex. 2041, 197–98. Welch and Burgess (among others) also authored a second 1999 paper that assesses results for various nucleotides

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13 Hiatt et al., U.S. 5,808,045, Sept. 15, 1998 ("Hiatt") (Ex. 1106).

14 Jones, U.S. 5,858,671, Jan. 12, 1999 ("Jones") (Ex. 2099).

15 Similarly, Patent Owner's expert, Dr. Menchen, opines that assembly of sequenced fragments requires accurate sequences of twenty base pairs or greater. Ex. 2114 ¶¶ 92–93. Petitioner has previously taken the position that an SBS process "should be able to determine the sequence of at least 20 consecutive nucleotides . . . to be effective." Ex. 2029, 6.

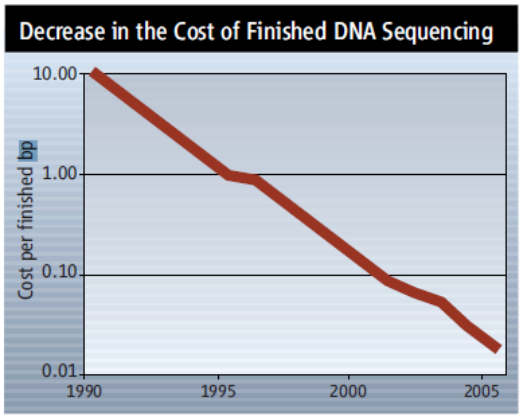
16 Kevin Burgess is also a co-author of the Metzker reference.

and concludes "[i]t seems clear that modifications to the polymerase enzyme as well as to the nucleoside triphosphate are required if [SBS] is to be developed into a viable sequencing scheme." Ex. 1023, 956. This paper cites both Tsien and Metzker. *Id.* at 960. Stemple,[17] a patent application filed in 1999, states that SBS is "plagued by any inefficiencies of incorporation and deprotection" and that "a need still remains in the art for a rapid, cost effective, high throughput method for sequencing unknown nucleic acid samples . . . ." Ex. 2013, 2–3.

In international patent applications filed in August 2003, after the priority date of the '985 patent but before publication of the underlying patent application, Solexa described use of the 3'-O-allyl group. Ex. 1124, 22:34–23:24; Ex. 1125, 111:4–115:1. One of Solexa's applications refers back to Metzker. Ex. 1124, 23:21–24 ("[w]here the blocking group is an allyl group, it may be introduced into the 3'-position using standard literature procedures such as that used by Metzker").

After the present application's October 2000 priority date, genome sequencing technologies continued to advance. The initial draft of the first human genome sequence was finished in 2001 and cost an estimated $300 million. Ex. 1120, 1544. The final draft and all technology that made it possible cost nearly $3 billion. *Id.* In 2004, the NIH launched a $70 million grant program seeking to reduce sequencing costs to just $1,000. *Id.* The chart below, reproduced from a March 2006 issue of Science magazine, illustrates the decreasing cost of DNA sequencing over time.

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



Free fall. As with computer technology, the plunging cost of DNA sequencing has opened new applications in science and medicine.

Id. The above chart plots the cost per finished bp (base pair) over time and shows the cost was over $10 per base pair in 1990 and plunged to just a few cents by 2005. *See also* Ex. 1017, 6339 (2007 article by Metzker stating "Next-generation technologies are being developed to advance sequencing to the $100,000, and eventually the $1,000 genome.").

4. *Other Evidence Regarding Suitability of an Allyl Group*

As explained above, Tsien teaches that a "successful use of a 3'-blocking group[]" as an end cap for a nucleotide analogue requires, generally, (1) accurate and efficient incorporation of the blocking group, (2) availability of mild conditions for rapid and quantitative deblocking, and (3) ability of a polymerase enzyme to reinitiate synthesis after deblocking. Ex. 1013, 20:25–21:3.

Petitioner, when addressing its own patent in IPR2017-02174, has previously argued that use of a blocking group would not have been obvious without meeting these three "primary requirements." Ex. 2027, 5–6. For example, Petitioner argued that, despite Dower teaching an azidomethyl group, a person having ordinary skill in the art would not have been motivated to use an azidomethyl moiety because a person having skill in the

art would not have expected efficient and accurate incorporation (*id.* at 29–40), mild removal conditions (*id.* at 40–44), and efficient cleavability (*id.* at 45–47). Because the parties dispute incorporation and cleavability in this proceeding, we address facts concerning those issues below.[18]

i. Efficient incorporation

As explained above, several references teach that efficient incorporation is a requirement for a successful blocking group. Resp. 5–6 (citing Ex. 1013; Ex. 1015; Ex. 2013).

Patent Owner's expert, Dr. Menchen, opines that Metzker's referent to "Termination*" means that the 3'-O-allyl nucleotide is inefficiently incorporated and, therefore, not suitable for SBS. Ex. 2114 ¶¶ 33–51.

Petitioner's expert, Dr. Romesberg, opines that Metzker's experiments were contaminated and having termination despite this contamination would mean that 3'-O-allyl derivative "was a promising reagent for [SBS]." Ex. 1119 ¶¶ 65–67. Dr. Romesberg also opines that a person having ordinary skill in the art would have understood that increasing 3'-O-allyl nucleotide concentration or increasing reaction time would lead to more efficient incorporation. *Id.* ¶¶ 75–76. Dr. Romesberg further opines that a person having ordinary skill in the art would have understood increasing concentration of the 3'-O-ally-nucleotides could achieve efficient incorporation. *Id.* ¶¶ 75–91 (citing, *e.g.*, Ex. 1016, 4262, Figs. 3A, 4B). The 1994 Canard and Sarfati paper Patent Owner cites (Sur-Reply 13) indicates that higher concentration levels can reach high incorporation levels where a chain terminator is inefficient. Ex. 2031, 3 ("Taken with the fact that high

[18] The parties do not dispute the third criterion—ability to reinitiate.

concentrations . . . were needed to reach high incorporation levels, this may indicate that these modified [nucleotides] are not very efficient chain terminators . . . .").

The evidence also indicates, however, that increasing nucleotide concentration too much can cause problems, such as hindered selectivity, insertion or deletion of nucleotide residues during synthesis, and increased mutation rates. Ex. 2081 ¶ 15; Ex. 2140, 173:2–6. Dr. Romesberg, did not take a position as to what mutation rate would be significant. Ex. 2140, 166:25–170:1. Dr. Romesberg previously indicated, however, that a person of skill in the art developing SBS methods would have been dissuaded from pursuing protecting groups that require high concentrations (such as 1 mM to 2 mM) due to hindered selectivity at high nucleotide concentrations. Ex. 2081 ¶ 17.[19]

Dr. Menchen testified in deposition that he included the 3'-O-allyl blocking group in his own 1998 and 1999 patent disclosures because of Metzker's disclosure. Ex. 1112, 189:5–13. Dr. Menchen's patents, however, relate to Sanger sequencing rather than SBS (*see, e.g.*, Ex. 1112, 154:22–155:3), and Dr. Romesberg concedes that Sanger sequencing requires low termination rates (in contrast to the high termination rates SBS requires). Ex. 2140, 146:3–147:24.

[19] In this declaration, Dr. Romesberg was providing testimony with respect to Petitioner's U.S. Patent No. 8,158,346. That patent has a priority date no earlier than December 4, 2002, so considerations as to what a person of skill in the art would have considered may have been different.

ii. Appropriate cleavability conditions

The 1976 Boss reference[20] teaches that the allyl group of an allyl ether may be cleaved using palladium. Ex. 1035, 559. Tsien states that "[a]llyl ethers are cleaved by treatment with Hg(II) in acetone/water (Gigg and Warren, 1968)." Ex. 1013, 24. The 1997 Qian reference[21] teaches removal of an O-allyl group using palladium ($PdCl_2$) provides the end product "in quantitative yield." Ex. 1036, 2184. The 1998 Kamal reference[22] teaches a method of cleaving allyl ethers "employing chlorotrimethylsilane and sodium iodide" that is "rapid and efficient and proceed[s] under mild conditions." Ex. 1037, 371–72.

A 1994 article by Genet[23] discloses an efficient water-soluble palladium catalyst for cleaving allyl groups. *See, e.g.*, Ex. 1094, 499. In 2006, a doctoral student at Columbia University suggested that mild methods of cleaving allyl groups had been known for "decades":

> In the past decades, chemists have developed efficient catalysts to cleave allyl groups from allyl ethers, allyl carbonates or allyl carbamates; these are composed of palladium (0) or (II)

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[20] Roland Boss & Rolf Scheffold, *Cleavage of Allyl Ethers with Pd/C*, 15 ANGEW. CHEM. INT. ED. ENGL. 558–59 (1976) (Ex. 1035) ("Boss").

[21] 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'Y, 2184–85 (1998) (Ex. 1036) ("Qian").

[22] 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) ("Kamal").

[23] Genet et al., *Practical Palladium-Mediated Deprotective Method of Allyloxycarbonyl in Aqueous Media*, 50 Tetrahedron 497–03 (1994) (Ex. 1094) ("Genet").

> combined with suitable ligands or other reagents.[] Some of them are performed in relatively mild conditions and may be a potential choice for our DNA sequencing system.

Ex. 1116, 163–64. The paper refers to several different papers relating to palladium cleaving of allyl groups including Genet. *Id.* at 163–67. A 2006 article from a named inventor of the '985 patent, Dr. Jingyue Ju, similarly cites Genet and other references when stating that palladium mediated deallylation under aqueous conditions "has been widely used." Ex. 1093, 5934.

