UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLETE GENOMICS, INC.
Petitioner

v.

ILLUMINA CAMBRIDGE LTD.
Patent Owner

Case IPR2017-02172
Patent 7,566,537 B2

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,566,537 B2

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I. INTRODUCTION

Petitioner requests *inter partes* review of claims 1-6, and 8 of U.S. Patent No. 7,566,537 B2 ("'537," Ex. 1001) as obvious under 35 U.S.C. § 103. The '537 patent claims a method for labeling nucleic acid molecules where the label is attached to the base via a cleavable linker, and the 3′-OH of the sugar moiety is reversibly blocked with a protecting group comprising an azido group, such as azidomethyl. Based on prior proceedings, there can be no dispute that all of the limitations of the challenged independent claim are present in a single reference (Tsien, Ex. 1003), except for the azido protecting group, which was disclosed in multiple other references—including Zavgorodny (Ex. 1008), Loubinoux (Ex. 1006), and Young (Ex. 1051)—and would have been obvious to a person of ordinary skill in the art ("POSITA"). Indeed, the '537 patent itself admits that suitable protecting groups would be apparent to a POSITA, that such groups could be formed from any suitable group described in the go-to reference of Greene & Wuts (Ex. 1005), and that the conditions for attaching and removing such groups were within the knowledge of a POSITA. Ex. 1001, 7:57-8:4.

The '537 patent was previously challenged by another party in two IPRs. One resulted in cancellation of claims 7 and 11-14 in response to Illumina's request for adverse judgment. Exs. 1088 & 1089 (IPR2013-00518). The other petition was instituted on the basis of Tsien or Ju (Ex. 1038) in combination with Zavgorodny, but the combination of Tsien or Ju in combination with Greene & Wuts was denied

on the basis of redundancy. Ex. 1091, 5, 15 (IPR2013-00517). In the Final Written Decision, the Board found that Tsien in combination with Zavgorodny disclosed each element of the claims, but that the petitioner nevertheless failed to meet its burden to establish obviousness. Ex. 1094, 7, 18, 21-22. On review, the Federal Circuit noted that the "Board's precise legal underpinnings are difficult to discern," and that the Board's decision was improper to the extent it was based on an absence of a reasonable expectation of success. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1365-67 (Fed. Cir. 2016). The Federal Circuit affirmed the Board's judgment on the basis that "the petitioner's ***sole*** argument for why one of skill in the art would be motivated to combine Zavgorodny's azidomethyl group with Tsien's [sequencing-by-synthesis ("SBS")] method was because it would meet Tsien's quantitative deblocking requirement" and that the Board had not abused its discretion in refusing to consider new arguments raised in IBS's Reply brief and evidence filed therewith. *Id.*, 1368-70. Because many critical "motivation to combine"-related issues were not adequately addressed in the Petition, and were then belatedly — and still inadequately — addressed in the Reply and supporting declarations, the Board's decision and the Federal Circuit's affirmance were based on an incomplete and factually flawed record presented by the prior petitioner. *See id.*; Ex. 1094, 14-19.

Nevertheless, the prior IPRs and Federal Circuit decisions demonstrate several key facts. First, all of the limitations of claims 1-6 and 8 of the '537 patent are disclosed in Tsien or Tsien in combination with Prober, except the azido and

azidomethyl protecting groups (821 F.3d at 1363-64; Ex. 1094, 22; Ex. 1091, 12), which is disclosed by Zavgorodny and Greene & Wuts. 821 F.3d at 1364-65, 1368. Second, none of the challenged claims require removal of the protecting group (*i.e.*, deblocking), much less quantitative deblocking. *Id.*, 1367. Finally, the Federal Circuit determined that a POSITA would have had a reasonable expectation of success in combining the teachings of Tsien with the azidomethyl protecting group of Zavgorodny to arrive at the challenged claims. *Id.*

This petition focuses on explaining that Tsien's reference to "quantitative deblocking" would not have deterred a POSITA from combining an azidomethyl protecting group with Tsien's SBS-related teachings. In particular, the POSITA would have understood that, while high efficiency of the deblocking reactions is desirable (*i.e.*, a high percentage of blocking groups are removed to reveal a 3′-OH), Tsien itself teaches that the methods described therein will work at less than 100% efficiency. Moreover, the reported ***yields*** following synthesis and purification in the blocking group art were positive indicators to a POSITA that — when used with conditions known to be appropriate for SBS — the azidomethyl protecting group would be cleaved with high efficiency. In addition, a POSITA would have appreciated that use of Tsien's methods with an azidomethyl protecting group as claimed in the '537 patent would be useful for applications where quantitative deblocking was not required, such as the detection of polymorphisms. *See* Ex. 1001, 2:7-9; Ex. 1101, ¶¶88-89. Thus, a POSITA would have had ample motivation to combine Tsien with the azidomethyl group disclosed in Zavgorodny and Greene &

Wuts.

