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Paper 20
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

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

IPR2020-00988
Patent 10,407,458 B2

Before SUSAN L. C. MITCHELL, JAMES A. WORTH, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

MITCHELL, *Administrative Patent Judge*.

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

I. INTRODUCTION

a. BACKGROUND

On May 29, 2020, Illumina, Inc., ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1 and 2 (the "challenged claims") of U.S. Patent No. 10,407,458 B2 (Ex. 1001, "the '458 patent"). *See* 35 U.S.C. §§ 311–319. On September 9, 2020, Trustees of Columbia University in the City of New York ("Patent Owner") filed a Preliminary Response to the Petition. Paper 11 ("Prelim. Resp."). On October 8, 2020, Petitioner filed an authorized Reply addressing discretion to institute under 35 U.S.C. §§ 314(a) and 325(d) and claim construction of the term "chemical linker." Papers 13, 15 ("Reply"). On October 15, 2020, Patent Owner filed an authorized Sur-Reply responding to Petitioner's statements concerning discretion to institute and claim construction. Papers 13, 17 ("Sur-Reply").

We have the authority and discretion to determine whether to institute an *inter partes* review. 35 U.S.C. § 314; 37 C.F.R. § 42.4. We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). For the reasons provided below, we determine that the Petitioners have satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Therefore, we institute an *inter partes* review of the challenged claims.

b. REAL PARTIES IN INTEREST

Petitioner identifies itself as the real party-in-interest for Petitioner. Pet. 70. Patent Owner identifies itself as the real party-in-interest for Patent Owner. Paper 4, 1.

c. RELATED PROCEEDINGS

This Petition is part of a third set of petitions Illumina filed challenging claims of several of Patent Owner's patents. The remaining petitions in this set involve the following four patents: U.S. Patent Nos. 10,407,459; 10,457,984; 10,435,742; and 10,428,380. The petitions involving each of these patents are as follows: IPR2020-01065; IPR2020-01125; IPR2020-01177; and IPR2020-01323, respectively. Patent Owner asserted these patents in the parallel district court litigation, *The Trustees of Columbia Univ. in the City of New York v. Illumina, Inc.*, 19-1681-CFC (D. Del.) ("the Delaware litigation").

The first set of petitions between the parties involved three of Patent Owner's patents, U.S. Patent Nos. 7,790,869; 7,713,698; and 8,088,575 ("the '869, '698, and '575 patents", respectively). Pet. 72–73; Paper 4, 2. The Board held all challenged claims of these patents unpatentable, and the United States Court of Appeals for the Federal Circuit ("Federal Circuit") affirmed that judgment. *See Illumina, Inc. v. Trustees of the University of Columbia in the City of New York*, IPR2012-00007, Paper 140 (PTAB March 6, 2014) (Ex. 1021); *Illumina, Inc. v. Trustees of the University of Columbia in the City of New York*, IPR2012-00006, Paper 128 (PTAB March 6, 2014) (Ex. 1022); *Illumina, Inc. v. Trustees of the University of Columbia in the City of New York*, IPR2013-00011, Paper 130 (PTAB March 6, 2014) (Ex. 1023); *Trustees of Columbia Univ. in the City of New York v. Illumina, Inc.*, 620 F. App'x. 916 (Fed. Cir. 2015) (Ex. 1029); Pet. 72–73; Paper 4, 2.

Petitioner asserts that the challenged claims held unpatentable in the '869, '698, and '575 patents in the first set of petitions "were nearly identical to claim 1 of the '480 patent [U.S. Patent No. 9,725,480 (Ex. 1019)]." Pet.

72–73. The Board held claim 1 of the '480 patent unpatentable over much of the same art asserted here in the second set of petitions Illumina filed against five patents including the '480 patent. *See* Pet. 70–72; Ex. 1024, 76. Petitioner also asserts that claim 1 of the '480 patent is "nearly identical to claims 1 and 2 of the '458 patent" at issue here. Pet. 71. More specifically, Petitioner asserts that the only difference between the unpatentable claims of the '480 patent and the '458 patent "is that this latest set excludes an allyl capping group (which the Board determined was unpatentable in the last round of IPRs)." *Id.* at 72.

In addition to the '480 patent, the remaining four patents of Patent Owner that Illumina challenged in this second set of petitions are as follows: U.S. Patent 9,718,852; 9,719,139; 9,708,358; and 9,868,985. Pet. 70–72; Paper 4, 1. Illumina challenged these patents in IPR2018-00291; IPR2018-00318; IPR2018-00322; IPR2018-00797, respectively; and IPR2018-00385 challenged the '480 patent. The Board held all challenged claims of these patents unpatentable. *See* Exs. 1024, 1028. Patent Owner has appealed these judgments. *See* Pet. 72; Paper 4, 1.

Petitioner also identifies its own patents that it has asserted against Patent Owner and that Patent Owner has challenged before the Board. Pet. 73–74; Paper 4, 2. The Board upheld the patentability of the challenged claims of one of Petitioner's patents, U.S. Patent No. 7,566,537. Pet. 74; Paper 4, 2; Ex. 1068 (IPR2013-00517); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016).

d. THE '458 PATENT (EX. 1001)

The '458 patent issued from a series of continuation applications, two of which issued as the '575 and '869 patents that were challenged in the first set of petitions Illumina filed. Ex. 1001, code (60) (stating the only two

applications in the priority chain that were not continuations were the earliest application and the second earliest application, neither of which matured into patents at issue in the series of *inter partes* reviews between Petitioner and Patent Owner). The '458 patent issued September 10, 2019, subject to a terminal disclaimer, and is titled "Massive Parallel Method for Decoding DNA and RNA." *Id*. (45), (54). The named inventors are Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki. *Id*. at code (72).

The subject matter of the '458 patent involves "methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction." Ex. 1001, Abst. The nucleotide analogs described in the '458 patent are made 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. This method is generally referred to as the "DNA sequencing by synthesis" approach or "SBS," because the sequence of the DNA is determined by identifying the successive additions of labeled nucleotides to

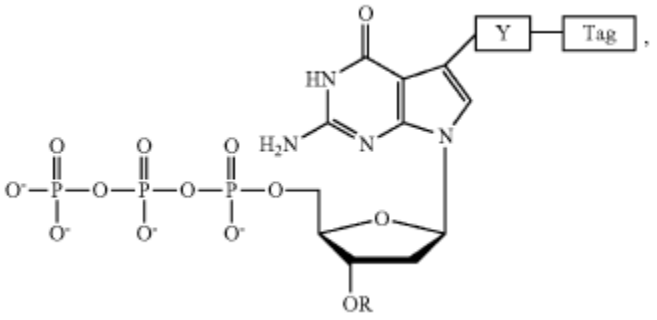
a strand of DNA as it is synthesized using a complimentary DNA strand as a template. *Id*. at 3:44–54, 4:25–32.

In describing the 3'-OH capping moiety, the Specification of the '458 patent provides that using small chemical moieties that can be easily cleaved chemically with high yield is desired because such nucleotide analogues incorporating such moieties "should also be recognized as substrates for DNA polymerase." *Id*. at 3:22–26. The Specification of the '458 patent provides that "[i]t is known that MOM ($–CH_2OCH_3$) and allyl ($–CH_2CH{=}{=}CH_2$) groups can be used to cap an –OH group, and can be cleaved chemically with high yield." *Id*. at 3:41–44 (citations omitted).

e. CHALLENGED CLAIMS

Petitioner challenges the two claims of the '458 patent, both of which are independent and are directed to a guanine deoxyribonucleotide analogues. Pet. Claim 1 is illustrative and recites:

1. A guanine deoxyribonucleotide analogue having the structure:



wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue, (b) does not interfere with recognition of the analogue as a substrate by DNA polymerase, (c) is stable during a DNA polymerase reaction, (d) does not contain a ketone group, and (e) is not a $–CH_2CH{=}{=}CH_2$ group;

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

wherein the covalent bond between the 3'-oxygen and R is stable

during a DNA polymerase reaction;

wherein tag represents a detectable fluorescent moiety;

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

wherein the guanine deoxyribonucleotide analogue:

(i) is recognized as a substrate by a DNA polymerase,

(ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,

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

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

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

Id. at 33:28–34:29.

f. PRIOR ART AND ASSERTED GROUNDS OF UNPATENTABILITY

Petitioner argues that claims 1 and 2 of the '458 patent are unpatentable based on the following grounds:

Claims Challenged	35 U.S.C. §	References
1, 2	103(a)[1]	Tsien,[2] Prober,[3] Hiatt[4]

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102, 103, and 112, effective March 16, 2013. Because the '458 patent issued from a series of continuation applications, the earliest of which was filed prior to the effective date of the AIA, we apply the pre-AIA version of 35 U.S.C. § 103.
[2] Tsien, WO 91/06678, published May 16, 1991 (Ex. 1031, "Tsien").
[3] Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336–41 (1987) (Ex. 1041, "Prober").
[4] Hiatt et al., U.S. Patent No. 5,763,594, issued June 9, 1998 (Ex. 1043, "Hiatt").