Dr. Menchen, opines that the Boss, Tsien, Qian, and Kamal cleaving methods are each incompatible with SBS. In particular, Dr. Menchen explains that Boss's cleaving method is not mild (would denature DNA) and does not result in rapid cleavage. Ex. 2114 ¶¶ 66–69. He notes that Tsien's cleaving method (as Gigg and Warren teaches) is not aqueous and is not mild. *Id.* ¶¶ 54–58. He states that Kamal is not aqueous, not mild, and does not result in quantitative cleavage. *Id.* ¶¶ 59–65. He states that Qian's use of palladium chloride in methanol is not aqueous, not mild, and does not result in rapid or reliable, quantitative cleavage. *Id.* ¶¶ 71–81.

Dr. Romesberg agrees with Dr. Menchen in some respects. Dr. Romesberg testifies that a person of ordinary skill in the art would have understood that applying the Gigg and Warren method (which Tsien references) at high concentrations of potassium t-butoxide would damage DNA and that a skilled artisan, therefore, would not have used Gigg and Warren's conditions for SBS. Ex. 2126, 231:22–232:15. Dr. Romesberg also agrees that Kamal's method is "not compatible with water." *Id.* at 235:3–8.

In other respects, Dr. Romesberg disagrees with Dr. Menchen. For example, Dr. Romesberg testifies that: "It was also known that allyl groups were generally efficiently removed using palladium, including under aqueous conditions." Ex. 1078 ¶ 77 (citing Boss and Qian); *see also id.* ¶ 100. Dr. Romesberg opines that Boss (Ex. 1035) also teaches use of a milder *p*-toluenesulfonic acid. Ex. 1119 ¶ 44.[24] Dr. Romesberg testified that a person having skill in the art would have known that the Qian method (using palladium) could be performed with added water with a high probability of success. Ex. 2126, 158:1–159:2; *see also* Ex. 2113, 71:23–72:10 (Dr. Romesberg testifying that there would have been an "expectation of success" if Qian's conditions were modified "based on the Qian report" but they "would have had to run the experiment" because "[n]o one can predict the future").[25]

Both experts agree that "[s]mall differences" in cleavability conditions can impact results. Ex. 2114 ¶ 75 (Dr. Menchen stating "small changes to a

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[24] Dr. Romesberg testifies that he would consider para-toluenesulphonic acid a strong acid and "a stronger acid than a lot of other things," but he also testified that "'strong' is a relative term." Ex. 2140, 182:3–13.
Dr. Romesberg also testifies that the cleavage data from Boss did not relate to nucleotides. *Id.* at 86:15–18. Boss's data shows from 78% to greater than 95% cleavage, depending on the allyl ether. Ex. 1035, Table 1.
Dr. Romesberg's testimony indicates uncertainty as to what percent cleavage Boss would have obtained for a nucleotide. Ex. 2140, 86:19–90:20.

[25] In Sur-Reply, Dr. Menchen disagrees by emphasizing that Qian's palladium chloride is not soluble in water and that Dr. Romesberg's testimony that a person of skill could have added a solubilizing agent as well as water is speculative. Ex. 2114 ¶ 77.

reaction's conditions can affect its cleavage efficiency"); Ex. 2113, 71:23–72:10 (Dr. Romesberg stating "[s]mall differences can have impact").

F. '985 Patent Ground 1: Obviousness of Claim 1 over Tsien and Prober

Petitioner argues that the combination of Tsien and Prober would have rendered obvious to a person of ordinary skill in the art the subject matter of '985 patent claim 1. Pet. 18–51. Patent Owner disagrees. Resp. 11–61. Based on our review of the arguments and evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of '985 patent claim 1 would have been obvious over the combination of Tsien and Prober, as explained below.[26]

1. It is Undisputed that the Prior Art Discloses or Suggests Many Limitations of the '985 Patent Claim 1

Petitioner explains how the combination of Tsien and Prober teaches each limitation of claim 1. For example, Petitioner explains that Tsien discloses the detecting step of claim 1. Pet. 19–21 (citing, *e.g.*, Ex. 1013, 8:18–26, 10:7–10; 11:27–13:35, Fig. 2; Ex. 1006, 3, 11; Ex. 1007, 3, 19; Ex. 1008, 33). Petitioner also explains that Tsien discloses deoxyribonucleotide triphosphate (dNTP) analogues including the pyrimidine analogues that claim 1 depicts as (C) and (D). *Id.* at 21–26 (citing, *e.g.*, Ex. 1013, 12:27–29, 20:24–25:34, Fig. 2; Ex. 1078 ¶ 74). Petitioner also explains that Tsien recommends using Prober's nucleotides

[26] For brevity, we do not repeat all factual findings in the analysis portion of this decision, but certain findings may be mentioned again for emphasis. Our analysis with respect to all challenges is based upon determining whether Petitioner has met the preponderance of the evidence standard based on all evidence in the record as a whole.

and cites Prober for "show[ing] enzymatic incorporation." Pet. 32 (citing Ex. 1013, 28:16–18, 29:12–16; Ex. 1014, 337, 340). We find that Tsien's recommendation provides an express reason to combine the teachings of the references.

To the extent Patent Owner does not address the merits of any of Petitioner's assertions, Patent Owner's arguments are waived. *Cf. In re NuVasive Inc.*, 842 F.3d 1376, 1381 (Fed. Cir. 2016) (explaining that a patent owner waives an argument presented in the preliminary response if it fails to renew that argument in the patent owner response after trial is instituted). Because a preponderance of the evidence (as demonstrated by the citations to supporting evidence above) supports Petitioner's arguments relating to the teachings of the prior art, we adopt Petitioner's arguments as our own. *See* Pet. 18–51; *see also In re NuVasive*, 841 F.3d 966, 974 (Fed. Cir. 2016) (explaining that the Board need not make specific findings as to claim limitations that Patent Owner does not dispute are disclosed in the prior art).

We address the arguments Patent Owner raises below.

2. Tsien Suggests Use of an Allyl (-$CH_2CH=CH_2$) Blocking Group

Petitioner argues that Tsien teaches an allyl blocking group having the chemical formula -$CH_2CH=CH_2$. Pet. 26–28 (quoting, *e.g.*, Ex. 1075, 3:41–44 as stating "[i]t 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"). Petitioner alleges that this group meets the limitation of claim 1 "wherein R(a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3′ position of the deoxyribose of [the] deoxyribonucleotide analogue." *Id.* Patent Owner alleges that Tsien's

reference to "allyl ethers" merely refers to a genus rather than the particular $–CH_2CH=CH_2$ species and that, therefore, Tsien does not teach or suggest a "small" group within the meaning of claim 1. *See, e.g.*, Resp. 52–56.

The preponderance of the evidence favors Petitioner's position on this issue. In particular, Tsien suggests use of a "wide variety of hydroxyl blocking groups" and names "2,4-Dinitrobenzenesulfenyl groups," "Allyl ethers," and "Tetrahydrothiofuranyl ethers" as possible blocking groups. Ex. 1013, 24:24–25:3. Tsien cites "Gigg and Warren, 1968" as describing a method of cleaving allyl ethers. *Id.*; *see also supra* Section III.E.2.ii (findings of fact regarding Tsien).

Gigg and Warren, in turn, is entitled "The Allyl Ether as a Protecting Group in Carbohydrate Chemistry, Part II." Ex. 1046, 1903; *see also* Reply 5 ("the title of Gigg [and Warren] unambiguously refers to 'The Allyl Ether'"). Importantly, Gigg and Warren identifies eighteen different blocking groups for an organic molecule. Ex. 1046, 1905. The blocking group numbered XXXV (fifteen) is $-CH_2CH=CH_2$. Gigg and Warren, in turn, refers to group XXXV as "the allyl ether." *Id.* at 1905–06 ("For this purpose the allyl ether (XXXV) was hydrolysed by methanolic hydrogen chloride . . . ."); *see also id.* at 1906–07 (referring to "the allyl ether (LI)" which is defined as $-CH_2CH=CH_2$), 1910 (referring to "The allyl ether (XXXV) . . . .").

We find that a person of skill in the art seeking to further understand Tsien's reference to "[a]llyl ethers" would have reviewed Gigg and Warren and would have understood that Gigg and Warren used the term "allyl ether" to refer to a $-CH_2CH=CH_2$ group. Thus, a person of skill in the art would have understood that Tsien suggested use of the $-CH_2CH=CH_2$ group. The

International Union of Pure and Applied Chemistry ("IUPAC"), defining "allyl" as "-$CH_2CH=CH_2$," further supports our determination. Ex. 1099, 13, 305; *see also* PO Reply 5–7 (citing, *e.g.*, Ex. 1101, 67; Ex. 1102, 2–71, Ex. 1103, 24; Ex. 1039, 503; Ex. 1104, 254; Ex. 1105, 209) (demonstrating industry recognition of the IUPAC definition).

Patent Owner, for its part, presents evidence that chemists have, at times, used the term allyl ether to refer to a genus. Sur-Reply 20–22. In our view, however, the fact that, in other contexts, chemists have used "allyl ether" to refer to a genus does not outweigh the evidence above that supports that, in the context of reviewing Tsien, a person of skill in the art would have understood "[a]llyl ethers" as referring to or suggesting the -$CH_2CH=CH_2$ group. We have reviewed, for example, Dr. Romesberg's testimony that Patent Owner cites (Sur-Reply 21), and this testimony does not contradict our finding above regarding how a person having ordinary skill in the art would have understood Tsien in view of its reference to Gigg and Warren.

We also recognize that, in an *ex parte* reexamination proceeding, Petitioner took the position that "neither *Tsien* nor *Dower* . . . teaches or suggests a nucleoside 5' triphosphate having an allyl removable blocking moiety protecting the 3' position . . . ." Ex. 2065, 88; *see also* Resp. 56–59. The Examiner, however, ultimately disagreed with Petitioner on this point, and Petitioner's position in these proceedings is consistent with the Examiner's determination in that matter. Ex. 2065, 101; PO Reply 23–24.[27]

[27] Patent Owner argues that Petitioner is estopped in this proceeding based on this prior position. Resp. 56–60. We separately address estoppel arguments below.

