

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INTELLIGENT BIO-SYSTEMS, INC.,  
Petitioner,

v.

ILLUMINA CAMBRIDGE LTD,  
Patent Owner.

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Case IPR2013-00517  
Patent 7,566,537 B2

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Before LORA M. GREEN, FRANCISCO C. PRATS, and  
SCOTT E. KAMHOLZ, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

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

## I. INTRODUCTION

### A. *Statement of the Case*

Intelligent Bio-Systems, Inc. (“Petitioner”) filed a revised Petition (Paper 7, “Pet.”) requesting *inter partes* review of claims 1–6 and 8 of U.S. Patent No. 7,566,537 B2 (Ex. 1001, “the ’537 patent”). Illumina Cambridge Ltd (“Patent Owner”) waived the filing of a preliminary response (Paper 10). We instituted trial on the following grounds of unpatentability:

| References                               | Basis | Claims challenged |
|------------------------------------------|-------|-------------------|
| Ju, <sup>1</sup> Zavgorodny <sup>2</sup> | § 103 | 1–6, 8            |
| Tsien, <sup>3</sup> Zavgorodny           | § 103 | 1–6, 8            |
| Tsien, Zavgorodny, Prober <sup>4</sup>   | § 103 | 3                 |

Decision to Institute 15 (Paper 16, “Dec.”).

After trial was instituted, Patent Owner filed redacted and unredacted versions of its Patent Owner Response (Papers 32 and 33, “PO Resp.”), along with a Motion to Seal and proposed Protective Order (Paper 34).

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<sup>1</sup> U.S. Patent No. 6,664,079 B2 (filed Oct. 5, 2001) (Ex. 1002).

<sup>2</sup> Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry*, 32 TETRAHEDRON LETTERS 7593–96 (1991) (Ex. 1004).

<sup>3</sup> Roger Y. Tsien, WO 91/06678 A1 (published May 16, 1991) (Ex. 1008).

<sup>4</sup> James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336–41 (1987) (Ex. 1009).

Petitioner filed unredacted and redacted versions of its Reply (Papers 54 and 55, “Pet. Reply”), along with its own Motion to Seal (Paper 52).

Both parties filed Motions to Exclude Evidence. Paper 61 (“Pet. Mot. to Exclude”) and Paper 62 (“PO Mot. to Exclude”). Patent Owner’s Motion to Exclude Evidence was accompanied by an additional Motion to Seal. Paper 63.

Both parties filed Oppositions to the Motions to Exclude Evidence. Paper 68 (“Pet. Opp.”); Papers 71, 72 (“PO Opp.”). Patent Owner’s Opposition was accompanied by a Motion to Seal (Paper 70); Paper 72 is the unredacted version of Paper 71. Both parties filed Replies to the Oppositions to the Motions to Exclude Evidence. Papers 74, 75.

Patent Owner filed a Motion for Observations on Cross Examination. Paper 64 (“PO Mot. Obs.”). Petitioner filed a Response to that Motion. Paper 67 (“Resp. to Mot. Obs.”).

Petitioner supports its Petition with a Declaration by Bruce P. Branchaud, Ph.D. Ex. 1011 (“Branchaud Pet. Decl.”). Petitioner supports its Reply with a second Declaration by Dr. Branchaud (“Branchaud Reply Decl.”), and a Declaration by Michael L. Metzker, Ph.D. (“Metzker Decl.”). Ex. 1031; Ex. 1046. Patent Owner relies on Declarations by Floyd Romesberg, Ph.D. (“Romesberg Decl.”) and Kevin Burgess, Ph.D. (“Burgess Decl.”). Ex. 2011; Ex. 2089.

Oral Hearing was held on October 10, 2014, and the Hearing Transcript (“Tr.”) has been entered in the record. Paper 84.

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). We conclude that

Petitioner has not proved by a preponderance of the evidence that claims 1–6 and 8 of the '537 patent are unpatentable. Petitioner's Motion to Exclude Evidence is dismissed as moot. Patent Owner's Motion to Exclude Evidence is dismissed as moot also.