Claims Challenged	35 U.S.C. §	References
1, 2	103(a)	Dower,[5] Prober, Hiatt
1, 2	103(a)	Tsien, Prober
1, 2	103(a)	Dower, Prober, Metzker[6]

Petitioner submits the Declaration of Floyd Romesberg, Ph.D., in support of its Petition. *See* Ex. 1038 ("the Romesberg Declaration"). Patent Owner submits the Declaration of Kenneth A. Johnson, Ph.D, in support of its arguments in the Preliminary Response. *See* Ex. 2020.

II. ANALYSIS

a. APPLICATION OF 35 U.S.C. § 314(A) – PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL

Institution of an *inter partes* review under 35 U.S.C. § 314(a) is discretionary. *See* 35 U.S.C. § 314(a) (stating "[t]he Director *may not* authorize an *inter partes* review to be instituted unless the Director determines that the information presented in the petition . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition" (emphasis added)); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) ("[T]he agency's decision to deny a petition is a matter committed to the Patent Office's discretion."); *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018) ("[Section] 314(a) invests the Director with discretion on the question whether to institute review . . . ." (emphasis omitted)); *Harmonic Inc. v. Avid*

[5] Dower et al., U.S. Patent 5,547,839, issued Aug. 20, 1996 (Ex. 1030, "Dower").
[6] Metzker et al., *Termination of DNA Synthesis by Novel 8'-modified-deoxyribonucleoside 5'-triphosphates*, 22 NUCLEIC ACIDS RES. 4259–67 (1994) (Ex. 1039, "Metzker").

Tech., Inc., 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("[T]he PTO is permitted, but never compelled, to institute an IPR proceeding.").

Patent Owner asserts that we should exercise our discretion under section 314(a) because it "would be inefficient use of Board resources in light of a parallel district court litigation involving the same parties, the same claims, the same prior art, and the same invalidity arguments." Prelim Resp. 50 (citing the Delaware litigation). Petitioner responds that:

> The Board has extensive experience with the subject matter in this third-wave of IPRs. A Final Written Decision ("FWD") here would mark nearly a decade of Board adjudication between identical parties, patent specifications, and Tsien and Dower prior art. The claims at issue are identical to those previously adjudicated, with a single negative limitation added. Pet. 1–4. The instant panel retains two judges from the second-wave of IPRs and is well-situated to adjudicate this matter.

Reply 1. Both parties provide a more detailed analysis applying the factors set forth in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB March 20, 2020) (precedential) ("*Fintiv*"), for determining whether we should exercise our discretion to deny the Petition. *See* Prelim. Resp. 50–55; Reply 1–5; Sur-Reply 1–3.

Fintiv identifies the following factors that we should consider and weigh when a patent owner raises an argument for discretionary denial due to an earlier trial date in a parallel proceeding:

1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
3. investment in the parallel proceeding by the court and the parties;

4. overlap between issues raised in the petition and in the parallel proceeding;
5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
6. other circumstances that impact the Board's exercise of discretion, including the merits.

Fintiv, Paper 11 at 5–6. According to *Fintiv*, these factors relate to "efficiency, fairness, and the merits" and require the Board to take "a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6. Our analysis of the *Fintiv* factors is set forth below.

i. Factor 1: Likelihood of a Stay

Patent Owner notes that the district court in the Delaware litigation has not issued a stay, but does not indicate whether any party has sought such a stay or plans to seek such a stay should we institute an *inter partes* review. *See* Prelim. Resp. 51. Thus, this factor is neutral.

Patent Owner touts that the Delaware litigation was filed over a year ago in September 2019, has a trial date earlier than the projected statutory deadline for the Final Written Decision in this case, and that the parties and the district court have expended significant resources in the parallel Delaware litigation. *Id*. at 51–52 (citing Ex. 2027; Ex. 2028). Patent Owner, however, does not explain how these facts are relevant to a stay in the Delaware litigation. We find these facts more relevant to the next two *Fintiv* factors and discuss them below.

ii. Factor 2: Proximity of Trial Date to the Board's Projected Statutory Deadline

Patent Owner asserts that trial is scheduled to begin in the Delaware litigation on November 15, 2021, which is about three weeks prior to the

projected statutory deadline for our final written decision in this case. *See* Prelim. Resp. 52–53. Patent Owner asserts that the Board generally weighs this factor in favor of denying institution when the trial date of the parallel litigation is set before the projected statutory deadline for a final written decision. *Id*. at 53.

Petitioner counters that the trial date may slip as the district court already has granted many extensions in the Delaware litigation and asserts that additional district court delays are likely. Reply 1–2 (citing Ex. 1154, 18; Exs. 1146–1153). Specifically, Petitioner asserts that the parties have extended the deadline for completing document production by nearly two months, *see* Ex. 1152, and Patent Owner has filed a motion for reconsideration of the District Court's *Markman* Order, causing further extension. Reply 1–2. Patent Owner responds that such extensions are routine in patent litigations and posits that they rarely affect trial dates. Sur-Reply 1–2.

Because the trial date and the date of our final written decision are around the same time, our decision to institute implicates other factors, such as the investment factor. *See Fintiv*, Paper 11 at 9. Accordingly, we find that the close proximity of the trial date to our projected final written decision statutory deadline in this case weighs only marginally in favor of exercising our discretion to deny institution.

iii. Factor 3: Investment in Proceedings

Patent Owner asserts that the parties and the district court have expended significant resources in the Delaware litigation. Prelim. Resp. 51–52. Patent Owner details these efforts, indicating that *Markman* briefing is complete, the *Markman* hearing has been held, and the district court has issued a decision construing the claims. *Id*. at 52.

Petitioner counters that the district court extended the document production deadline by almost two months, indicating limited investment in the Delaware litigation, Patent Owner has produced just ten documents that are non-duplicative with prior litigations, no fact witness depositions have been scheduled, and no expert discovery on the merits has begun. Reply 1–2. Patent Owner responds that it has produced over 89,000 pages of documents, albeit documents previously produced in a related litigation and considered re-produced in the Delaware litigation by agreement of the parties. Sur-Reply 2.

Petitioner also asserts that it promptly filed this request for an *inter partes* review about eight months after the Delaware litigation began, time which encompassed lockdown phases under the current pandemic. Reply 2. Patent Owner considers this eight-month delay in filing a petition for an *inter partes* review an attempt to gain a tactical advantage to avoid any opportunity for Patent Owner to evaluate the consistency of positions taken in the Petition at issue here as compared to Petitioner's positions taken in the pending appeal of the immediately previous set of petitions. Prelim. Resp. 54.

Fintiv provides the following guidance with respect to factor 3:

> [I]f, at the time of the institution decision, the district court has issued substantive orders related to the patent at issue in the petition, this fact favors denial. Likewise, district court claim construction orders may indicate that the court and parties have invested sufficient time in the parallel proceeding to favor denial. If, at the time of the institution decision, the district court has not issued orders related to the patent at issue in the petition, this fact weighs against exercising discretion to deny institution under *NHK*.