On balance, the preponderance of all of the evidence favors Petitioner's position regarding how a person of skill in the art would have understood Tsien and its reference to Gigg and Warren. Thus, we determine that Petitioner demonstrates, by a preponderance of the evidence, that Tsien suggests use of an allyl ($-CH_2CH=CH_2$) blocking group.[28]

3. A Person of Skill in the Art Would Have Had Reason to Select Tsien's Allyl ($-CH_2CH=CH_2$) Blocking Group

As explained above, Tsien suggests use of an allyl ($-CH_2CH=CH_2$) blocking group.[29] Although Tsien suggests other groups as well, Tsien's suggestion of "allyl ethers" is prominent. Ex. 1013, 24:24–25:3. Indeed, Tsien references allyl ethers as a blocking group as its second possibility in the paragraph immediately following its discussion of appropriate criteria for blocking groups. *Id.* at 23:27–25:3. The present facts are distinguishable from the situation in which only an immense genus is disclosed and a person of skill in the art would not have had reason to select an individual species from within the genus. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (holding that disclosure of particular claimed ingredient made the case different from cases "involving disclosure of a broad genus without reference to the potentially anticipating species"); *see*

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[28] Because Petitioner relies solely on the allyl group (Tr. 14:2–11), it is not necessary to address whether or not a person of skill in the art would have had reason to select any other groups that might be "small." Resp. 46–48.

[29] Patent Owner argues that a person of skill in the art would not have been motivated to select a small capping group. Resp. 46–48. This general proposition is unpersuasive because, as explained herein, the asserted references suggest selecting the allyl capping group in particular and there is no dispute on this record that the allyl capping group is small.

also In re Lamberti, 545 F.2d 747, 750 (CCPA 1976) (citation omitted) ("[A]ll disclosures of the prior art, including unpreferred embodiments, must be considered").

Despite Tsien's teaching, Patent Owner's primary argument is that a person of skill in the art would not have had reason to select an allyl blocking group. Resp. 11–48. In particular, Patent Owner argues that there would have been no reason to select the allyl blocking group because (A) "it had been described as being incapable of achieving the efficient incorporation requirement of SBS," (B) the cited references "do not teach quantitative, rapid cleavage of the allyl capping group under mild, aqueous conditions," and (C) a person of skill would have concluded the allyl group "was incompatible with SBS" because of its disadvantages. *Id.* at 12.

Claim 1 of the '985 patent recites that the R blocking group must be "chemically cleavable," but it does not otherwise explicitly require efficient incorporation, specific cleavage conditions, or compatibility with SBS. Petitioner, however, relies on Tsien as a primary reference, and Tsien is directed to SBS. Persons having ordinary skill in the art would not have had a reason to follow Tsien by using a nucleotide analogue with an allyl R blocking group unless they believed the analogue would be useful for SBS. Tsien, moreover, provides criteria for appropriate blocking groups. Ex. 1013, 23:27–24:23. We determine that a person of skill in the art would have considered this criterion when choosing a blocking group.

Below, we thus address each of Patent Owner's three arguments regarding reason and motivation to select the allyl blocking group (incorporation, cleavage, and incompatibility). In doing so, we remain cognizant of the guidance our reviewing court provided in, for example,

Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359 (Fed. Cir. 2016). That decision involves the Tsien reference and technology similar to that now at issue. Our reviewing court emphasized that there is a distinction between reasonable expectation of success and reason to pursue the references' teachings. *Id.* at 1366–68. According to *Intelligent Bio-Systems*, reasonable expectation of success only looks to "likelihood of success in combining references to meet the limitations of the claimed invention" and that, for example, appropriate cleavage conditions would have been irrelevant to the inquiry where such conditions are not required by the claim at issue. *Id.* at 1367. Inquiry into motivation to combine, however, considers whether a person having skill in the art would have believed that there was a reason for reaching the claimed invention in the first place. *Id.* at 1368; *see also KSR Int'l Co.*, 550 U.S. at 418 ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does").

i. Efficient incorporation

Patent Owner argues that, based primarily on the Metzker reference, a person of skill in the art would have been discouraged from selecting an allyl blocking group because of inefficient incorporation. *See, e.g.*, Resp. 13–21.

To address this argument, we first set the stage by emphasizing the knowledge and motivations of a person of skill in the art as of the critical date—October 6, 2000. As explained above, a person of skill in the art would have been educated in chemistry, molecular biology, or a similar discipline, and would have been one among a team of scientists developing nucleotide analogues or addressing DNA techniques. That team would have

been highly interested in sequencing genomes including the human genome. At that time, no draft of the human genome sequence existed, but scientists were working on such sequencing and were willing to undergo great expense to try to reach such a sequence. Ex. 1120, 1544. Although SBS was known to have inefficiencies and problems at that time, scientists were nonetheless still investigating SBS and seeking to improve the SBS process. *See, e.g.*, Ex. 2099 2:34–47; Ex. 2041, 197–98; Ex. 1023, 956; Ex. 2013, 2–3. A process so efficient that an entire genome could be sequenced at once was far from reality, but the scientists would have been interested in SBS methods that could approach or reach sequencing twenty base pairs or more. Ex. 2029, 6; Ex. 2114 ¶¶ 92–93. In other words, we find that a person of skill in the art would have been interested in sequencing even short DNA sequences in this time frame. *Cf.* Ex. 2099, 2:45–47 (indicating that inefficiency limits SBS's ability to sequence anything but short sequences). We also find that a person of skill in the art would have been interested in pursuing all possible sequencing methods even if the methods were relatively expensive or inefficient (compared to modern standards). *See* Ex. 1120.

Tsien suggests that the allyl ether blocking group would have had sufficient incorporation to inspire a person of skill in the art to pursue that group in October 2000. By prominently identifying the allyl ether as a potential candidate for a blocking group shortly after listing criteria for blocking groups and criteria for a successful deblocking method (Ex. 1013, 20:24–21:3, 23:27–25:3), Tsien suggests that the allyl group can be appropriately incorporated as a blocking group. Tsien also indicates that its methods can assemble "25 to 300, or more" nucleotides (*id.* at 17:34–

18:2)—more than the twenty nucleotides that would have made a method of interest to the ordinarily skilled artisan as of the relevant date (*see* Section III.E.3, *supra*). Tsien also suggests a procedure to continue sequencing if incorporation rates are low. *Id.* at 16:31–35.

Metzker confirms that Tsien's suggestion to use an allyl blocking group has merit, at least in part, by indicating that one polymerase was able to incorporate an allyl blocking group. Ex. 1016, 4265. In its table, Metzker reports "Termination*" of the O-allyl group meaning that "the activity was incomplete at a final concentration of 250 μM." *Id.* at 4263. The parties' experts disagree as to the import of "incomplete" activity at this particular concentration, and Metzker does not further explain what "incomplete" means.

Metzker's top few blocking group candidates did not include O-allyl. *Id.* at 4265 (indicating groups with "Termination" rather than "Termination*"), 4267 (indicating that Metzker was further evaluating the 2-nitrobenzyl group). At a minimum, however, Metzker identifies "O-allyl" as a better blocking group candidate than other groups for which there is no termination or "Termination*" at all. *Id.* at 4265; *see also In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes").

A person of skill in the art also would have known that poor termination could potentially be overcome. For example, Dr. Romesberg credibly opines that one of ordinary skill in the art would have known that increasing concentration or reaction time could help incorporation efficiency. Ex. 1119 ¶¶ 65–67, 75–76. And Metzker suggests that

increasing concentration can resolve certain incorporation issues. Ex. 1016, 4266; *see also* Ex. 2031, 3 (indicating that higher concentrations were needed to reach high incorporation levels). Although some evidence indicates that use of high concentration can cause problems (Ex. 2081 ¶ 15; Ex. 2140, 173:2–6), the weight of the evidence does not support a finding that these problems would have discouraged the skilled artisan from using concentrations above Metzker's 250 µM concentration. Moreover, Tsien also suggests a procedure to continue sequencing if incorporation rates are low. *Id.* at 16:31–35.

The fact that the '985 patent lacks data establishing good incorporation further weighs against Patent Owner on this issue. *See* Ex. 1112, 284:6–18 (Dr. Menchen's testimony that he does not remember seeing in the '985 patent's application how allyl groups could be incorporated efficiently); *see also Trustees of Columbia Univ. in the City of New York v. Illumina, Inc.*, 620 F. App'x 916, 933 (Fed. Cir. 2015) (non-precedential) ("[I]f novel and nonobvious chemistry was needed to practice the claimed inventions, Dr. Ju would have been obligated to disclose this chemistry in the patent"). Indeed, the '985 patent admits the allyl group can be used as a cap "using well-established synthetic procedures" and cites Metzker for those procedures. Ex. 1075, 26:22–25; 28:15–18; *see also PharmaStem*, 491 F.3d at 1362 ("Admissions in the specification regarding the prior art are binding on the patentee . . . .").

In sum, although the evidence indicates that as of October 6, 2000, a person of skill in the art would have faced some uncertainty if pursuing allyl as a blocking group, that same person would have had reason to pursue the group because of high incentives to reach better sequencing methods. The

preponderance of the evidence supports our determination that a person of skill in the art would have understood that there was a reasonable likelihood of overcoming any incorporation obstacles, even if at some cost or effort, to achieve at least modest SBS sequencing success. And, at the relevant time, even a chance at modest success was worth pursuing. *See In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (holding that a prior art reference's "quasi-agnostic stance . . . cannot fairly be seen as dissuading one of ordinary skill" from pursuing other prior art teachings and instead "would have aroused a skilled artisan's curiosity"). Thus, Petitioner demonstrates, by a preponderance of the evidence, that a person of skill in the art would have had reason to pursue the allyl blocking group despite any incorporation concerns that, for example, the Metzker reference may have raised.

ii. Availability of appropriate cleavage conditions

Patent Owner argues that there would have been no reason to select the allyl blocking group because Petitioner's references do not satisfy the cleavage requirements for SBS. Resp. 31–46. In particular, Patent Owner argues that the prior art teaches that successful SBS requires "quantitative, rapid cleavage of the capping group under mild, aqueous conditions" and that none of Petitioner's cited references teach conditions for such cleavage. *Id.* at 31–32 (emphasis omitted).