*B. Related Proceedings*

Petitioner states that the '537 patent is “the subject of the litigation captioned *The Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 1:12-cv-00376-GMS, currently pending in the United States District Court for the District of Delaware (the ‘Delaware Action’)” in which Patent Owner alleges infringement by Petitioner of the '537 patent. Pet. 3.

Also, concurrently with the Petition in this proceeding, Petitioner filed a petition requesting cancellation of claims 7 and 11–14 of the '537 patent. Pet. 3; IPR2013-00518. That proceeding was terminated upon Patent Owner's request for adverse judgment. IPR2013-00518, Papers 28 and 29.

Petitioner states that it also filed three other petitions for *inter partes* review, IPR2013-00128, IPR2013-00266, and IPR2013-00324, challenging the patentability of claims of two related patents, U.S. Patent Nos. 7,057,026 B2 and 8,158,346 B2, which also are asserted in the Delaware Action, and which “share inventors, specifications, and a priority date with the '537 Patent.” Pet. 3.

Final Judgment was entered in IPR2013-00128 on July 25, 2014, and Patent Owner appealed that decision on September 24, 2014. IPR2013-00128, Papers 92 and 95. Final Judgment was entered in IPR2013-00266 on October 28, 2014, and Patent Owner appealed that decision on November

26, 2014. IPR2013-00266, Papers 73 and 75. The Board declined to institute trial in IPR2013-00324. IPR2013-00324, Paper 19.

*C. The '537 Patent (Ex. 1001)*

The '537 patent discloses a nucleotide or nucleoside molecule “having a base that is linked to a detectable label via a cleavable linker.” Ex. 1001, 2:23–24. The labeled nucleotide or nucleoside also has a protecting group removably attached to the 2' or 3' oxygen of the molecule's deoxyribose or ribose moiety. *Id.* at 2:26–27. “The protecting group can be removed to expose a 3'-OH.” *Id.* at 2:27–28. The '537 patent describes a method of labeling nucleic acids, in which a terminal transferase, a polymerase, or a reverse transcriptase is used to incorporate a labeled nucleotide into a nucleic acid molecule. *Id.* at 2:32–38.

The '537 patent also describes nucleic acid sequencing methods that are performed by synthesizing the complementary strand of a single-stranded polynucleotide of interest, using a polymerase to incorporate the labeled nucleotides into the complementary strand. *Id.* at 2:50–53; 8:50–57. The protecting group allows the polymerase to incorporate only one nucleotide at a time into the complementary strand. *See id.* at 7:51–54. The detectable label allows identification of the particular type of nucleotide incorporated into the complementary strand. *Id.* at 2:55–57. After removing the label and protecting group, subsequent nucleotides may be added one at a time, and their identities determined in sequential fashion, thereby determining the sequence of the nucleic acid of interest. *See id.* at 2:67–3:3.

Claim 1, the only independent claim under review, is reproduced below (emphasis added):

1. A method of labeling a nucleic acid molecule, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule, wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker and the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2' or 3' oxygen atom, *and said protecting group can be modified or removed to expose a 3' OH group and the protecting group comprises an azido group.*

## II. DISCUSSION

### A. Claim Construction

Consistent with the statute and legislative history of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), the Board interprets claims in an unexpired patent using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b). Under that standard, claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

In the Decision to Institute, we construed claim 1 as encompassing the use of any protecting group attached via the 2' or 3' oxygen atom of a ribose or deoxyribose moiety, in which the protecting group can be modified or removed to expose a 3' OH group. Dec. 6–7. In doing so, we clarified that,

under the broadest reasonable construction standard, claim 1 does not require removal of the protecting group to allow subsequent nucleotide incorporation. *Id.* The parties do not dispute that claim construction and we see no reason to modify it in light of the record developed during trial.