Fintiv, Paper 11 at 9–10. *Fintiv* explains that "[t]his investment factor is related to the trial date factor, in that more work completed by the parties and

the court in the parallel proceeding tends to support the arguments that the parallel proceeding is more advanced, a stay may be less likely, and instituting would lead to duplicative costs." *Id.* at 10.

Although the *Markman* phase of the Delaware litigation is substantially complete, fact discovery appears to be in its early stages, and the parties have not yet begun expert discovery on the merits. As a result, we find that this factor weighs slightly in favor exercising our discretion to deny institution of a trial here. We do not consider the timing of the filing of the Petition here to weigh in favor of or against exercising our discretion to deny institution because we are not aware of any evidence that the Delaware litigation had progressed significantly at the time Petitioner filed the Petition. *See Fintiv*, Paper 11 at 11 (explaining how the timing of a petition's filing may weigh in favor of or against exercising discretion to deny institution). In fact, Patent Owner's summary of the Delaware litigation and the docket it submitted from the litigation indicate that the parties had served contentions, discovery requests, and responses to discovery requests, and that *Markman* briefing had not yet begun. *See* Prelim. Resp. 51–52; Ex. 2028, D.I. 25, 27, 28, 30 (notice of service entries reflecting contentions, discovery requests, and responses to discovery requests), 47, 52, 53 (notice of service entries reflecting *Markman* briefing). Finally, we take no position concerning Patent Owner's argument that Petitioner was seeking a tactical advantage through the timing of the Petition's filing.

iv. Factor 4: Overlap of Issues

Patent Owner asserts that this Petition and the Delaware litigation "include identical patent claims, identical prior art, and substantially identical invalidity arguments." Prelim. Resp. 54; *compare* Pet., *with*

Ex. 2004. Petitioner asserts that some grounds in the Delaware litigation "overlap with this IPR, while most do not." Reply 3 (citing Ex. 2004, 5–11).

Although the Delaware litigation appears to have far more invalidity contentions involving more art and combinations of that art than presented in the unpatentability grounds here, the grounds presented in the Petition here appear to overlap with those contentions. *Compare* Pet. 10–11, *with* Ex. 2004, 5–11. Thus, we find that this factor weighs in favor of exercising our discretion to deny institution.

v. Factor 5: Whether the Petitioner and the Defendant in the Parallel Proceeding are the Same Party

Petitioner is a party in the Delaware litigation. Prelim. Resp. 55. Therefore, this factor weighs in favor of exercising our discretion to deny institution.

vi. Factor 6: Other Circumstances, Including the Merits

Patent Owner asserts that the merits of this Petition "are particularly weak." Prelim. Resp. 55. Patent Owner further states that:

> The Columbia inventors were the first to conceive the use of the MOM capping group for SBS, and Illumina has not argued otherwise. Thus, the present situation is unlike the Allyl Claim IPRs, where the prior art allegedly suggested the use of the allyl capping group (which Columbia continues to dispute on appeal). Here, despite a decade of efforts to practice SBS, it is undisputed that not a single researcher proposed the use of the MOM capping group for SBS.

Id.

Petitioner responds:

> The Board has extensive experience with the subject matter in this third-wave of IPRs. A Final Written Decision ("FWD") here would mark nearly a decade of Board adjudication between identical parties, patent specifications,

> and Tsien and Dower prior art. The claims at issue are identical to those previously adjudicated, with a single negative limitation added. Pet. 1–4. The instant panel retains two judges from the second-wave of IPRs and is well-situated to adjudicate this matter.

Reply 1. Petitioner also asserts that Patent Owner presents arguments previously presented and adjudicated in past *inter partes* reviews, a position with which we agree. *Id.*; *see supra* Section I.c. (setting forth the relatedness of the '458 patent to Patent Owner's other patents that the Board previously adjudicated in several *inter partes* review proceedings between these same parties).

Based on our review of the arguments and evidence presented on the preliminary record, as discussed below in Section II.e, we find that the strong merits weigh against exercising discretion to deny institution.

vii. Balancing the Fintiv Factors

We decline to exercise our discretion to deny the Petition under § 314(a). We determine that the strength of the merits and history of IPR proceedings between Petitioner and Patent Owner involving substantially similar claims and prior art outweigh the other *Fintiv* factors. We agree with Petitioner that "[t]he claims deemed unpatentable in the second wave of IPRs are *identical* to the claims challenged in this IPR, with the exception that a single species of allyl capping group was removed from the claim genus." Pet. 3; *compare* Ex. 1009, 34:2–35:4, *with* Ex. 1001, 33:29–35:4 (adding the allyl proviso: "is not a $–CH_2CH{=}{=}CH_2$ group" (claim 1) and "is not . . . an allyl ether group" (claim 2)). In evaluating the *Fintiv* factors with a holistic view, we are not persuaded to exercise discretion to deny institution of *inter partes* review.

b. APPLICATION OF 35 U.S.C. § 325(D) – PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL

Patent Owner, relying on arguments Petitioner made in related Board proceedings, argues that we should exercise our discretion under 35 U.S.C. § 325(d) to deny institution for two reasons pertaining to Petitioner's reliance in this proceeding on teachings from references Hovinen[7] and Hiatt. *See* Prelim Resp. 55–57. First, Patent Owner argues that Petitioner's contention in this case that a skilled artisan would have pursued use of the MOM capping group in an SBS method based on Hovinen's teachings "ignores that the Board[8] declined [in a prior set of cases] to adopt Illumina's prior contention that disclosure of a capping group for use in ***Sanger sequencing*** would motivate a POSA to use said capping group for ***SBS***," a characterization with which we disagree. *Id*. at 55–56; *see infra* Section II.e.ii. Patent Owner cites a statement from the Board's Allyl Claim IPR Decision that Illumina's expert "concede[d] that Sanger sequencing requires low termination rates (in contrast to the high termination rates SBS requires)." Prelim. Resp. 56 (quoting Ex. 1024, 32). Patent Owner argues that the Board's rejection of the stated reasoning in the prior cases similarly justifies the exercise of discretion to deny the Petition here, where Petitioner relies on the teachings of Hovinen, a Sanger sequencing reference. *Id*.

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[7] Hovinen et al., *Synthesis of 3′-O-(ω-Aminoalkoxymethyl)thymidine 5′-Triphosphates, Terminators of DNA Synthesis that Enable 3'-Labeling*," 1 J. CHEM. SOC. PERKIN TRANS. 211–217 (1994) (Ex. 1060, "Hovinen").
[8] Patent Owner refers to the Board's *per curiam* Final Written Decision in *Illumina, Inc. v. Trustees of Columbia Univ*., IPR2018-00291, IPR2018-00318, IPR2018-00322, IPR2018-00385 Paper 67 at 32, (PTAB June 21, 2018) (Ex. 1024) ("Allyl Claim IPR Decision" or "Allyl Claim IPR").

Second, Patent Owner argues that the Board's statements in the Allyl Claim IPR Decision concerning Hiatt are "relevant here, where Illumina now uses Hiatt in the asserted grounds." *Id.* Patent Owner notes that "Illumina previously argued that Hiatt provided motivation for a POSA to select a particular capping group, specifically the allyl capping group," but the Board found that Hiatt "presents an immense number of possibilities for the blocking group." *Id.* (citing Ex. 1024, 27). Patent Owner concedes that the Board's finding was "ultimately not dispositive in the prior case," but argues that "Illumina should not be permitted to ignore the Board's prior finding" and cites *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 16–28 (Dec. 15, 2017) (precedential as to section III.C.5, first paragraph) ("*Becton, Dickinson*") as "applying § 325(d) to deny institution of ground raising same arguments based on similar prior art." Prelim Resp. 56–57.

Analysis

If "another proceeding or matter involving the patent is before the Office," we have discretion to deny review where "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office.[9] *See also Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*") (setting forth the two-part framework under which the Board analyzes § 325(d)).

[9] The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a); *Advanced Bionics*, Paper 6 at 7 n.7.