As a threshold matter, we note that although claim 1 requires that the R capping group be "chemically cleavable," the claim does not require the particular cleavability conditions Patent Owner now argues must be present. The preponderance of the evidence, however, supports that a person of skill in the art would not have had reason to select a capping group unless it was, at least to some degree, capable of being cleaved under the cleavability

conditions Patent Owner argues. *See, e.g.*, Ex. 1013, 20:24–21:3, 23:27–24:5.

The preponderance of the evidence supports Petitioner's position that a person of skill in the art would not have been deterred from pursuing allyl as a blocking group based on cleavage conditions. PO Reply 18–21. The prior art references provide reasonable possibilities for cleaving an allyl ether blocking group. Indeed, the '985 patent admits that the allyl group "can be removed chemically with high yield" and cites the Kamal reference as providing an appropriate method for cleavage. Ex. 1075, 26:13–29. The '985 patent further indicates that Kamal's cleavability method provides mild and specific cleavage in three minutes with "more than 93% yield." *Id.*; *see also* Ex. 2126, 70:12–18 (Dr. Romesberg testifying that greater than 95% cleavage would be sufficient for SBS). In view of this admission, Patent Owner's argument that a person of skill in the art would not have expected Kamal to provide appropriate cleavage conditions is unpersuasive. *See also Trustees of Columbia Univ. in City of New York v. Illumina, Inc.*, 620 F. App'x at 933 (explaining patentee's obligation to disclose any necessary but nonobvious chemistry needed to practice claimed invention).

Petitioner also asserts that the Boss and Qian prior art references would have provided appropriate methods of cleaving an allyl blocking group. Pet. 26–27; Ex. 1078, ¶ 77 (Dr. Romesberg opines that "[i]t was also known that allyl groups were generally efficiently removed using palladium, including under aqueous conditions"); Ex. 1035, 559, Table 1; Ex. 1036, 2184. Although the parties' experts disagree on the suitability of the Boss and Qian cleavage conditions, after reviewing all relevant testimony, we find the testimony of Petitioner's expert, Dr. Romesberg, more credible on this

point. For example, we credit Dr. Romesberg's testimony that a person of skill in the art would have had reason to believe successful cleavage of an allyl blocking group under SBS conditions was reasonably likely by following Boss' and Qian's teachings. Ex. 1078 ¶ 77; Ex. 1119 ¶ 44; Ex. 1035, 158:1–159:23; Ex. 2114, 71:23–72:10. Also, Dr. Romesberg's testimony is credible in view of the '985 patent's admissions regarding cleavability of the allyl blocking group.

We also note that one of Petitioner's patents, filed in 2003, states "there is to date, no concrete embodiment of the successful cleavage of a 3'-allyl group under DNA compatible conditions, i.e. conditions under which the integrity of the DNA is not wholly or partially destroyed." Ex. 2015, 2:52–65. This evidence weighs against Petitioner's credibility in arguing that cleavage conditions were well known, but it does not completely undermine the assertion that a person of skill in the art, in October 2000, would have nonetheless had reason to pursue the allyl group based on a reasonable belief that appropriate cleavage conditions would have been available. *See, e.g.*, Ex. 1013, 24:24–25:3.

In sum, the preponderance of the evidence supports our determination that a person of skill in the art would have had reason to believe that appropriate cleavage conditions could be achieved for an allyl blocking group. Again, the high incentives to achieve DNA sequencing would have provided reason for a person of skill to move forward despite some (but not an unreasonable amount of) uncertainty. Patent Owner's argument that cleavage conditions would have dissuaded a person of skill in the art from following Tsien's teaching of using the allyl blocking group is, therefore, unpersuasive.

iii. Disadvantages of the allyl group

Patent Owner also argues that a person of ordinary skill in the art would not have chosen an allyl capping group after weighing the group's disadvantages against its potential benefits. Resp. 44–46. Patent Owner, however, only identifies lack of appropriate incorporation and cleavability as disadvantages (*id.*), which we have addressed above.

Because, as of October 6, 2000, a person of ordinary skill in the art would have been interested in achieving genome sequencing even if the process for doing so was difficult or expensive, we determine that uncertainty regarding incorporation or cleavage would not have dissuaded a person of skill in the art from pursuing the allyl capping group.

4. A Person of Skill in the Art Would Have Had a Reasonable Expectation of Success in Arriving at the Limitations of Claim 1

Tsien teaches use of the allyl group in conjunction with nucleotide analogues for SBS, and Metzker reports actually achieving such a molecule. Accordingly, the preponderance of the evidence supports our determination that a person of ordinary skill in the art would have had a reasonable expectation of success and reasonable likelihood of success in "meet[ing] the limitations" of claim 1 to the extent the claim requires using such an analogue. *Intelligent Bio-Systems, Inc.*, 821 F.3d at 1367.

Patent Owner argues that there would have been no reasonable expectation of success in achieving the "does not interfere with recognition of the analogue as a substrate by a DNA polymerase" limitation of claim 1 of the '985 patent. Resp. 51–52. Patent Owner's argument is based on its theory of Metzker teaching incomplete incorporation. As explained above,

the preponderance of the evidence does not support Patent Owner's arguments in this regard.

Patent Owner also argues there would have been no reasonable expectation that thymine, cytosine, or guanine nucleotides with an allyl capping group would have been "incorporated at the end of a growing strand of DNA during a DNA polymerase reaction" as claim 1 recites. Resp. 50–51; Sur-Reply 25–26. In particular, Patent Owner emphasizes that only Metzker provides data on incorporation and that Metzker only tested an adenine nucleotide. Resp. 50 (citing Ex. 1016, 4263; Ex. 2116 ¶ 95).

Petitioner, however, explains that Tsien teaches nucleotides being incorporated into a growing molecule (ground 1) and also explains that Dower[30] discloses incorporation of nucleotide analogues (ground 3). *See, e.g.*, Pet. 19–21, 34–40, 31–32, 57–58, 62–63. Petitioner also explains that Metzker and Prober teach incorporation into a growing strand of DNA. *See, e.g.*, *id.* at 32, 63. Petitioner further argues that Metzker provides potential solutions for unexpected differences in nucleobase incorporation, that the Kutateladze reference[31] demonstrates incorporation of all four 3'-O-methyl-dNTPs, and that the specification of the '985 patent does not disclose any unique polymerases for efficiently incorporating all four nucleotides. *See, e.g.*, Reply 22–23 (citing, *e.g.*, Ex. 1016, 4266; Ex. 1118, 206–08; Ex. 1040, 3228, 3230; Ex. 1041, 4832–33; Ex. 1119 ¶¶ 78–81).

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30 We address other aspects of ground 3 at Section H, *infra*.

31 Kutateladze et al., *3'-Hydroxymethyl 2'-deoxynucleoside 5'-triphosphates are inhibitors highly specific for reverse transcriptase*, 207 FED'N OF EUR. BIOCHEM. SOCIETIES 205–12 (1986) (Ex. 1118).

Although Tsien, Prober, Dower, and Metzker do not provide particular data for incorporation of allyl capped thymine, cytosine, or guanine analogues, the references collectively suggest that the analogues discussed therein are capable of being incorporated at the end of a growing strand of DNA. Indeed, as discussed in the Fact Findings above, Tsien, Dower, and Metzker all teach SBS methods, and SBS requires incorporation of the nucleotide into a growing strand of DNA. *See supra* Section III.E. Accordingly, Petitioner has established by a preponderance of the evidence that a person having ordinary skill in the art would have had a reasonable expectation of success in reaching claim 1's limitation "incorporated at the end of a growing strand of DNA during a DNA polymerase reaction."

Patent Owner also argues that claim 1 requires multiple cycles of sequencing and that "accurate sequences of 20 base pairs or greater were necessary to permit the assembly of the sequenced fragments." Resp. 48–50 (citing Ex. 2114 ¶ 92; Ex. 2029, 6; Ex. 2126, 22–24, 60; Ex. 2035, 179). Patent Owner further argues that a person having ordinary skill in the art would not have had a reasonable expectation of conducting multiple cycles of DNA sequencing using a nucleotide with an allyl capping group and a base label. *Id.* at 49–50. We disagree. As we find in Section III(F)(3)(i), *supra*, a person having ordinary skill in the art would have reasonably expected that such a nucleotide analogue could be used to perform an SBS method that could approach or reach sequencing twenty base pairs or more.

5. A Lead Compound Analysis Would Not Dictate a Different Result

Neither party asserts that we should apply a "lead compound analysis" when assessing obviousness in these proceedings. Pet. 43; Resp. 61. We nonetheless address this analysis here out of an abundance of caution and

because our reviewing court sometimes applies this analysis. Under a lead compound analysis, first, "the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts," and second "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify the lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012). A lead compound need not be the single best compound in the prior art. *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

As explained above, Tsien teaches use of the allyl blocking group for dNTP analogues. As Dr. Romesberg credibly opines, "[a] person of ordinary skill in the art would have recognized Tsien's 3'-O-allyl dNTP disclosures as a natural starting point for further development efforts . . . ." Ex. 1078 ¶ 123. Patent Owner argues that the allyl group is incompatible with SBS (Resp. 61), but, as explained above, a preponderance of the evidence does not support this argument. Accordingly, applying a lead compound analysis would not change our determination that Petitioner has established by a preponderance of the evidence that the subject matter of claim 1 of the '985 patent would have been obvious over Tsien and Prober.