*B. Obviousness of Claims 1–6 and 8 over Tsien and Zavgorodny*

Petitioner cites Tsien as describing a nucleic acid sequencing process substantially as required by claims 1–6 and 8, in which the nucleic acid is labeled by incorporating into the nucleic acid molecule a labeled nucleotide having a removable 3' OH protecting group. Pet. 31–37. Petitioner notes Tsien's disclosure that the protecting group may include an azido moiety. *Id.* at 34. Petitioner cites Zavgorodny to show that an azidomethyl group, encompassed by claim 1 and recited in claim 6, was known in the art to be a suitable 3' OH protecting group. *Id.* at 33–34, 36. Based on the references' teachings, Petitioner contends that an ordinary artisan, "to improve the efficiency, reliability, and robustness of the sequencing by synthesis method taught in *Tsien*, would have been motivated to use other protecting groups that meet the criteria of *Tsien*, such as the azidomethyl group taught by *Zavgorodny*." *Id.* at 38.

Petitioner contends further that, because an ordinary artisan would have recognized that Zavgorodny's azidomethyl group met Tsien's criteria for a suitable 3' OH protecting group, the artisan "would have expected to succeed in combining the teachings of *Tsien* and *Zavgorodny* to carry out a nucleic acid labeling method using a modified nucleotide having a protecting group attached via the 3' oxygen atom, wherein the protecting

group comprises an azido group, such as azidomethyl.” *Id.* at 39. Thus, Petitioner concludes, “*Tsien* combined with *Zavgorodny* renders claims 1-6 and 8 obvious under 35 U.S.C. § 103(a).” *Id.* at 40.

Patent Owner contends that an ordinary artisan would not have considered it obvious to employ *Zavgorodny*’s azidomethyl group as the 3’ hydroxyl protecting group in *Tsien*’s sequencing by synthesis (SBS) processes, because the pyridine used in removing *Zavgorodny*’s azidomethyl protecting group was known in the art to denature DNA. PO Resp. 19–20. Thus, Patent Owner argues, the conditions described by *Zavgorodny* for removing its azidomethyl group would not have been considered sufficiently mild for use in *Tsien*’s sequencing methods. *Id.* at 21–23.

Patent Owner contends also that an ordinary artisan would not have expected the azidomethyl group to meet *Tsien*’s criteria of quantitative and rapid removal from a nucleic acid molecule. *Id.* at 23–30. In particular, Patent Owner contends that an ordinary artisan would have understood *Tsien*’s requirement for quantitative removal of the 3’ OH protecting group to mean essentially 100% removal. *Id.* at 24 (citing Branchaud Deposition 98:8–16 (Ex. 2039)). In contrast, Patent Owner argues, prior art of record, including the Loubinoux<sup>5</sup> reference, demonstrates that an ordinary artisan would have expected *Zavgorodny*’s azidomethyl group to be removed at a much lower efficiency than required by *Tsien*’s methods. *Id.* at 24–29. In

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<sup>5</sup> Bernard Loubinoux et al., *Protection of Phenols by the Azidomethylene Group Application to the Synthesis of Unstable Phenols*, 44 TETRAHEDRON 6055–64 (1988) (Ex. 1006) (as translated).



sum, Patent Owner contends, Petitioner “offered no evidence that one of ordinary skill in the art would have expected Zavgorodny’s azidomethyl group to have quantitative and rapid cleavage when combined with Tsien’s methods, and the evidence of record demonstrates that no such expectation existed.” *Id.* at 30.

We agree with Patent Owner that Petitioner has not shown, by a preponderance of the evidence, that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl group as the 3’ hydroxyl protecting group in Tsien’s processes.

In *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court emphasized “an expansive and flexible approach” to the obviousness question, noting in particular that the 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.” *Id.* at 418; *see also id.* at 421 (“A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.”).

Nonetheless, the Court reaffirmed that a conclusion of obviousness requires a reasonable expectation of success:

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.

*Id.* at 421 (emphases added).

As the Court of Appeals for the Federal Circuit has explained, “[a]lthough predictability is a touchstone of obviousness, the ‘predictable result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.” *Depuy Spine, Inc v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (citations omitted).

In the instant case, Tsien describes a process of sequencing a nucleic acid in which labeled and blocked nucleotides are incorporated into a nucleic acid molecule by a polymerase. Ex. 1008, Abstract (“The method employs an unknown primed single stranded DNA sequence which is immobilized or entrapped within a chamber with a polymerase so that the sequentially formed cDNA can be monitored at each addition of a blocked nucleotide by measurement of the presence of an innocuous marker on specified deoxyribonucleotides.”). As claim 1 of the ’537 patent requires, Tsien discloses that each of its deoxyribonucleotides has a protecting group attached to the 3’ oxygen atom of the deoxyribose moiety, the protecting group being removable to expose a 3’ hydroxyl group:

The blocking group present on the 3’-hydroxyl position of the added dNTP [deoxyribonucleotide triphosphate] prevents inadvertent multiple additions. . . .