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and, (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several nonexclusive factors, including:

(a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;

(e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18.

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10 (". . . although Becton, Dickinson factor (d) pertains to arguments made "during examination," this factor more broadly provides guidance as to whether the arguments presented in the petition are 'the same or substantially the same' as the arguments previously presented to the Office during *any* proceeding" and referencing AIA proceedings as an example proceeding before the Office). Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id*. Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id*.

Same or Substantially the Same Art or Arguments Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. Patent Owner raises no argument under § 325(d) regarding Petitioner's asserted grounds 3 and 4. *Id*. Patent Owner's arguments under § 325(d) focus on asserted grounds 1 and 2, which include Hiatt. Hovinen is not included in any of Petitioner's asserted grounds and also was not included in the asserted grounds the Board addressed in the Allyl Claim IPR. *See* Pet. 10–11 (listing asserted grounds); Ex. 1024, 2–3 (Allyl Claim IPR Decision's table of asserted grounds). Rather, as we explain below, Petitioner's cites to Hovinen only as further evidence that 3'-O-MOM capped nucleotides were recognized as a substrate

and incorporated by polymerase. *See infra* section II.e.ii.(4)a). Thus, we do not agree with Patent Owner that the Board previously considered Hovinen's teachings in determining that the challenged claims in the Allyl Claim IPR were unpatentable. Accordingly, we are not persuaded that Hovinen was previously presented to the Office within the meaning of § 325(d). *See Advanced Bionics*, Paper 6 at 7–8.

With regard to Hiatt, there is no dispute that both grounds 1 and 2 of the Petition rely on Hiatt's disclosure of a 3'-O-MOM capping group as teaching or suggesting the "R group" of claims 1 and 2, a capping group for reversibly blocking a nucleotide's 3'-OH moiety during enzymatic DNA synthesis. *See, e.g.*, Pet. 16–30. In the Allyl Claim IPR Decision, however, none of Petitioner's asserted grounds relied upon Hiatt. *See* Ex. 1024 at 2–3 (listing grounds). Further, as Patent Owner acknowledges (Prelim. Resp. 56), the Board's statement regarding the scope of Hiatt's disclosure was not dispositive to the decision to find the claims in the Allyl Claim IPR unpatentable. Nor did this statement form the foundation of the Board's reasoning in doing so. *See* Ex. 1024 at 35–67 (explaining reasoning regarding unpatentability). Accordingly, we are not persuaded that Hiatt was previously presented to the Office within the meaning of § 325(d). *See Advanced Bionics*, Paper 6 at 7–8.

Therefore, weighing factors (a), (b), and (d) with regard to all four grounds at issue in this proceeding, we find that the statements Patent Owner cites, while pertinent to the teachings of Hovinen and Hiatt, did not sufficiently bear on the patentability determination of the claims at issue in the Allyl Claim IPR to be considered the "same or similar arguments" under *Advanced Bionics*. That these statements do not relate to half of the grounds at issue in this proceeding bolsters our conclusion. *See* SAS Q&A's, Part D,

Effect of *SAS* on Future Challenges that Could Be Denied for Statutory Reasons, D1 (June 5, 2018) ("SAS Q&A's, Part D"), available at https://www.uspto.gov/sites/default/files/documents/sas_qas_20180605.pdf (the Board "evaluate[s] the challenges and determine whether § 325(d) is sufficiently implicated that its statutory purpose would be undermined by instituting on all challenges"). Accordingly, we decline to exercise our discretion to deny institution.

c. LEVEL OF ORDINARY SKILL IN THE ART

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007) (stating that obviousness is determined against the backdrop of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art). Factual indicators of the level of ordinary skill in the art include "the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field." *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner contends that a person of ordinary skill in the art would have "have been a member of a team of scientists developing nucleotide analogues, researching DNA polymerases, and/or addressing DNA sequencing techniques. Such a person would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience."

Pet. 13. Patent Owner does not dispute this definition for purposes of this *inter partes* review. Prelim. Resp. 5.

In the second set of *inter partes* reviews, we adopted Petitioner's definition as set forth above. *See* Ex. 1024, 15. We see no reason to deviate from that definition here. We have considered the contentions of the parties, and for purposes of this decision on this record, we apply Petitioner's definition of a person of ordinary skill in the art.

d. CLAIM CONSTRUCTION

We construe claims using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.100 (2019). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art ("POSA"), at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.* Only those terms that are in controversy need be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Petitioner offers a construction of the term "allyl ether" as set forth in claim 2 of the '458 patent, *see* Pet. 11–12, and Patent Owner offers a construction of the term "small" and assigns a "plain and ordinary meaning" to the term "chemical linker," *see* Prelim. Resp. 6–8. Petitioner asserts that we should construe the term "allyl ether" to mean "—$CH_2CH{=}{=}CH_2$," which Petitioner asserts "does not exclude the known 2-methylallyl (–

$CH_2C(Me)==CH_2$) and 3-methylallyl (—$CH_2CH=CH-CH_3$) ethers." Pet. 11–12. We determine that it is not necessary to construe this term to decide whether to institute an *inter partes* review. There is no dispute on this record at this stage of the proceeding that a methoxymethyl or "MOM" capping group, i.e., -CH_2OCH_3 that Petitioner asserts meets the claim limitation for a 3'OH capping moiety is not an allyl ether. *See* Pet. 20; Prelim. Resp. 9; Reply 1 ("On the merits, Columbia's [Preliminary Response] concedes that the prior art meets all claim limitations."); Ex. 1036, 4.

Patent Owner construes a "small" capping group to mean "a capping group that is less than 3.7A in diameter." Prelim. Resp. 5. Patent Owner does not appear to challenge that a MOM capping group is "small." Prelim. Resp. 9; Reply 1. In fact the Specification of the '458 patent identifies MOM as an appropriate capping group, along with allyl, that "can be used to cap an —OH group, and can be cleaved chemically with high yield." Ex. 1001, 3:41–44 (citations omitted). Therefore, we determine that it is not necessary to construe this term to decide whether to institute an *inter partes* review.

Finally, although Patent Owner asserts that we need not construe the claim phrase "chemical linker," *see* Prelim. Resp. 6, Patent Owner offers a construction as the plain and ordinary meaning of the term as "the chemical structure, made up of one or more chemical groups, that links the base to the tag." *Id*. This construction contravenes the District Court's construction in the parallel Delaware litigation that the chemical linker "Y" is "a single linker that directly connects the base to the label." *Id*. at 6 n.3. We find that we need not expressly construe "chemical linker" here, as Patent Owner

does not dispute at this time that the asserted prior art teaches such a chemical linker. *See* Prelim. Resp. 9; Reply 1.

e. PATENTABILITY ANALYSIS

i. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR*, 550 U.S. at 406. The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of

> innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles. In making such an analysis, we find that Petitioner has shown a reasonable likelihood of prevailing in establishing that claims 1 and 2 of the '458 patent are unpatentable.

ii. The Tsien Grounds

Petitioner asserts that claims 1 and 2 of the '458 patent are unpatentable over Tsien and Prober, or Tsien, Prober, and Hiatt. Pet. 10–11. Petitioner provides an analysis of how each claim limitation is taught by Tsien, Prober, and Hyiatt and how a POSA would have reason to combine the teachings with a reasonable expectation of success. Pet. 13–38. Petitioner relies on the declaration of Dr. Romesberg in support of its positions. *See* Ex. 1038.

Patent Owner responds that one of skill in the art would not have had a reason to choose the MOM capping group based on what was known about SBS at the relevant time, and would have had no reasonable expectation of success of efficient incorporation of the MOM capping group, as Tsien requires. Prelim. Resp. 9–23. Patent Owner also asserts that one of skill in the art would have had no motivation "to combine Hiatt's non-SBS methods

with Tsien's or Dowers' SBS methods to achieve the claimed nucleotides for SBS." Prelim. Resp. 23–40.

For the following reasons, we find that Petitioner has shown a reasonable likelihood of success in establishing that claims 1 and 2 of the '458 patent would have been obvious in light of the Tsien combinations. We begin our analysis of Petitioner's challenges with a description of the pertinent teachings of the asserted art.