G. '985 Patent Ground 2: Obviousness of Claim 2 over Tsien, Prober, and Pallas

Petitioner argues that the combination of Tsien, Prober, and Pallas would have rendered obvious to a person of ordinary skill in the art the subject matter of '985 patent claim 2. Based on our review of the arguments

and evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of '985 patent claim 2 would have been obvious over the combination of Tsien, Prober, and Pallas, as explained below.

Petitioner explains that Pallas teaches the recitation of claim 2 and that Pallas provides an express motivation to combine its teachings with Tsien's SBS technology. Pet. 51–54. For example, Pallas teaches "a system for simultaneously analyzing the nucleotide sequences of a population of polynucleotides." *Id.* at 51 (quoting Ex. 1080, 2:30–31). Pallas also teaches that its method is compatible with "base-by-base" approaches and cites Tsien as disclosing a base-by-base approach. Pet. 52–53 (quoting Ex. 1080, 16:26–33).

Patent Owner does not dispute the teachings of Pallas or dispute that a person of skill in the art would have had reason to combine the teachings of Pallas and Tsien. Resp. 62–63 (relying on its arguments regarding claim 1 with respect to claim 2). Because Patent Owner does not address the merits of Petitioner's assertions regarding this ground (except to the extent Petitioner raised arguments as to claim 1), any such arguments are waived. *Cf. In re NuVasive*, 842 F.3d 1376 at 1381. Because a preponderance of the evidence (as demonstrated by the citations to supporting evidence above and as presented by Petitioner) supports Petitioner's arguments relating to the teachings of the prior art, we adopt Petitioner's arguments as our own. *See* Pet. 51–54; *see also In re NuVasive*, 841 F.3d at 974.

H. ’985 Patent Ground 3: Obviousness of Claims 1 and 2 over Dower, Prober, and Metzker

Petitioner argues that the combination of Dower, Prober, and Metzker would have rendered obvious to a person of ordinary skill in the art the subject matter of ’985 patent claims 1 and 2. Pet. 56–63. Patent Owner disagrees. Resp. 63–64. Based on our review of the arguments and evidence of record, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the subject matter of claims 1 and 2 would have been obvious over the combination of Dower, Prober, and Metzker, as explained below.[32]

1. The Prior Art Discloses or Suggests the Limitations of ’985 Patent, Claims 1 and 2

Petitioner explains how the combination of Dower, Prober, and Metzker teach each limitation of claims 1 and 2. With respect to claim 1, Petitioner explains that Dower teaches sequencing using deoxyribonucleotide triphosphate analogues including analogues of adenine, cytosine, guanine, and thymine. Pet. 57 (citing, *e.g.*, Ex. 1015, 14:41–47, Fig. 8A). The adenine analogue has a removable 3'-blocking group and a removable fluorescent label. *Id.* at 57–58 (citing, *e.g.*, Ex. 1015, 14:41–59, 15:1–10, 15:35–40, 25:4–12, Fig. 8A; Ex. 1078, ¶ 155).

Petitioner further notes that Dower cites to Prober’s disclosure of labeled cytosine and thymidine analogues with removable labels. *Id.* at 59–

[32] For brevity, we do not repeat all factual findings in the analysis below, but certain findings may be mentioned again for emphasis. Our analysis with respect to all challenges is based upon determining whether Petitioner has met the preponderance of the evidence standard based on all evidence in the record as a whole.

60 (citing, *e.g.*, Ex. 1015, 5:35–37, 15:1–3, 15:35–40, 18:64–19:10, Fig. 8A, Fig. 9). Indeed, Petitioner argues that Dower repeatedly cites Prober's disclosure of labeled nucleotide analogues. *Id.* at 60 (citing Ex. 1015, 25:4–12, 25:44–47, 20:39–42, 23:16–26, 28:6–17, 17:35–36). Prober, in turn, teaches 5-substituted analogues. *Id.* (citing Ex. 1014, 337–38, Fig. 2A). Dr. Romesberg credibly opines that a person of skill in the art would have considered Prober's nucleobases for use in Dower's nucleotides analogues and methods based on Dower's repeated citations to Prober. Ex. 1078 ¶¶ 159–161.

Petitioner explains that Metzker, as discussed above, discloses the 3'-O-allyl ether capping group. Pet. 62 (citing, *e.g.*, Ex. 1016, 4265). Dr. Romesberg credibly opines that a POSA would have selected Metzker's 3′-O-allyl group because (1) it was shown to be incorporated by a polymerase and (2) it is removable. Ex 1078 ¶¶ 165–168.

With respect to claim 2, Petitioner explains that Dower discloses "simultaneous parallel sequence analysis of a large number of biological polymer macromolecules." Pet. 75 (quoting Ex. 1015, Abstract). Petitioner asserts that the motivation and expectation of success for using Dower's methods to simultaneously sequence a plurality of different nucleic acids in parallel was recognized in the prior art. *Id.* at 76 (citing, *e.g.*, Ex. 1085, 1:16–18, 4:15–25, 60:51–61:57; Ex. 1078 ¶ 218).

To the extent Patent Owner does not address the merits of Petitioner's assertions, we are persuaded by Petitioner's arguments. Because Petitioner's arguments are supported by a preponderance of the evidence (as demonstrated by the citations to supporting evidence above), we adopt Petitioner's arguments as our own. *See* Pet. 54–73; *see also In re NuVasive*,

841 F.3d at 974 (explaining that Board need not make findings as to undisputed claim limitations). We address the arguments Patent Owner raises below.

2. Patent Owner's Arguments Raised with Respect to Ground 1 Still Fail

Patent Owner argues, for example, incorporation and cleavage conditions, by referring back to its ground 1 arguments. Resp. 62–63. As explained above, each of those positions is not persuasive because the preponderance of the evidence fails to support it.

3. "Chemically Cleavable, Chemical Linker"

Patent Owner argues that Petitioner's ground fails because none of Dower, Prober, or Metzker discloses a "chemically cleavable, chemical linker." Resp. 63–64 (citing Ex. 2114 ¶ 110). Particularly, Patent Owner asserts that Dower does not disclose a chemical linker attaching a label to the base, but rather, only discloses labels that are directly attached to the base. *Id.* (citing Ex. 1015, Fig. 9; Ex. 2114 ¶ 111; Ex. 2036, 14–15). Patent Owner further asserts that to the extent Petitioner relies on Dower's exemplary FMOC[33] label as the required "chemically cleavable, chemical linker," the FMOC is not attached to a carbon and, therefore, cannot satisfy the claim limitation. Sur-Reply 22–25. And Patent Owner argues that although Prober discloses attaching fluorescent labels to the base of ddNTPS using an acetylenic linker (propargyl amine), that linker is not cleavable under DNA-compatible conditions. Resp. 64 (citing Ex. 1014, 338; Ex. 2114 ¶ 111; Ex. 2113, 124).

[33] FMOC is shorthand for a fluroenylmethyloxycarbonyl group.

We are not persuaded. Patent Owner attacks the teachings of Dower and Prober individually, but Petitioner's argument is premised on what the combined teachings of Dower and Prober would have disclosed or suggested to the ordinary artisan given the state of the art—namely, a nucleotide analogue having a tag attached through a cleavable linker. *E.g.*, Pet. 42 ("Prober discloses . . . a label attached through a linker at the 7-position"); *see In re Keller*, 642 F.2d 413, 425 (CCPA 1981) ("[T]he test [for obviousness] is what the combined teachings of the references would have suggested to those of ordinary skill in the art.") (citation omitted). In that regard, Petitioner directs us to Dower's teaching of a fluorescent label as a removable moiety that can be cleaved chemically. Pet. 65–66 (citing Ex. 1015, 5:35–37, 15:52–56, 21:32–40, 25:35–40, Fig. 9); *see also* Ex. 1015, 15:52–53 ("One important functional property of the [dNTP] monomers is that the label be removable."); Ex. 1078 ¶ 183. Petitioner also points to Dower's citations to Prober for disclosing labeled nucleotide analogues, and Dr. Romesberg testifies that Prober discloses suitable reaction conditions for making such analogues. *See, e.g.*, Pet. 66 (citing Ex. 1015, 20:39–42, 23:16–26, 25:4–12, 25:44–47); Ex. 1078 ¶¶ 180–81; *see* Ex. 2014, 337–38 (Prober's disclosure of nucleotide analogues having a linked fluorescent label).