. . . .

[A] deblocking solution is added . . . to remove the 3’ hydroxyl labeled blocking group. This then generates an active

3' hydroxyl position on the first nucleotide present in the complementary chain and makes it available for coupling to the 5' position of the second nucleotide.

*Id.* at 12:27–13:22.

Tsien discloses the following regarding suitable protecting groups at the 3' hydroxyl position:

The criteria for the successful use of 3'-blocking groups include:

- (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 20:28–21:3.

As to the azido protecting group required by claim 1, as Petitioner points out (Pet. 34), Zavgorodny describes the chemical synthesis of a number of 3' hydroxyl-substituted nucleosides, among them, an azidomethyl-substituted nucleoside. *See* Ex. 1004, 7594. Zavgorodny explains that its substituted nucleosides “are useful specifically blocked synthons . . . . Azidomethyl group is of special interest, since it can be removed under very specific and mild conditions, *viz.* with triphenylphosphine in aqueous pyridine at 20 °C.” *Id.* at 7595.

In urging that claims 1–6 and 8 would have been obvious over the combination of Tsien and Zavgorodny, Petitioner pointed to Zavgorodny's teaching that its azidomethyl moiety was a suitable protecting group for the

3' hydroxyl position of nucleosides, precisely the position requiring protection in Tsien's process, as well Zavgorodny's disclosure that the azidomethyl group was cleavable from the nucleoside under specific and mild conditions, thus meeting another requirement of Tsien's protecting group. Pet. 38–39.

As Patent Owner points out, however, Tsien's second set of criteria for removal of the 3' hydroxyl protecting group includes "quantitative deblocking," in addition to mild conditions. Ex. 1008, 20:34; PO Resp. 24. As Patent Owner contends (PO Resp. 30), the Petition does not point to any specific evidence explaining why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet that requirement (*see* Pet. 31–40), despite acknowledging the "quantitative deblocking" requirement of Tsien's methods (*id.* at 37).

As Patent Owner contends (PO Resp. 24), Petitioner's expert, Dr. Branchaud, testified that quantitative deblocking would have been understood to mean essentially 100% removal of the protecting group:

Q. And could you explain to me what does it mean that the use of a three prime blocking group must include criteria 2 that would be availability of mild conditions for rapid and quantitative deblocking? . . .

A. Well, again, I think that's an operational definition. It's just saying that in order for the process to happen effectively or efficiently, that deblocking step has to be rapid and -- and efficient.

Q. Is efficient analogous to quantitative?

A. Not necessarily. I think it could be. Rapid means it goes fast. *Quantitative means it goes in high, essentially hundred percent yield.*

Ex. 2039, 97–98 (Branchaud Deposition, emphasis added). In contrast, as Patent Owner points out, Loubinoux discloses that removal of an azidomethyl protecting group from a phenolic hydroxyl using triphenylphosphine, followed by water in tetrahydrofuran at 25 °C, resulted in deprotected phenols “as pure products at a yield between 60 and 80%.”

Ex. 1006, 5; PO Resp. 24.

Patent Owner also advances evidence that an ordinary artisan would have expected an azidomethyl group to be removed from a simple aliphatic alcohol, such as that present at the 3' hydroxyl of a deoxyribonucleotide, at a lower efficiency than that described in Loubinoux, because a phenol is a better leaving group. See PO Resp. 24–25 (citing Ex. 2026 (“Greene and Wuts”<sup>6</sup>), 248 (“Ethers are the most widely used protective groups for phenols, and in general, they are more easily cleaved than the analogous ethers of simple alcohols.”)). Petitioner acknowledges that Greene and Wuts “is widely recognized by those of skill in the art as the definitive guide to techniques for the formation and cleavage of protecting groups in organic synthesis.” Pet. 13.