(1) Tsien (Ex. 1031)

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. 1031, 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.* at [22], [30], [43].

Tsien describes an SBS method. Ex. 1031 ¶ 45; Ex. 2020 ¶ 25. In particular, Tsien describes determining the sequence of a single stranded DNA molecule by synthesizing the complementary DNA molecule. Ex. 1031, 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 depicting Tsien's synthesis process is reproduced below.

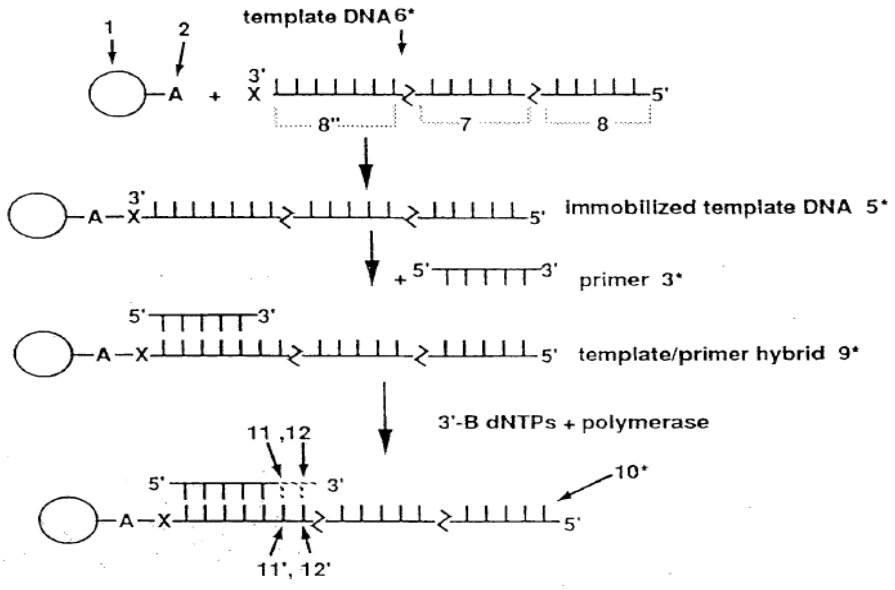


FIG. 1B

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. The method must:

> (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:

> For the present invention, 3'-blocked dNTPs are used that can be incorporated in a template-dependent fashion and easily deblocked to yield a viable 3'-0H terminus. The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications to the 3'-OH position of dNTPs

> include the introduction of groups such as -F, -NH_2, -OCH_3, -N_3, -OPO_3, -$NHCOCH_3$, 2-nitrobenzene carbonate, 2,4-dinitrobenzene sulfenyl and tetrahydrofuranyl ether. Incorporation and chain termination have been demonstrated with dNTPs containing many of these blocking groups (Kraevskii et al., [Molecular Biology, 21:25–29 (1987)]).

Id. at 21:9–19.

(2) *Prober (Ex. 1041)*

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:

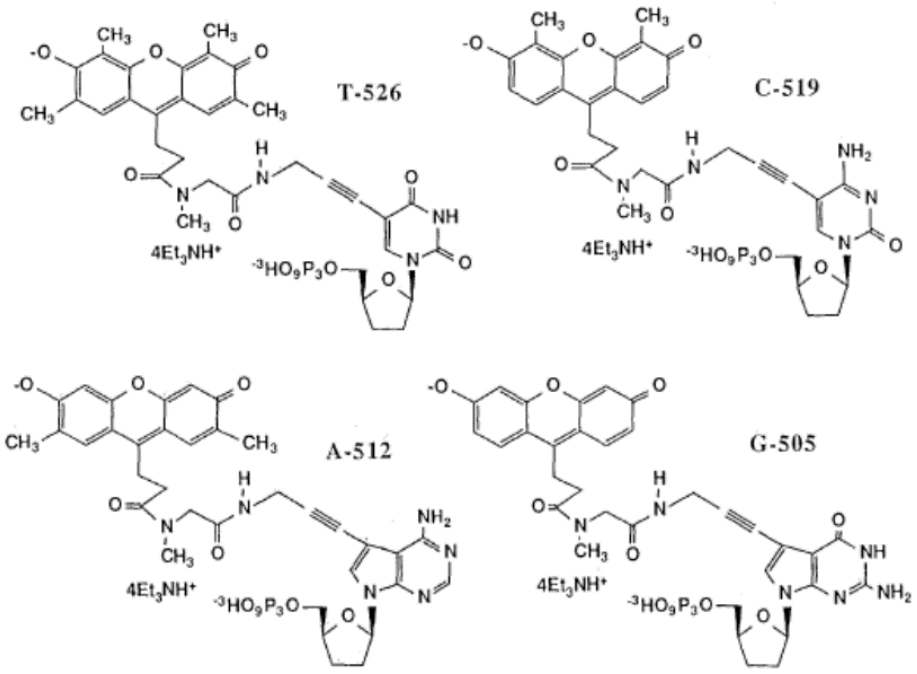


Figure 2A depicts "[c]hemical structures of the reagents used in modified dideoxy reactions for DNA sequencing." *Id.* at 338. Prober discloses that succinylfluorescein is attached via a linker to a heterocyclic base, i.e., a nucleotide analogue. *See id.* at 337. In particular, the linker is attached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

(3) Hiatt (Ex. 1043)

Hiatt is titled "3' Protected Nucleotides for Enzyme Catalyzed Template-Independent Creation of Phosphodiester Bonds," and relates to a

> method for the stepwise creation of phosphodiester bonds between desired nucleotides resulting in the synthesis of polynucleotides having a predetermined nucleotide sequence by preparing an initiation substrate containing a free and unmodified 3'-hydroxyl group; attaching a mononucleotide selected according to the order of the predetermined nucleotide sequence to the 3'-hydroxyl of the initiating substrate in a solution containing a catalytic amount of an enzyme capable of catalyzing the 5' to 3' phosphodiester linkage of the 5'-phosphate of the mononucleotide to the 3'-hydroxyl of the initiating substrate, wherein the mononucleotide contains a protected 3'-hydroxyl group, whereby the protected mononucleotide is covalently linked to the initiating substrate and further additions are hindered by the 3'-hydroxyl protecting group.

Ex. 1043, Abst.; *see id.* at 4:12–43. This process is depicted in Figure 1 set forth below.

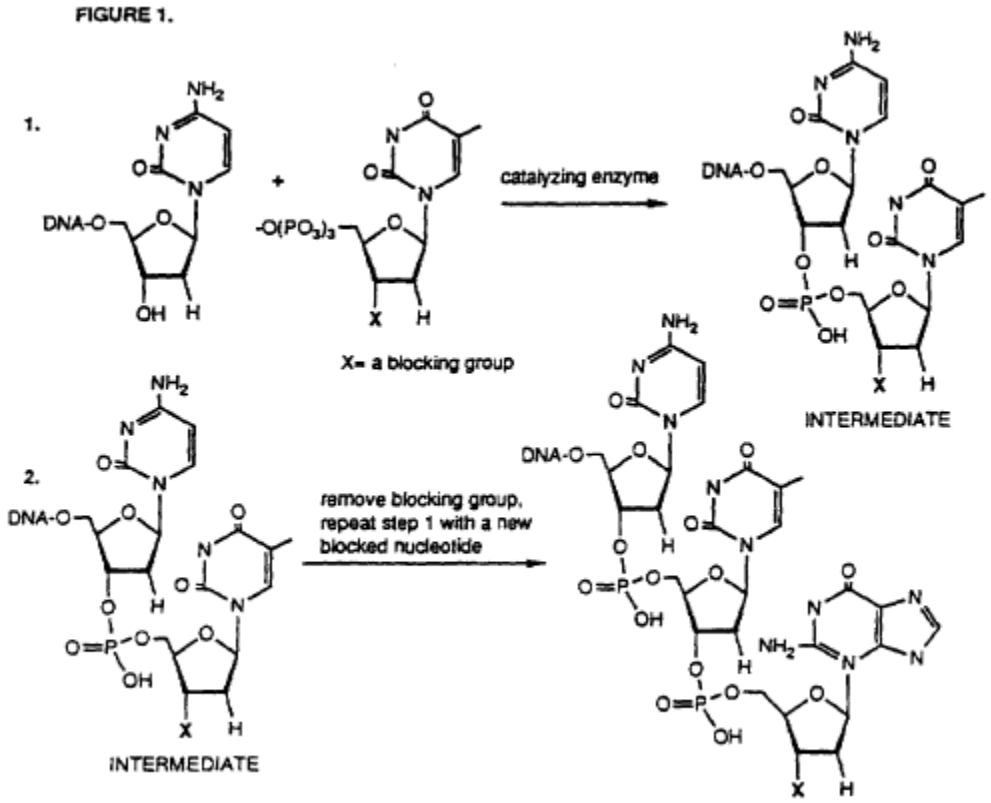
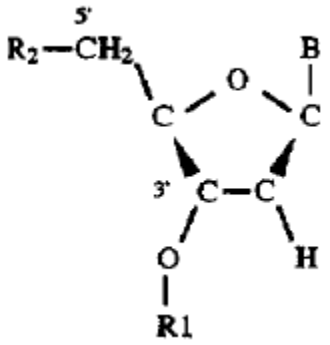