Although we agree with Patent Owner that Prober's propargyl amine linker is not cleavable under DNA-compatible conditions, the evidence of record suggests that a person of ordinary skill in the art would have been able to identify and to use an appropriate chemically cleavable, chemical

linker or linkers, and that using such a linker or linkers[34] was well within the level of ordinary skill in the art. For example, during prosecution of the application that matured into the '985 patent, the patent applicant explained that a skilled artisan "would have been familiar with both the term chemically cleavable, chemical linker and numerous examples [of such linkers] from the prior art." Ex. 1076, 21. In addition, Petitioner directs us to the Board's decision (affirmed by our reviewing court) that a person of ordinary skill in the art would have had a reasonable expectation of success in making nucleotide analogues having a label cleavably linked to the base. Pet. 40 (citing Ex. 1005, 26–35; Ex. 1008, 31; Ex. 1028, 166:3–168:4, 170:7–171:5, 177:13–178:15, 179:7–23, 191:23–192:5, 342:19–343:9, 387:5–388:23), 73–74 (referring to Pet. § VIII.B.16 as explaining how the steps for preparing nucleotide analogues that the combination of Dower, Prober, and Metzker disclose "were within the level of ordinary skill"). And Dr. Romesberg testifies credibly that ordinary artisans would have known how to prepare 7-substituted 7-deaza-purine nucleotides (e.g., dATP) with chemically cleavable linkers. Ex. 1078 ¶¶ 114–117; 210–213 (providing references that disclose how to prepare the nucleotides with alkynylamino

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[34] Patent Owner argues that claim 1 excludes a linker attached to a propargyl amine because the claim requires one linker, not two linkers. Sur-Reply 24–25. We disagree. "As a general rule, the words 'a' or 'an' in a patent claim carry the meaning of 'one or more.'" *01 Communique Lab., Inc. v. LogMeln, Inc.*, 687 F.3d 1292, 1297 (Fed. Cir. 2012) (quoting *TiVo, Inc. v. EchoStar Commc'ns Corp.*, 516 F.3d 1290, 1303 (Fed. Cir. 2008)). The exceptions to the rule are "extremely limited" and require that a patentee "evince a clear intent to limit 'a' or 'an' to 'one.'" *Id.* (quoting *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008)). Patent Owner's bare argument does not establish such a clear intent.

linkers and allyl linkers and explaining that the cleavable linker that Seitz[35] discloses for attaching a fluorescent group to a molecule having an amine group would have been recognized as being suitable to attach the allyl linker to the propargylamine group that Prober uses at the 7-position of the 7-deaza-adenine); *see* Pet. 40 (citing Dr. Romesberg's testimony).

Given the foregoing, we determine that Petitioner establishes, by a preponderance of the evidence, that combined teachings of Dower and Prober would have disclosed or suggested a chemically cleavable, chemical linker. We, therefore, determine that Petitioner has established by a preponderance of the evidence that the subject matter of claim 1 of the '985 patent would have been obvious over the combination of Dower, Prober, and Metzker.

IV. DISCUSSION OF ESTOPPEL AND PRECLUSION ISSUES

A. Petitioner's Argument that Estoppel Arises from Previous IPRs

In its Petition, Petitioner argues that Patent Owner "should be barred from participating in the present proceeding under the Board's patent owner estoppel regulation." Pet. 9 (citing 37 C.F.R. § 42.73(d)(3)(i)). We authorized additional briefing on questions of collateral estoppel, i.e., whether the previous proceedings[36] decided issues raised in the current

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[35] Oliver Seitz & Horst Kunz, *HYCRON, an Allylic Anchor for High-Efficiency Solid Phase Synthesis of Protected Peptides and Glycopeptides*, 62 J. ORGANIC CHEM. 813, 815 (1997) (Ex. 1052).

[36] *Illumina, Inc. v. Trustees of Columbia University in the City of New York*, IPR2012-00007, IPR2012-00006, and IPR2013-00011, respectively ("the previous proceedings").

proceedings or would otherwise have a collateral estoppel effect on the current proceedings. *See* Paper 59, 4–5. For the reasons set forth below, we determine that the claims of the '985 patent have material differences from the claims at issue in the previous proceedings, and that there is no inconsistency between Patent Owner's positions in the current proceeding and in the previous proceedings. Accordingly, we determine that there is no estoppel attaching to Patent Owner with respect to the present *inter partes* reviews. Below, we provide a brief history of the previous proceedings and then address Petitioner's contentions.

1. The Previous Proceedings

The same parties previously came before the Board in three *inter partes* reviews with respect to related U.S. Patent Nos. 7,790,869 B2 (Ex. 1010, "the '869 patent"), 7,713,698 B2 (Ex. 1081, "the '698 patent"), and 8,088,575 B2 (Ex. 1054, "the '575 patent") in *Illumina, Inc. v. Trustees of Columbia University in the City of New York*, IPR2012-00007, IPR2012-00006, and IPR2013-00011, respectively. In the previous proceedings, the Board conducted AIA trials and issued final written decisions, holding all challenged claims from the '869, '698, and '575 patents unpatentable. Paper 3, 1; IPR2012-00007, Paper 140 (Ex. 1005); IPR2012-00006, Paper 128 (Ex. 1006); IPR2013-00011, Paper 130 (Ex. 1007). The Federal Circuit affirmed the Board's unpatentability determinations from the previous proceedings in *Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 620 F. App'x 916 (Fed. Cir. 2015) (Ex. 1008). Paper 3, 1.

In IPR2012-00007, Petitioner challenged the patentability of certain claims of the '869 patent, including claims 12, 13, 15, 17, 28, and 31 (*see* Ex. 1005, 7), which recited as follows:

> 12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group, wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.
>
> 13. The nucleotide of claim 12, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3'OH group is cleaved by chemical means.
>
> . . .
>
> 15. The nucleotide of claim 12, wherein the base is a deazapurine.
>
> . . .
>
> 17. The nucleotide of claim 12, wherein the detectable label is a fluorophore.
>
> . . .
>
> 28. The nucleotide of claim 12, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.
>
> . . .
>
> 31. The nucleotide of claim 12, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.

Ex. 1010, 33:40–34:50. The Board held these claims unpatentable.

Ex. 1005, 49.

In that proceeding, Petitioner did not challenge claim 19, which depended from claim 12 and further recited "wherein said cleavable chemical group comprises $-CH_2CH=CH_2$." Ex. 1010, 34:21–22; *see* Ex. 1005, 2.

Also in that proceeding, Columbia filed a motion to amend, in which it proposed canceling claims 12–33 and replacing them with substitute claims 34–54. Ex. 1005, 46. Proposed claim 34 would have been similar to original claim 15, but rewritten in independent form and reciting features of original claim 12:

> [Proposed claim 34] A nucleotide ~~of claim 12~~ having a base that is attached to a detectable label through a cleavable linker, wherein the base is a deazapurine, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group, wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, and heat, ~~and light~~ and wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, and heat, ~~and light~~.

See id.; IPR2012-00007, Paper 79, App. A, 3. Proposed claim 40 would have contained the recitation of unchallenged claim 19, depending from claim 34. Ex. 1005, 46–47. The Board concluded that the proposed substitute claims were not responsive to a ground raised in that proceeding's petition. *Id.* at 47 (citing 37 C.F.R. § 42.121(a)(2)). The Board did say "[n]onetheless, we considered the amended claim language and found that the amended claims remain unpatentable because the alternative claimed cleaving means are described in Tsien and Stemple. See *supra* at pp. 11 (Tsien), 12 (Stemple III), 16-17 (Stemple III), and 31 (Tsien)." *Id.* at 47.

In IPR2013-00011, Petitioner challenged the patentability of certain claims of the '575 patent, including claim 1 (*see* Ex. 1007, 1), which recited as follows:

> 1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising: a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template; b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and contains a small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, wherein said small cleavable chemical group does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate; and c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.

Ex. 1054, 33:29–34:31. The Board held this claim unpatentable. Ex. 1007, 45.

In IPR2012-00006, Petitioner challenged the patentability of certain claims of the ’698 patent, including claims 1 and 2 (*see* Ex. 1006, 2), which recited as follows:

> 1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:
>
> a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template;
>
> b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a

> base labeled with a unique label and contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, and wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and
>
> c) detecting the unique label of the incorporated nucleotide analogue,
>
> so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.
>
> 2. The method of claim 1, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of the incorporated nucleotide analogue, thereby permitting the incorporation of a further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.

Ex. 1081, 35:1–28. The Board held these claims unpatentable. Ex. 1006, 45.

2. Petitioner's Arguments for Estoppel

Petitioner variously argues that Patent Owner should be estopped from arguing the patentability of present claim 1 based on claims 12, 13, 17, 28, and 31 of the '869 patent, claim 1 of the '575 patent, claim 2 of the '698 patent, and on proposed substitute claim 40, which was proffered in a motion to amend filed in IPR2012-00007. Pet. 9; Pet. Supp. Br. 3, 7, 12–13, 15; Pet. Supp. Reply 2–5.

We noted in Paper 61 (Order authorizing briefing) that the Supreme Court held that a prior Trademark Trial and Appeal Board (TTAB) decision may apply with issue preclusive effect where there is no material difference between marks. *See* Paper 61, 3–4 (quoting *B & B Hardware, Inc. v. Hargis Industries, Inc.*, 135 S. Ct. 1293, 1302–03 (2015)). In *B&B Hardware*, the Court explained that "[w]hen an issue of fact or law is actually litigated and

determined by a valid and final judgment, and the determination is essential to the judgment, the determination is conclusive in a subsequent action between the parties, whether on the same or a different claim." *Id.* (quoting Restatement (Second) of Judgments § 27, p. 250 (1980); citing *id.* § 28, 273).

i. Arguments Based on Proposed Claim 40 Proffered in a Motion to Amend in IPR2012-00007

Petitioner argues that the Board has previously determined that proposed substitute claim 40 (which would have depended from proposed substitute claim 34) in IPR2012-00007 was obvious and that this decided the issue of whether an allyl group would have been obvious to use as a 3'-OH blocking group. Pet. Supp. Br. 12–13, 15; Pet. Supp. Reply 2–5. After reviewing the Board's Final Written Decision in IPR2012-00007 (Ex. 1005), we determine that this issue was not essential to the judgment (and might not have been decided). First, we note that the Board concluded that the proposed substitute claims were not responsive to a ground raised in the petition, and denied the motion to amend on that basis as a procedural matter even before discussing any of the substance. Ex. 1005, 46. Accordingly, we determine that any substantive discussion that followed would have been in the nature of dicta and would not have been "essential to the judgment," as required for collateral estoppel.[37]

[37] We note that even if Patent Owner had wished to present the subject matter of present claim 1 in the previous proceedings, it would not have had an opportunity to do so for the same reason, i.e., that the proposed amendment was not responsive to a ground in the *inter partes* review.