In sum, despite having acknowledged the quantitative deblocking requirement in Tsien (Pet. 37), the Petition did not provide a specific or credible explanation why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative

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<sup>6</sup> THEODORA W. GREENE & PETER G.M. WUTS, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 246–92 (John Wiley & Sons, Inc., 3d ed. 1999) (Ex. 2026).

deblocking requirement under conditions suitable for use in Tsien's sequencing methods. As discussed above, moreover, the prior art suggests that an ordinary artisan would not have expected Zavgorodny's azidomethyl group to be removed quantitatively, as Tsien requires. We, therefore, agree with Patent Owner that Petitioner has not shown that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl protecting group in Tsien's sequencing methods.

Petitioner does not persuade us to the contrary. In particular, we find that Petitioner's Reply exceeds the proper scope of a reply. As provided in 37 C.F.R. § 42.23(b), a "reply may only respond to arguments raised in the corresponding opposition or patent owner response." Thus, "a reply that raises a new issue or belatedly presents evidence will not be considered and may be returned. The Board will not attempt to sort proper from improper portions of the reply." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012). One indication that a new issue has been raised in a reply is where a petitioner submits "new evidence necessary to make out a *prima facie* case" of unpatentability of an original claim. *Id.*

As noted above, in urging obviousness based on Tsien and Zavgorodny, the Petition relies expressly on the fact that "*Zavgorodny* teaches the desired property [in Tsien] that the azidomethyl group 'can be removed under very specific and mild conditions.'" Pet. 38–39 (quoting Ex. 1004, 7595 (*Zavgorodny*)). The Reply, presented with evidence that an ordinary artisan would not have considered Zavgorodny's conditions suitably mild for Tsien's sequencing purposes, offers a distinct new line of

reasoning—that an ordinary artisan would have considered it obvious to use deprotecting conditions *other* than those described in Zavgorodny:

[Patent Owner]’s argument is based on the faulty assumption that a POSITA would be limited to the specific removal conditions discussed in Zavgorodny. . . . A POSITA would use ordinary creativity *to modify* the removal conditions suggested by Zavgorodny to meet the requirements of Ju and Tsien, if needed.

Reply 4–5 (quotations removed, citations omitted, emphasis added). Thus, the Reply presents new issues by changing the unpatentability rationale from express reliance on Zavgorodny’s deprotecting conditions, to asserting that those conditions would have been obvious to modify, as well as presenting new evidence to support the new rationale and explain the modifications to Zavgorodny. *See id.* at 5–6 (citing Ex. 1031 (Branchaud Reply Decl.)).

Moreover, despite having acknowledged the quantitative deblocking requirement in Tsien (Pet. 37), the Reply does not indicate where, in the Petition, Petitioner explained specifically why an ordinary artisan would have expected Zavgorodny’s azidomethyl moiety to meet Tsien’s quantitative deblocking requirement for the 3’ hydroxyl protecting group. On that issue, the Reply advances, instead, a number of arguments which were not presented previously, as well as Dr. Branchaud’s Reply Declaration. Reply 7–8 (citing Ex. 1031). In his Reply Declaration, Dr. Branchaud, in turn, expands on the assertions in the Reply by presenting a number of additional new arguments explaining why quantitative deblocking would have been expected, and cites a number of non-patent literature references which were not relied upon to support unpatentability in the

Petition. *See* Ex. 1031 ¶¶ 19–26. Because the Petition did not address Tsien’s quantitative deblocking requirement, and because the Reply proffers argument and evidence not presented previously on that issue, the Reply presents new issues, rather than merely rebutting the Patent Owner Response.

In addition, in asserting that quantitative deblocking would have been expected using Zavgorodny’s conditions, the Reply relies extensively on in-depth explanations and supporting documentary evidence presented in Dr. Branchaud’s Reply Declaration. The Reply does not explain, however, the basis of its arguments with nearly the same degree of specificity as that presented in Dr. Branchaud’s Reply Declaration, nor does the Reply cite any of the exhibits advanced in Dr. Branchaud’s Declaration. *See* Reply 7–8. For example the Reply states that, “[f]or SBS, a POSITA would use a much higher concentration of cleavage reagent to drive the reaction rapidly to completion.” *Id.* at 8 (citing Ex 1031 ¶¶ 25–26). None of the extensive reasoning or analysis or evidence cited in paragraphs 25 and 26 of the Branchaud Reply Declaration appears in the Reply, however. Accordingly, the Reply also does not comply with 37 C.F.R. § 42.6(a)(3), which states that “[a]rguments must not be incorporated by reference from one document into another document.”