Figure 1 is a diagram of enzymatic synthesis of an oligonucleotide using a template independent polymerase and a nucleoside 5'-triphosphate having a removable blocking moiety at its 3' position. *Id*. at 5:41–44.

Hiatt further states that the removable blocking moieties that block the 3'position of the nucleoside 5'-triphosphates are used in the described method, and "[p]referred removable blocking moieties can be removed in under 10 minutes to produce a hydroxyl group of the 3' position of the 3' nucleoside." *Id*. at 4:59–64. Such removable blocking groups include carbonitriles, phosphates, carbonates, carbamates, esters, ethers, borates, nitrates, sugars, phosphoramidates, phenylsulfenates, sulfates, and sulfones. *Id*. at 4:64–67.

Hiatt identifies that:

> In more preferred embodiments, a nucleoside 5'phosphate of the present invention has a removable blocking

> moiety protecting the 3' position which is an ether and which has the following formula:
>
> 
>
>
> wherein R2 is triphosphate, diphosphate or monophosphate; and wherein R1 is CH_3, $CH_3(CH_2)N$ where N is an integer from 1–10, methyl, methoxymethyl, methoxyethoxymethyl, trimethlsilyl, and triethylsilyl.

Id. at 13:35–52.

(4) Analysis – Obviousness over Tsien, Prober, and Hiatt

Petitioner explains sufficiently how Tsien, Prober, and Hiatt teach each limitation of claims 1 and 2 of the '458 patent, and also provides citations to our previous decision concerning the claim of the '480 patent in which we found that the prior art taught many of the same claim limitations. *See* Pet. 13–30. The only difference between claim 1 of the '458 patent and claim 1 of the '480 patent is the addition of the limitation "wherein R [the 3'-hydroxyl protecting group] . . . (e) is not a —$CH_2CH{=}{=}CH_2$ group." *Compare* Ex. 1019, 34:2–35:4, *with* Ex. 1001, 33:29–34:29. This limitation appears to have been added to overcome prior art that we found taught claim 1 of the '480 patent. Our focus in this decision on institution will test the sufficiency of the evidence that the prior art teaches such a 3'-hydroxyl capping group, and that a POSA would have had reason to combine the teachings of the references to render the challenged claims obvious.

a) Petitioner's Case

In describing the state of the art in the relevant time frame, Petitioner explains how nucleotide analogues were known for use in identifying the sequence of DNA through the Sanger sequencing and the SBS methods. Pet. 7 (citations omitted). Petitioner states:

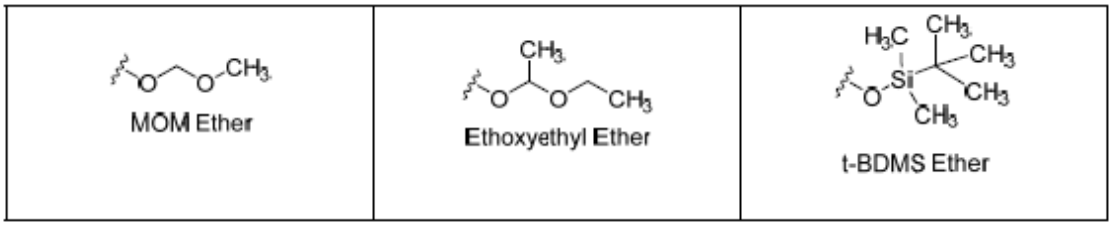
> Sanger sequencing and SBS use a polymerase to incorporate modified nucleotides (i.e., "nucleotide analogues") containing a detectable label into DNA. The label on the incorporated analogue is 'read' to determine the DNA sequence. Several labeled nucleotide analogues were known, including analogues containing: (1) removable 3'-OH capping groups, and (2) labels attached to the base through a linker.

Id. at 7 (citing Ex. 1038 (Romesberg Declaration) ¶¶ 45, 53–56).

Petitioner also asserts that small 3'-capping groups were known to be desirable. *Id*. at 7–8. Petitioner cites to both Dower and Tsien as disclosing this desirability, which Tsien provides minimizes steric interference for polymerase incorporation. *Id*. (citing Ex. 1030, 25:48–51, 14:47–48; Ex. 1031, 26:17–27:1; Ex. 1038 ¶¶ 57–58). Petitioner asserts that Tsien "specifically recommends an alkyl ether capping group." *Id*. at 31 (citing Ex. 1031, 21:9–13, 21:20–28).

Petitioner then points to Hiatt as identifying a 3'-O-MOM capping group as a preferred embodiment, and providing a working example synthesizing the nucleotide. *Id*. at 16 (citing Ex. 1043, 13:35–52, 30:22–40). Petitioner goes on to state that:

> This nucleotide is one of only three 3'-ether capped nucleotides that Hiatt prepares, thereby elevating the MOM group in prominence.
>
> Hiatt's MOM group is also the smallest of Hiatt's three prepared ethers:



> By 2000 . . . smaller capping groups were desirable. Thus, a MOM group would have been the most desirable choice from among Hiatt's three ethers.

Pet. 16–17 (citations omitted).

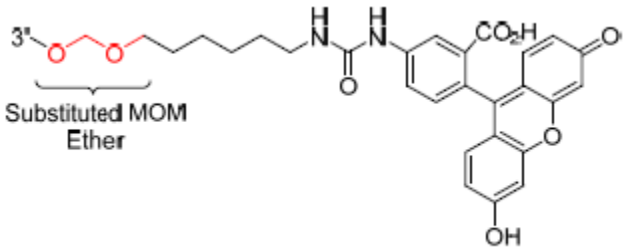
Petitioner concludes:

> Columbia's later selection of Hiatt's MOM group was not inventive. The PTO during re-examination awarded Hiatt a claim to a nucleotide having a MOM group at the 3'-position. Ex. 1043: Page 30 (claim 1). Hiatt was filed in 1994. In the interlude between Hiatt's filing and Columbia's filing, researchers were using polymerase crystal structures to evaluate nucleotides for SBS and proposed modifying the 3'-capping group to avoid those that "tend to be too big to fit into the active site of DNA polymerases." Ex. 1033: 956; Ex. 1038 ¶¶57-71. By 2000, a POSA with knowledge of this intervening emphasis on smaller groups would have found Hiatt's MOM group obvious as a reversible alkyl ether capping group presented in a reference discussing polymerase-mediated DNA synthesis. Ex. 1038 ¶¶90-102.
>
> Columbia even admitted that MOM was a known capping group that could be cleaved chemically in high yield under DNA-compatible conditions. Ex. 1001: 3:41-51, 25:46-50; Ex. 1032 ¶22 (admitting that a MOM capping group meets the "structural and functional features recited in the claim.").

Id. at 17.