Second, Petitioner does not identify any dispositive factual finding on point from a previous decision. The Board stated that "we considered the amended claim language and found that the amended claims remain unpatentable because the alternative claimed cleaving means are described in Tsien and Stemple." *Id.* at 46–47. However, the language of proposed claim 40 corresponded to original claim 19, which was not challenged in that IPR, and was not found unpatentable as part of the Final Written Decision. Petitioner does not point us to any factual finding with respect to the original challenged claims determining that it would have been obvious to use an allyl group as a 3'-OH blocking group in the context of the relevant invention.[38] It is, therefore, at best ambiguous whether the Board made such a finding, and we do not conclude that there was a finding for allyl groups that was "actually litigated and determined" much less "essential to the judgment" on that basis.

Third, we observe that proposed claim 40 would have contained a Markush group because it would have depended from proposed claim 34. Proposed claim 34 recited different members of a claimed genus (e.g., cleaving by physical means, chemical means, and heat). Accordingly, even if the Board had found proposed claim 40 (and an allyl blocking group to have been obvious), there would not have been a finding that cleaving by

[38] The Board's statement might be read to be an acknowledgement that Tsien refers to allyl groups as one of several disclosed groups, as we discuss elsewhere with respect to the asserted grounds in this proceeding. However, in context, the extent to which the whole subject matter of claim 40 was actually litigated and determined to have been obvious is ambiguous.

chemical means, as present claim 1 requires, would have been "essential to the judgment."[39]

ii. Arguments Based on Claim 31 of the '869 Patent and Claim 1 of the '575 Patent

Petitioner argues that the 3'-OH blocking group limitation in present claim 1 is indistinguishable from a 3'-OH blocking group limitation in the previously adjudicated claims, and in particular from the "small" 3'-OH blocking group recited in claim 31 of the '869 patent and claim 1 of the '575 patent. Petitioner argues that the applicant improperly asserted during prosecution that its inventive insight *for the present patent* was the 3′-OH capping group being "small." Pet. 9–10 (citing, *e.g.*, Ex. 1005, 8–11, 19–35); Pet. Supp. Br. 3, 7 (citing Ex. 1005, 11; Ex. 1010, 34:48–50; Ex. 1007, 11, 13, 16–17; Pet. 61, 65; Ex. 1054, 33:40–44). However, present claim 1 contains additional structural limitations, i.e., the 3'-OH blocking group cannot be a ketone group, a methoxy group, or an ester group. *See* Ex. 1075, 35:27–36:1 ("wherein R . . . (d) does not contain a ketone group; wherein OR is not a methoxy group or an ester group").

By way of illustration, Petitioner argues that a prior art allyl group (e.g., as recited in Tsien) meets the 3'-OH blocking group limitation of claim 1. *See, e.g.*, Pet. 30. It is undisputed that an allyl group is a different structure than a ketone, a methoxy, or an ester. *See id.*; PO Supp. Br. 6.[40]

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[39] For similar reasons, present claim 1 would have been different than proposed claim 40 because proposed claim 40 would have been broader, with multiple possible means for cleaving a 3'-OH capping group other than chemical means.

[40] The structural differences are also tied to functional differences. These are all different functional groups. For example, an allyl group is its

Petitioner fails to persuade us that the additional limitations do not add further structural requirements to the requirement of the 3'-OH blocking group being "small," as recited in claim 31 of the '869 patent and claim 1 of the '575 patent. Nor has Petitioner argued that the further limitations of present claim 1 would fall within a doctrine such as nonfunctional descriptive matter, printed matter, intended use, or some other doctrine that even arguably falls within the meaning of being not limiting. *See, e.g., In re Distefano*, 808 F.3d 845, 848 (Fed. Cir. 2015) (printed matter that has no functional or structural relationship to the associated substrate is given no patentable weight).

Based on the additional structural limitations of present claim 1, we determine that present claim 1 is materially different than claim 31 of the '869 patent and claim 1 of the '575 patent.

iii. Arguments Based on Claims 12, 13, 17 and 28 of the '869 Patent and Claim 2 of the '698 Patent

Petitioner asserts that collateral estoppel applies on the issues of "smallness, incorporation, and cleavability" because independent claim 12 and dependent claim 28 of the '869 patent would have required "a cleavable chemical group capping the 3'-OH group," dependent claim 13 of the '869

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own functional group to a person of ordinary skill with its own functional properties, and forms an *ether* linkage (rather than an ester linkage). *See, e.g.*, Ex. 2012 ¶ 27. We find that these are nontrivial variations. *See B&B Hardware*, 135 S. Ct. at 1308 ("Materiality, of course is essential—trivial variations between the usages set out in an application and the use of a mark in the marketplace do not create different 'issues,' just as trivial variations do not create different 'marks.'"). Thus, the presence of different functional groups in this context creates a material difference to a person of ordinary skill, and does not present the same issue as that previously adjudicated.

patent would have required cleavability by chemical means, and dependent claim 2 of the '698 patent recited "permitting the incorporation" of a nucleotide analogue. Pet. Supp. Br. 7, 11 (citing Ex. 1010, 33:40–50, 33:51–54). Although these claims require a cleavable or removable chemical group capping the 3'-OH group, we determine that the further structural limitations of present claim 1 (the 3'-OH blocking group is not a ketone, methoxy, methoxy, or ester) are materially different than claims 12, 13, 17 and 28 of the '869 patent and claim 2 of the '698 patent, for similar reasons.

iv. Petitioner's Arguments Based on 37 C.F.R. § 42.73(d)(3)(i)

Petitioner argues that Patent Owner should be barred from this proceeding based on 37 C.F.R. § 42.73(d)(3)(i). *See* Pet. 9–10. In particular, Petitioner asserts that present claim 1 is patentably indistinct from the claims discussed above, referring to the prosecution of the '985 patent. *See id.* Patent Owner argues, *inter alia*, that 37 C.F.R. § 42.73(d)(3)(i) applies only to pre-issuance examination and not to post-issuance *inter partes* proceedings conducted under 35 U.S.C. § 311. *See* PO Supp. Reply 1 (citing *Gen. Elec. Co. v. United Techs. Corp.*, IPR2017-00428, slip op. 8–9) (PTAB June 22, 2018) (Paper 38)).

Section 42.73(d)(3)(i) of Title 37 C.F.R. provides:

> (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).

We agree with Patent Owner that subsection (i) of 37 C.F.R. § 42.73(d)(3) does not apply to *inter partes* review proceedings because Patent Owner is not "obtaining" a patent in this post-issuance proceeding, as the language of 37 C.F.R. § 42.73(d)(3) that introduces subsection (i) requires. *See Gen. Elec. Co. v. United Techs. Corp.*, IPR2017-00428, slip op. 8–9 (PTAB June 22, 2018) (Paper 38). Petitioner is seeking the cancellation of issued claims and Patent Owner is not seeking any additional claims at this time.

We note that the body of § 42.73(d)(3) also provides that a Patent Owner is precluded from taking action inconsistent with an adverse judgment. Even assuming that a Patent Owner is precluded from taking action inconsistent with an adverse judgment, we determine that Patent Owner's participation in this *inter partes* review is not inconsistent with the previous proceedings because present claim 1 is materially different than the previously adjudicated patent claims, for the reasons set forth above. *See* Section IV.A.2.i, ii, *supra*.

We, therefore, decline Petitioner's request to bar Patent Owner from participation in this proceeding.

B. Patent Owner's Argument that Estoppel Arises From the '465 Reexamination

Patent Owner argues that Petitioner should be judicially estopped based on positions taken by Solexa during the '465 reexamination.[41] *See*

[41] U.S. Patent 6,232,465 ("the '465 patent"), then-assigned to Solexa and later assigned to Petitioner, was the subject of an *Ex Parte* Reexamination ("the '465 reexamination") pursuant to a request from a third party requester. *See* Ex. 2065, 1–2, 47; Ex. 2038, 1–2.

Resp. 56–59 (citing Ex. 2065, 101; *New Hampshire v. Maine*, 532 U.S. 742, 750–51 (2001)).[42] According to Patent Owner, (a) Petitioner's position in this proceeding contradicts its position in the '465 reexamination; (b) Petitioner persuaded the Examiner to accept its position in the '465 reexamination (citing Ex. 2065, 127, 124–26); and (c) allowing Petitioner to maintain its new position in this proceeding would be unfair to Columbia. Resp. 58, 60. Patent Owner relies on two arguments Solexa made during the '465 reexamination, and we address each in turn.

First, Patent Owner asserts that Solexa argued during the '465 reexamination that Tsien does not disclose an allyl blocking group. *See* Resp. 56–57. Petitioner disputes that the Examiner adopted the argument that Tsien fails to disclose an allyl group. *See* Reply 23–24 (citing Ex. 2065, 101). We agree with Petitioner on this point. The Examiner did not agree with Solexa's assertion that Tsien fails to disclose allyl groups. Instead, the Examiner stated that

> [e]ven though Tsien et al. does not explicitly teach an allyl group protecting the 3'-OH of the ribosyl group, by referencing the ribosyl through the use of the term 'remote,' the person of skill in the art would immediately envision the 3'-OH protected by an allyl group because the prior art clearly teaches allyl as a standard protecting group for hydroxyl groups.

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[42] Patent Owner argues that Solexa made admissions in that proceeding that are now attributable to Petitioner. *See id.* (citing Ex. 2038, 1–2; Ex. 2065, 91; Ex. 2024, 3; Ex. 2055, 1; Ex. 2119, 2; Ex. 2120, ILMN_COL0100771-773; Ex. 2121, ILMN_COL0145607; Ex. 2122; Ex. 2123; Ex. 2124, ILMN_COL0145635). We agree that Petitioner has acquired Solexa, and consider Petitioner to stand in the shoes of Solexa for purposes of this discussion. *See* Ex. 2055, 1.