Further, even if we were to overlook the procedural infirmities in Petitioner’s Reply arguments, we would not find them persuasive. Petitioner advances evidence that Loubinoux’s pure product yields of 60 to 80 percent (Ex. 1006, 5) would have been viewed as a “poor proxy for actual reaction efficiency” (Reply 7). The fact that pure product yields might be a poor



indicator of actual reaction efficiency does not substitute, however, for evidence showing that an ordinary artisan would have expected Zavgorodny's azidomethyl group to be removed quantitatively under conditions suitable for performing Tsien's sequencing processes. Moreover, while Petitioner cites to Exhibits 1038 and 1041 as evidence that an ordinary artisan would have expected a quantitative yield using Zavgorodny's deblocking conditions (Reply 8; Ex. 1031 ¶ 21; Resp. to Mot. Obs. 7), Petitioner does not explain why an ordinary artisan would have expected the deprotection conditions in those references to be suitable for use in the sequencing processes taught in Tsien, even if the concentration of cleavage reagent was increased significantly. As to the new patentability rationale advanced in the Reply, that an ordinary artisan would have used reagents different from those taught in Zavgorodny (Reply 5–6), Petitioner fails to explain with adequate specificity why an ordinary artisan would have considered TCEP (tris(2-carboxyethyl)-phosphine) an obviously equivalent removal reagent to that described in Zavgorodny. Moreover, the sole reference cited by Petitioner to show that TCEP would have been expected to provide the quantitative removal required by Tsien has a publication date after the August 23, 2002 effective filing date of the '537 patent. *Compare* Ex. 1036<sup>7</sup> (cited in Ex. 1031 ¶ 18 (Branchaud Reply Decl.)), *with* Ex. 1001, front page ('537 patent). Lastly, as to Petitioner's argument that an ordinary

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<sup>7</sup> Anne-Marie Faucher et al., *tris(2-Carboxyethyl)phosphine (TCEP) for the Reduction of Sulfoxides, Sulfonylchlorides, N-Oxides, and Azides*, 33 SYNTHETIC COMMUNICATIONS 3503–11 (2003).

artisan would have been prompted to combine Tsien and Zavgorodny for reasons other than performing Tsien's sequencing processes (Reply 8–9), Petitioner does not direct us to any specific non-sequencing-related teachings in those references that would have prompted the references' combination, nor does Petitioner explain, specifically, where that rationale for combining the references was advanced in the Petition.

In sum, for the reasons discussed, we determine that Petitioner has not shown that a preponderance of the evidence supports a conclusion that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl protecting group in the processes described in Tsien. Accordingly, we conclude that Petitioner has not established by a preponderance of the evidence that the processes recited in claims 1–6 and 8 of the '537 patent would have been obvious under § 103(a), over Tsien and Zavgorodny.

*C. Obviousness of Claims 1–6 and 8 over Ju and Zavgorodny*

Petitioner's obviousness challenge based on Ju and Zavgorodny is very similar to the ground of unpatentability based on Tsien and Zavgorodny, discussed above. Petitioner cites Ju as describing nucleic acid sequencing methods in which the nucleic acid is labeled by incorporating into the nucleic acid molecule a labeled nucleotide having a removable 3' hydroxyl protecting group, substantially as required by claims 1–6 and 8. Pet. 18–23. As above, Petitioner cites Zavgorodny as evidence that an ordinary artisan would have considered it obvious to use an azidomethyl group as the 3' hydroxyl protecting group in Ju's process, noting in

particular that the mild removal conditions described in Zavgorodny would have met one of Ju's criteria for 3' hydroxyl protecting groups. *Id.* at 24–26.