In addition to relying on Patent Owner's alleged admission during prosecution that Hiatt's MOM group satisfies the structural and functional features recited in the claims, Petitioner also cites to Hovinen as further evidence that 3'-O-MOM capped nucleotides were recognized as a substrate

and incorporated by polymerase. Pet. 18–19 (citing Ex. 1060, 212–13, Fig. 1; Ex. 1038 ¶¶ 104–111). Petitioner asserts that "Hovinen discloses recognition and incorporation of a nucleotide having a substituted 3'-O-MOM group," which is depicted below. *Id*. at 18.



Hovinen's substituted 3'-O-MOM group shown above has the residual MOM group highlighted in red. Pet. 18. Petitioner posits with supporting testimony from Dr. Romesberg that "[t]he incorporation of a substituted MOM group provides a reasonable expectation that the unsubstituted MOM group would not interfere with polymerase recognition." *Id*. at 19 (citing Ex. 1038 ¶ 111).

b) Patent Owner's Response

Patent Owner asserts that:

1. SBS prior art did not suggest using the MOM capping group;
2. A person of ordinary skill in the art would not have been motivated to use the MOM capping group because there was no expectation of efficient incorporation as required by Tsien, and would not have been motivated to combine Hiatt's non-SBS methods with Tsien and Dower's SBS methods; and
3. A person of skill in the art would not have been motivated to select Hiatt's MOM capping group, and would not have expected the MOM embodiment would satisfy the claim requirement of "not interfering with recognition of the analogue."

Prelim. Resp. 9, 8–41. We will address each of these issues in turn.

i. *Teachings of SBS Prior Art*

Patent Owner asserts that by 1990, Tsien and Dower described prophetic methods for SBS and listed a large number of 3'-O-capped nucleotides that were allegedly potentially useful for their methods. Prelim. Resp. 10 (citing Ex. 1031, 21; Ex. 1030, 18:52–63; Ex. 1024, 23). Patent Owner also lists other researchers in the interim decade between 1990 and 2000 that pursued 3'-O-capped nucleotides for SBS, but "[d]espite these efforts, by the October 2000 priority date, not a single researcher had proposed using the MOM capping group for SBS." *Id*. at 11. Patent Owner concludes that "[d]espite a decade of efforts, nobody suggested using the MOM capping group for SBS, belying Illumina's hindsight-driven conclusion that doing so would have been obvious." *Id*. at 13.

Patent Owner does not credit, however, that in further developing SBS methods, one of skill in the art would have had reason to look at other methods beyond SBS. For instance, Although Tsien involves the SBS method and Prober involves Sanger sequencing, Dr. Romesberg testifies that "Tsien recommends using the nucleotide labeling scheme described in Prober," and Tsien states that Prober shows "enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™." Ex. 1038 ¶¶ 45, 46, 85. Dr. Romesberg notes that "Tsien cites to Prober five times, inviting a person of ordinary skill in the art to consider Prober's disclosure." *Id*. (citing Ex. 1031, 28:5–18, 29:10–14, 31:11, 5:22–23, 2:25). We find on the record before us that one of skill in the art would have looked beyond references describing SBS in its further development.

We also credit Dr. Romesberg's testimony that although Hiatt's enzyme uses the template-independent polymerase TdTase, Hiatt is not

limited to that polymerase. Ex. 1038 ¶ 93. Dr. Romesberg testifies that "TdTase (also called simply 'TdT') was known to be structurally and functionally similar to polymerase mu, . . [and is] also related to polymerase beta." *Id*. (citing Ex. 1115, Abst., 1732; Ex. 1116, 4045, 4047). Because both polymerases mu and beta are template-dependent DNA polymerases as those used in SBS, "the known interrelatedness of TdT with other template-dependent polymerases would have also made Hiatt's disclosure of interest to a person of ordinary skill in the art conducting template-dependent DNA synthesis," such as SDS. *Id.*

We also note that the '458 patent expressly states that "[i]t is known that MOM ($–CH_2OCH_3$) and allyl ($–CH_2CH{=}{=}CH_2$) groups can be used to cap an –OH group, and can be cleaved chemically with high yield." Ex. 1001, 3:41–44. Thus, it appears that Patent Owner acknowledges that MOM groups were known to be used as 3'-hydroxyl capping moieties as recited in claims 1 and 2 of the '458 patent. Therefore, although Patent Owner points out what appears to be not insubstantial delay in using MOM groups as 3'-hydroxyl capping moieties for SBS, it does not appear on the record before us that Petitioner's suggestion that such use would have rendered the challenged claims obvious is merely derived from impermissible hindsight analysis.

ii. *Efficient Incorporation*

Patent Owner asserts that Petitioner improperly ignores Tsien's efficient incorporation requirement that successful use of 3'-blocking groups includes "the ability of a polymerase enzyme to accurately and *efficiently* incorporate the dNTPs carrying the 3'-blocking groups into the cDNA chain." Prelim. Resp. 14 (quoting Ex. 1031, 20; Ex. 1030, 26:6–9 (Dower requiring same efficient incorporation)). Patent Owner supports such a

requirement by referencing our previous decision in which we allegedly "held that a POSA would not have been motivated to use a 3'-O-capped nucleotide in Tsien's or Dower's SBS methods unless the POSA believed that such nucleotide would meet the criteria for being useful for SBS." Prelim. Resp. 14 (citing Ex. 1024, 40, 52).

Patent Owner also points to Petitioner's alleged inconsistent positions when defending its own patents that any 3'-hydroxyl capping moiety must meet the criteria Tsien sets forth for such moieties including efficient incorporation of the dNTPs. *See* Prelim. Resp. 15–17. Patent Owner concludes:

> Despite having itself repeatedly advocated for this established framework concerning the state of the field at the relevant time, [Petitioner's] current Petition ignores the critical issue of whether a MOM-capped nucleotide would meet Tsien's and Dower's ***efficient*** incorporation requirement. This is consequential because Tsien's and Dower's efficient incorporation requirement was the primary issue litigated in the Allyl Claim IPRs, and it remains the primary issue in the ongoing appeal of those IPRs. Instead of addressing the efficient incorporation requirement in its current Petition, [Petitioner] circumvents it by mischaracterizing Tsien's criteria as requiring only "accurate incorporation."

Id. at 17.

Patent Owner overstates what we said in our previous decision in the second set of *inter partes* reviews involving these parties. In our previous decision, we noted that the claim at issue required that the R blocking group be "chemically cleavable," but did not otherwise expressly require "efficient incorporation, specific cleavage conditions, or compatibility with SBS." Ex. 1024, 40. That is also the case for claims 1 and 2 of the '458 patent. *See* Ex. 1001, 33:28–25:4. Nevertheless, because Tsien (upon which Petitioner

relies) is directed to SBS and sets forth criteria for appropriate blocking groups, we determined that "a person of skill in the art would have considered these criteria when choosing a blocking group." Ex. 1024, 40.

In analyzing how much emphasis one of skill in the art would have placed on Tsien's efficient incorporation criteria, we reviewed the knowledge and motivations of a person of skill in the art as of the critical date of October 6, 2000. *Id*. at 41–42. We concluded that:

> 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. 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. In other words, we find that a person of ordinary skill in the art would have been interested in sequencing even short DNA sequences in this time frame. 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).

Id. at 42.