Ex. 2065, 101. Thus, the Examiner did not adopt Solexa's argument as to what Tsien discloses. We, therefore, conclude that the '465 reexamination does not create an estoppel based on Solexa's argument on this point. *See Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1333 (Fed. Cir. 1999), *modified on reh'g by* 204 F.3d 1359 ("We also note that for Georgia-Pacific to be bound by the statement made to the PTO in connection with a later prosecution of a different patent, the statement would have to be one that the examiner relied upon in allowing the claims in the patent at issue) (citing *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1284–85 (Fed. Cir. 1986)); *see also Speedtrack, Inc. v. Endeca Techs., Inc.*, 524 F. App'x 651, 659 (Fed. Cir. 2013) (non-precedential) (holding that district court did not abuse discretion in refusing to apply judicial estoppel and noting, among other considerations, that the PTO never adopted contentions in reexamination).

Second, Patent Owner argues that Petitioner is now inconsistent in arguing that Tsien would have motivated a person of ordinary skill to select the allyl capping group. Resp. 58. Patent Owner relates that, in response to an obviousness rejection in that proceeding, Petitioner argued as follows:

> [W]hether a person of ordinary skill in the art would or would not have been motivated, on the basis of the teachings in Tsien, to make a compound comprising [a nucleotide] with a 3'-allyl ether group. . . . Basically, the evidence shows that even 6 years after the time the presently claimed invention was made [i.e., 6 years after September 1994, which is September 2000], persons skilled in the art would not have been motivated to prepare the compounds of claims 1, 3 and 7 [nucleotides with the allyl capping group], or compositions containing them, with a reasonable expectation that they could be used for DNA synthesis.

Resp. 59–60 (quoting Ex. 2065, 90).

Patent Owner points to pages 124–27 of Exhibit 2065 (excerpts from the reexamination file wrapper) for the proposition that the Examiner adopted Solexa's argument on this point. These portions of the file wrapper include (a) Reasons for Patentability/Confirmation (that the Examiner wrote), attached to a Notice of Intent to Issue an Ex Parte Reexamination Certificate and (b) an Interview Summary (that Solexa submitted). Ex. 2065, 124–27. These documents show that the Examiner's rationale for allowance was that a person of ordinary skill would not have expected an allyl protecting group or group of comparable size to allow elongation of a polynucleotide because of steric reasons. Ex. 2065, 126 (Reasons for Patentability/Confirmation). We agree with Patent Owner that the Examiner adopted Solexa's argument that a person of ordinary skill would not have had a reasonable expectation of success in using an allyl blocking group. However, we next proceed to consider whether this finding estops Petitioner from arguing in this proceeding that a person of ordinary skill would have had a reasonable expectation of success in using an allyl blocking group, for purposes of evaluating the patentability of the now challenged claims.

Petitioner argues that the reexamination was conducted from the perspective of a person of ordinary skill in the art in September of 1994 and does not take into account other material which would have been prior art by the time of the filing of the '985 patent at issue in this proceeding, including Metzker's evidence of polymerase incorporation and Qian's and Kamal's evidence of cleavage. *See* Reply 24 (citing Ex. 2065, 129; Exs. 1097, 1016, 1036, 1037). Although the existence of other prior art, by itself, is not

necessarily relevant to the question of whether a judicial estoppel forecloses relitigation of an issue, Petitioner persuades us that it is not estopped in this proceeding because this proceeding presents a different issue than that considered in the '465 reexamination.

Specifically, the Examiner's findings in the '465 reexamination considered the level of skill in the art (and reasonable expectations based thereon) as of September 2, 1994,[43] which was the earliest possible filing date to which the claims of the '465 patent could have been entitled. *See* Ex. 2065, 5. The issue in this proceeding is the level of skill in the art (and reasonable expectations based thereon) as of the filing date of the priority application for the '985 patent, which is October 6, 2000. *See, e.g.*, Pet. 17. This proceeding, therefore, presents a different issue. Even if the Examiner's findings in the '465 reexamination are binding on Petitioner, that would not necessarily be relevant to the level of skill in the art and the reasonable expectation of success relevant to the time of filing of the '985 patent. Thus, we conclude that Petitioner has not taken an inconsistent

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[43] Based on *Speedtrack*, any estoppel would be based on findings the Examiner adopted. 524 F. App'x at 659. Thus, the Examiner's findings would relate to September 2, 1994. We note that in the '465 reexamination, Solexa argued that the level of skill was the same for September 2000 as well. We determine that Petitioner is not held to an argument based on the level of skill in September 2000 for purposes of judicial estoppel because there is no evidence that the Examiner adopted a finding based on the level of skill in September 2000. Nevertheless, we recognize that under *Georgia-Pacific*, it might be sufficient for an Examiner to rely on an argument to create an estoppel. *See* 195 F.3d at 1333. Even if Solexa and Petitioner could be held to an argument based on the level of skill in September 2000, i.e., six years after the priority date of the '465 patent (*see* Ex. 2065, 90), we determine that October 2000 is still a later date.

position in this proceeding. *See New Hampshire*, 532 U.S. at 750 (citations omitted) ("First, a party's later position must be 'clearly inconsistent' with its earlier position.").

We also observe that Patent Owner was not a party to the '465 reexamination proceeding. *See, e.g.*, *Little Rock Cardiology Clinic PA v. Baptist Health*, 591 F.3d 591, 601 & n.7 (8th Cir. 2009) ("Because LRCC's previous position took place in an unrelated proceeding against a different party, we find that Baptist Health is not estopped from taking its current position"); *Strong v. Laubach*, 153 F. App'x 481, 485–86 (10th Cir. 2005) (non-precedential) (citation omitted) ("'Judicial estoppel may be invoked to prohibit assertion of inconsistent positions assumed in the course of the same judicial proceedings, or in subsequent proceedings involving identical parties and questions.'"); *cf. Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1381 (Fed. Cir. 2014) ("[S]tatements made during prosecution of a later, unrelated patent cannot form the basis for judicial estoppel"). Although the '465 patent was earlier in time than the '985 patent, the fact that Patent Owner was not a party to the '465 reexamination is an independent factor that also weighs against applying the doctrine of judicial estoppel in this context.

We also emphasize that judicial estoppel "is an equitable doctrine invoked by a court at its discretion." *New Hampshire*, 532 U.S. at 750. "[T]he circumstances under which judicial estoppel may appropriately be invoked are probably not reducible to any general formulation or principle." *Id.* Here, we also decline to invoke judicial estoppel because, on the present record, it is not clear that arguments in the Petition impose an unjust or unfair detriment on Patent Owner. The *New Hampshire* decision

related to the state of New Hampshire taking an inconsistent position regarding its boundary with Maine. *New Hampshire*, 532 U.S. at 745. A geographic boundary dispute between two adjacent entities is necessarily zero-sum; one gains land while another loses. Patents are not similar in this regard. Whether Petitioner previously obtained patent rights does not always bear directly on whether or not Patent Owner has different patent rights. Moreover, patent rights affect the public at large in a way that a geographic boundary dispute typically does not. *See Oil States Energy Services, LLC v. Greene's Energy Grp., LLC*, 138 S. Ct. 1365, 1374 (2018) ("[T]he grant of a patent is a matter between the public, who are the grantors, and . . . the patentee" (internal quotes and citation omitted)). Thus, it is not clear why, in this circumstance, Petitioner's positions necessarily impose an unfairness or injustice upon Patent Owner. Therefore, we determine that Petitioner is not estopped in this proceeding from arguing that a reasonable expectation of success existed as of October 6, 2000, the undisputed priority date of the '985 patent.

V. CONCLUSION

For the foregoing reasons, we determine that Petitioner establishes, by a preponderance of the evidence, that

(a) claim 1 of U.S. Patent No. 9,868,985 B2 is unpatentable under 35 U.S.C. § 103 as obvious over the combination of Tsien and Prober,

(b) claim 2 of U.S. Patent No. 9,868,985 B2 is unpatentable under 35 U.S.C. § 103 as obvious over the combination of Tsien, Prober, and Pallas, and

(c) claims 1 and 2 of U.S. Patent No. 9,868,985 B2 are unpatentable under 35 U.S.C. § 103 as obvious over Dower, Prober, and Metzker.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner establishes by a preponderance of the evidence that claims 1 and 2 of U.S. Patent No. 9,868,985 B2 are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *denied*; and

FURTHER ORDERED that this is a Final Written Decision; therefore, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.

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 MICHELLE N. ANKENBRAND, *Acting Vice Chief Administrative Patent Judge*, JAMES A. WORTH and BRIAN D. RANGE, *Administrative Patent Judges.*

Opinion Dissenting filed by *Administrative Patent Judge*, WORTH.

WORTH, *Administrative Patent Judge*, *Dissenting*.

I would determine that Metzker's experimental result of an asterisk ("Termination*"), indicating incomplete incorporation activity with an allyl nucleotide, would have sufficiently eroded the motivation created by Tsien to use an allyl nucleotide, such that Petitioner has not proven that it would have been obvious to a person of ordinary skill to combine the references as asserted. *Compare* Ex. 1013, 24:29–25:3, *with* Ex. 1016, 4263 & Table 2 (row [3] and legend). I would note that Dr. Romesberg's opinion that a

person of ordinary skill would have increased the concentration of an allyl nucleotide to increase incorporation is based on experiments done with a methoxy nucleotide rather than an allyl nucleotide, and I would still conclude that Metzker's experiment would have discouraged a person of ordinary skill from pursuing an allyl nucleotide. *See* Ex. 1119 ¶ 91 (citing Ex. 1016, 4264–65 & Figs. 3A, 4B); Ex. 1016, 4264–65 & Figs. 3A, 4B.

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