Patent Owner responds to this ground of unpatentability with arguments similar to those discussed above. Specifically, Patent Owner contends that an ordinary artisan would have understood Ju's sequencing methods to require nearly quantitative removal of the 3' hydroxyl protecting group under conditions in which the template and complement were not denatured. PO Resp. 38, 40. In contrast, Patent Owner contends, an ordinary artisan would not have expected Zavgorodny's method to remove azidomethyl groups to a degree sufficient for use in Ju's methods. *Id.* at 39. Moreover, Patent Owner argues, Zavgorodny's method would have been expected to denature the DNA being analyzed, because it uses pyridine. *Id.* at 40.

We find that the preponderance of the evidence does not support a conclusion that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl protecting group in Ju's sequencing methods.

Ju describes a process of labeling, and ultimately sequencing, a nucleic acid molecule, in which a polymerase is used to “incorporate a nucleotide analogue into the growing strand of DNA, wherein the incorporated nucleotide analogue terminates the polymerase reaction.” Ex. 1002, 4:31–35. As claim 1 of the '537 patent requires, Ju discloses that its nucleotide analogues have “a unique label attached through a cleavable linker to the base or to an analogue of the base.” *Id.* at 4:39–41. As claim 1 of the '537 patent also requires, Ju further discloses that its nucleotide

analogues have “a cleavable chemical group to cap an –OH group at a 3′-position of the deoxyribose.” *Id.* at 4:41–42.

Regarding the cleavable chemical group capping the 3′ hydroxyl of its nucleotide analogues, Ju discloses that “[a]ny chemical group could be used as long as the group 1) is stable during the polymerase reaction, 2) does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate, and 3) is cleavable,” as Petitioner contends. *Id.* at 10:4–7; Pet. 24.

As Patent Owner argues (PO Resp. 38), however, and Petitioner acknowledges (Pet. 21), Ju also teaches that the “group capping the 3′–OH need[s] to be removed *with high yield* to allow the incorporation and detection of the next nucleotide.” Ex. 1002, 21:11–13 (emphasis added). Evidence of record supports Patent Owner’s assertions (PO Resp. 38–39) that an ordinary artisan would have understood Ju’s sequencing processes to require nearly quantitative removal of the 3′ hydroxyl group. As Patent Owner argues (*id.* at 38), Ju describes using its methods to perform 100 sequencing cycles (Ex. 1002, 21:63–67) and disparagingly notes, in contrast, that pyrosequencing can only sequence up to 30 base pairs (*id.* at 2:20–21). Tsien’s teaching that even 98% protecting group removal efficiency can result in significant error rates after only 30 base additions (Ex. 1008, 16:21–30), supports Patent Owner’s assertion, and the underlying testimony of Dr. Romesberg, that sequencing 100 bases requires at least 98.5% efficiency. PO Resp. 38–39 (citing Ex. 2011 ¶ 33 (Romesberg Decl.)). In its Reply, Petitioner does not dispute specifically that an ordinary artisan would have understood Ju’s sequencing processes to require nearly quantitative removal

of the 3' hydroxyl group, nor does the Reply direct us to error in Patent Owner's analysis in that regard.

As discussed above, evidence of record also supports Patent Owner's assertions that an ordinary artisan would not have expected Zavgorodny's azidomethyl group to be removed quantitatively as required by Ju's sequencing methods. Specifically, Loubinoux describes only a 60–80% removal efficiency of azidomethyl groups from phenols, and Greene and Wuts suggests that removal from simple aliphatic alcohols, such as that present at the 3' position of nucleotides, would be less efficient, because phenol is a better leaving group. Ex. 1006, 5 (Loubinoux); Ex. 2026, 248 (Greene and Wuts). Moreover, despite acknowledging Ju's requirement for removal of the 3' hydroxyl protecting group with "high yield" (Pet. 21), the Petition does not explain with specificity why an ordinary artisan would have expected Zavgorodny's azidomethyl group to meet that requirement.

Accordingly, we agree with Patent Owner that Petitioner has not shown that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl protecting group in Ju's sequencing methods. In its Reply, Petitioner presents its rebuttal arguments relating to the combination of Ju and Zavgorodny in tandem with the arguments discussed above as to the combination of Tsien and Zavgorodny. For the reasons discussed above, we do not find Petitioner's arguments persuasive.