We see no reason on the record before us to depart from these previous findings and similarly do not here believe on the record before us that one of skill in the art would have dismissed MOM as an acceptable 3'-hydroxyl capping moiety for less than efficient incorporation. In fact, Dr. Romesberg testifies that in view of Tsien's criteria for the successful use of 3'-blocking groups of "the ability of a polymerase enzyme to accurately and effectively incorporate the dNTPs carrying the 3'-blocking groups into the cDNA chain . . . A person of ordinary skill in the art would have had a reasonable expectation that Hiatt's 3'-O-MOM group would not interfere with recognition by the DNA polymerases employed in SBS (i.e. template-

dependent DNA polymerases), especially in view of Hovinen (Ex. 1060) and the relatedness of TdT (which was shown by Hiatt to recognize 3'-O-MOM protected nucleotides) and several template-dependent polymerases." Ex. 1038 ¶ 104. *But see* Ex. 2020 ¶¶ 60–67; Prelim. Resp. 20–23. We acknowledge that Dr. Romesberg and Dr. Johnson disagree, and invite the parties to provide further evidence and argument on this issue during the trial.

iii. Motivation to Combine Hiatt with Tsien's SBS Methods with a Reasonable Expectation of Success

Patent Owner first asserts that one of skill in the art would have had no need to venture beyond Tsien or Dower's disclosures to look for additional 3'-hydroxyl capping groups, and would not have looked to Hiatt's non-SBS methods to implement in Tsien or Dower's methods. Prelim. Resp. 23–24. Patent Owner states that "[b]eyond Hiatt having different requirements than SBS, Hiatt uses a template-***independent*** polymerase (Terminal Transferase ("TdT")), which cannot be used for sequencing, whereas SBS requires template-***dependent*** polymerases." *Id*. at 24 (citing Ex 2020 ¶¶ 39–43).

We have already resolved on this record that one of skill in the art would not have looked to just SBS references in further development of SBS methods. *See supra* Section II.e.ii.(6)b)i. We also credited, for purposes of institution, Dr. Romesberg's testimony that Hiatt's teachings were not limited to a template-independent polymerase. *See id.* Therefore, we do not agree on the record before us that one of skill in the art would have had no motivation to look to Hiatt for a small 3'-hydroxyl capping group that would meet the requirements of claims 1 and 2 of the '458 patent.

Next, Patent Owner asserts that one of skill in the art would not have been motivated to select Hiatt's MOM capping group from the many possibilities presented in Hiatt. *See* Prelim. Resp. 25–27. Specifically, Patent Owner contends that:

(1) Tsien's preferred embodiments disclose a wide range of preferred capping groups, and Tsien does not single out alkyl ether blocking groups as preferred;

(2) One of skill in the art would not have known that small capping groups were required for SBS, citing Metzker's use of the large 2-nitrobenzyl group;

(3) One of skill in the art would not have been drawn to Hiatt's 3'-O-MOM capping group because all capping groups of Hiatt were labeled as preferred; and

(4) Petitioner merely speculates without support that because Hovinen's substituted capping group was incorporated, Hiatt's unsubstituted MOM group would have been expected to be incorporated. *Id*. at 28–38.

Petitioner provides a reasonable path through the prior art, supported with the testimony of Dr. Romesberg, that one of skill in the art would have been motivated to follow with a reasonable expectation of success, based on the teachings of the art in the relevant time frame, to arrive at the inventions in claims 1 and 2 of the '458 patent. *See supra* Section II.e.ii.(4)a). Patent Owner provides reasons why one of skill in the art may not follow such a path with a reasonable expectation of success. On balance, for purposes of institution, we find that these fact issues are better resolved at trial on a fully developed record.

c) *Conclusion*

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1 and 2 of the '458 patent are unpatentable over Tsien, Prober, and Hiatt.

(5) Analysis – Obviousness over Tsien and Prober Alone

Petitioner asserts that the disclosures of Tsien and Prober alone "render the instant claims obvious, notwithstanding the allyl proviso in the instant claims, because Columbia relied upon the obvious allyl group to secure issuance of the instant, patentably indistinct claims." Pet. 64. To support this assertion, Petitioner points to Patent Owner's response to 35 U.S.C. § 112 rejections of the claims by the Examiner during the prosecution of the '458 patent, in which Patent Owner twice relied on the allyl species as one of "the two examples provided in the application" to support the definiteness of the claims and providing written description support. Pet. 65 (citing Ex. 1036, 4–6, 8–9; Ex. 1032 ¶¶ 16, 22–23). Petitioner concludes that:

> The Board should not allow [Patent Owner] to embrace obvious subject matter during prosecution to establish § 112 support while avoiding the consequences of doing so. Illumina respectfully submits that Columbia is estopped by its reliance on the unpatentable allyl species. This is particularly so because Columbia never attempted to demonstrate that the instant claims are patentable over those previously-adjudicated obvious claims.

Id. at 66.

Patent Owner responds that and obviousness analysis "turns on the obviousness of ***claimed*** subject matter, not ***unclaimed*** subject matter. . . . Here, the claims do not extend to the allyl embodiment, and thus [Petitioner's] Grounds 3 and 4, which are based on the obviousness of the

unclaimed allyl embodiment, fail." Prelim. Resp. 47 (citations omitted). Patent Owner also counters that there is nothing untoward about its reliance on the allyl species for written description support, while excluding such species from the claims. *See id*. at 48 (citing *Erfindergemeinschaft UroPep GbR v. Eli Lilly*, 276 F. Supp. 3d 629, 652 (E.D. Tex. 2017) (Bryson, J., sitting by designation)).

Although Petitioner posits that claims 1 and 2 of the '458 patent are unpatentable based on Tsien and Prober alone, Petitioner does so relying exclusively on the theory that Patent Owner is estopped from asserting that these claims are not unpatentable. Petitioner bases the claim for such estoppel on the assertion that these claims are not patentably distinct from the claims held unpatentable in the second set of *inter partes* reviews that are identical to the claims at issue here but for the removal of a single species of allyl capping group from the claimed genus. Pet. 3, 64–69.

35 U.S.C. § 311(b), which defines the scope of an *inter partes* review, states that a Petitioner "may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and *only on the basis of a prior art consisting of patents or printed publications*." 35 U.S.C. § 311(b) (emphasis added). As Patent Owner points out, Petitioner does not articulate how the combination of teachings of Tsien and Prober teach or suggest the subject matter of claims 1 and 2 of the '458 patent. *See* Pet. 64–69. On the record before us, we find Petitioner does not articulate a challenge under § 102 or § 103 on the basis of a patent or printed publication. Nor does Petitioner identify case law supporting the proposition that the Board's finding of unpatentability of a non-identical claim in a prior proceeding creates an estoppel that would excuse Petitioner from meeting this requirement

We are not convinced that Petitioner has shown a reasonable a reasonable likelihood of succeeding on this ground, and we invite the parties to provide further explanation and evidence on these issues at trial, if they so desire.

iii. *The Dower Grounds*

Petitioner asserts that claims 1 and 2 of the '458 patent are unpatentable over Dower, Prober, and Hiatt, or Dower, Prober, and Metzker. Pet. 11. Petitioner offers Dower as teaching many of the same limitations as Tsien, and offers Prober and Hiatt as teaching the same limitations of claims 1 and 2 as set forth for the Tsien Grounds. *See* Pet. 38–64. Petitioner also points to where we have determined previously that Dower does teach these limitations. *Id*.

At this stage of the proceeding, Patent Owner does not dispute the teachings of Dower, but offers the same criticism of the Dower, Prober, Hiatt combination as set forth above for the Tsien Grounds. *See supra* Section II.e.ii. For the same reasons as set forth above for the Tsien Ground involving Tsien, Prober, and Hiatt, we find that Petitioner has shown a reasonable likelihood of success in establishing that claims 1 and 2 of the '458 patent would have been obvious in light of the Dower, Prober, and Hiatt.

Petitioner offers a similar reasoning for why the combination of Dower, Prober, and Metzker would have rendered obvious claims 1 and 2 of the '458 patent as for the Tsien/Prober Ground, namely, that Patent Owner is estopped from asserting the claims 1 and 2 are not unpatentable. *See* Pet. 69. For the same reasons as set forth above, we are not convinced that Petitioner has shown a reasonable likelihood of succeeding on this ground, and we

invite the parties to explain further their positions on this ground during trial, if they so desire.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1 and 2 of the '458 patent are unpatentable. A trial will proceed on all challenged claims and grounds. *See SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1355–56 (2018); Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018), https://www.uspto.gov/patents-application-process/patent-trial-and-appealboard/trials/guidance-impact-sas-aia-trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–2 of U.S. Patent No. 10,407,458 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of U.S. Patent 10,407,458 B2 shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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