In sum, for the reasons discussed, we determine that Petitioner has not shown that a preponderance of the evidence supports a conclusion that an ordinary artisan would have considered it obvious to use Zavgorodny's azidomethyl protecting group in the processes described in Ju. Accordingly,

we conclude that Petitioner has not established by a preponderance of the evidence that the processes recited in claims 1–6 and 8 of the '537 patent would have been obvious under § 103(a), over Ju and Zavgorodny.

*D. Obviousness of Claim 3 over Tsien, Zavgorodny, and Prober*

Claim 3 of the '537 patent recites “[t]he method of claim 1, wherein the base is a deazapurine.” Ex. 1001, 19:64-65. Petitioner contends that, even if Tsien is not viewed as incorporating Prober’s disclosure of deazapurine bases by reference, a process using the deazapurine recited in claim 3 would nonetheless have been obvious in view of the combined teachings of Tsien, Zavgorodny, and Prober, “because *Tsien* expressly teaches using the label attachment methods of *Prober*.” Pet. 45. Petitioner, thus, does not rely on the teachings of Prober in a manner that remedies the shortcomings, discussed above, in the combination of Tsien and Zavgorodny. Accordingly, we conclude that Petitioner has not shown by a preponderance of the evidence that claim 3 of the '537 patent would have been obvious over the combination of Tsien, Zavgorodny, and Prober.

*E. Motions to Exclude Evidence*

*1. Petitioner’s Motion to Exclude*

Petitioner moves to exclude Exhibits 2003, 2006–2009, 2027, 2028, 2045, 2050, 2055, 2057, 2059, 2062, 2075, 2076, 2087, 2089 (Burgess Decl.), and 2139–2152, as well as Exhibits 2058, 2060, and 2091–2121, cited in the Burgess Declaration. Pet. Mot. to Exclude 1. Because our decision does not rely on any of the challenged exhibits, we dismiss Petitioner’s Motion to Exclude Evidence as moot.

*2. Patent Owner's Motion to Exclude*

Patent Owner moves to exclude Exhibits 1018, 1019, 1024, 1031 (¶¶ 9–11, 14–18, 19–26, 37, and 38 (Branchaud Reply Decl.)), 1033–1040, 1043–1045, 1046 (¶¶ 26–31, 33–43, and 45–47 (Metzker Decl.)), 1047, 1049, and 1050 and all arguments based thereon. PO Mot. to Exclude 1.

With the exception of Exhibits 1019 and 1024, each of the exhibits Patent Owner seeks to exclude were presented in support of Petitioner's Reply, which, as discussed above, exceeds the proper scope of a reply under 37 C.F.R. § 42.23(b), and also improperly incorporates arguments and supporting evidence by reference under 37 C.F.R. § 42.6(a)(3).

Accordingly, we dismiss as moot Patent Owner's Motion to Exclude Evidence as to Exhibits 1018, 1031, 1033–1040, 1043–1047, 1049, and 1050.

As to Exhibit 1019, a non-patent literature reference, Petitioner states that it was used to impeach Dr. Romesberg's testimony. Pet. Opp. 4. Petitioner does not explain, however, where the record supports that assertion, or where Petitioner cited Exhibit 1019 in an argument impeaching Dr. Romesberg's testimony. Accordingly, because we do not rely on Exhibit 1019 in evaluating the parties' positions, we dismiss Patent Owner's Motion to Exclude Exhibit 1019 as moot.

As to Exhibit 1024, Petitioner states that it was used to impeach Dr. Burgess's testimony. Pet. Opp. 4. As noted above, however, our decision on the merits does not rely on the testimony of Dr. Burgess. Accordingly, as to Exhibit 1024, we dismiss Patent Owner's Motion to Exclude as moot.

### III. CONCLUSION

For the reasons given, we are not persuaded that Petitioner has shown by a preponderance of the evidence that claims 1–6 and 8 of the '537 patent are unpatentable based on the challenges on which trial was instituted.

### IV. ORDER

It is ORDERED that claims 1–6 and 8 of the '537 patent have not been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is dismissed as moot;

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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IPR2013-00517  
Patent 7,566,537 B2

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