This Petition provides new arguments, testimony, and secondary references demonstrating why it would have been obvious to a POSITA to combine an azidomethyl protecting group with Tsien's methods. This Petition and the Declaration of Dr. Sutherland also correct several scientific inaccuracies that appear to have had a material impact on the outcome of the prior proceeding. *See* Part IX.D, *infra*; Ex. 1101. For these reasons, Petitioner respectfully requests *inter partes* review and cancellation of the challenged claims.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

In accordance with 37 C.F.R. §42.8(b)(1), Petitioner Complete Genomics, Inc. ("CGI") identifies itself and the following entities as real parties-in-interest: BGI Shenzhen Co., Ltd.; BGI Groups USA Inc.; BGI Genomics Co., Ltd.; and BGI Americas Corporation.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is concurrently filing IPR2017-02174, which challenges the '537 patent on different grounds than asserted herein or in the prior proceeding.

Prior proceedings between Illumina and other parties may also affect this proceeding because they involved the challenged patent or patents with similar disclosures and/or claims. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) (appeal from IPR2013-00517); *Ilumina Cambridge Ltd. v. Intelligent Bio-Systems, Inc.*, 638 Fed.Appx. 999 (Fed. Cir. 2016)

(unpublished) (appeals from IPR2013-00128 and IPR2013-00266); *Trustees of Columbia University v. Illumina, Inc.*, 620 Fed.Appx. 916 (Fed. Cir. 2015) (unpublished) (appeals from IPR2012-00006, IPR2012-00007, and IPR2013-00011); *The Trustees of Columbia University v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.) ("Delaware Litigation"); *Illumina, Inc. et al. v. Qiagen, NV et al.*, 3-16-cv-02788 (N.D. Cal.); IPR2013-00128; IPR2013-00324; IPR2013-00266; IPR2013-00517; IPR2013-00518; IPR2012-00006; IPR2012-00007; IPR2013-00011. *See also* Ex. 1086 (summary chart).

In the Delaware Litigation, in 2012, Illumina and Intelligent Bio-Systems, Inc. ("IBS") each asserted that the other was infringing their respective SBS-related patents. Illumina asserted the '537 patent and two other related patents against IBS. In addition, The Trustees of Columbia University ("Columbia"), from whom IBS had licensed its SBS patents, asserted that Illumina was infringing five patents owned by Columbia and licensed to IBS (the "Ju patents"). The Ju patents have an earlier priority date than Illumina's and address the same subject matter — the use of reversibly terminated and labeled nucleotides in DNA sequencing reactions such as SBS. The Delaware Litigation was stayed while the parties filed IPRs against each other, challenging 60 claims of 6 patents in 8 IPRs (listed above). As of the date of the filing of this petition, all of those IPRs and appeals thereof are concluded. All challenged claims in 7 of the 8 IPRs were either cancelled by Illumina or by the PTAB, but as described below, certain claims of the '537 patent survived.

IBS challenged the '537 patent in two IPRs (IPR2013-00517 and -00518). In IPR2013-00518, claims 7 and 11-14 were cancelled in response to Illumina's request for adverse judgment. Exs. 1088 & 1089.

In IPR2013-00517, the Board found that all elements of claims 1-6 and 8 were disclosed by both Tsien and Ju, each in combination with the azidomethyl protecting group of Zavgorodny, and for claim 3, the claimed deazapurine base was further disclosed in Prober. Ex. 1094, 10-11, 18. However, because Petitioner's sole asserted motivation to combine was "to improve the efficiency, reliability, and robustness" of Tsien or Ju's SBS methods, the Board was persuaded by Illumina's counterarguments that, due to the reaction conditions and yields disclosed in Zavgorodny and Loubinoux, a POSITA would have been deterred from combining Tsien or Ju's SBS method with Zavgorodny's azidomethyl protecting group due to purported concerns that Tsien's "quantitative deblocking" requirement would not be met and that the reaction conditions could denature DNA. Ex. 1094, 12-14. While IBS attempted to address Illumina's arguments in its Reply, the Board found that IBS's arguments were improper because they were not presented in the Petition and that the Reply improperly incorporated by reference arguments from a supplemental expert declaration and evidence cited therein.

On appeal, the Federal Circuit implicitly agreed that the prior art taught all of the claim elements, finding that, to the extent the Board based its decision on a lack of reasonable expectation of success, the decision was erroneous. 821 F.3d at 1367. However, the Federal Circuit also found that the Board did not abuse its discretion

in refusing to consider IBS's arguments and evidence made in its Reply. Without considering the Reply's argument or evidence, the Federal Circuit affirmed the Board's decision that IBS had failed to establish that a POSITA would have been motivated to combine Zavgorodny's azidomethyl protecting group with Tsien or Ju's SBS methods "in order to improve the efficiency, reliability, and robustness" of those methods, and that was the only motivation that IBS had provided in the Petition. 821 F.3d at 1367-70 (citing Petition, Ex. 1090, 24, 42).

C. Lead and Back-up Counsel (37 C.F.R. §42.8(b)(3)-(4))

Petitioner designates the following Lead and Back-up Counsel:

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A concurrently filed power of attorney identifies the practitioners of Arnold & Porter Kaye Scholer LLP, including Jennifer A. Sklenar, Michael J. Malecek, and Katie J.L. Scott as attorneys of record.

D. Service Information (37 C.F.R. §42.8(b)(4))

Petitioner may be served by mail or hand-delivery at the service addresses found in Part C, *supra*, with courtesy copies sent to the following email addresses:

Jennifer.Sklenar@apks.com, Michael.Malecek@apks.com. Katie.Scott@apks.com. Petitioner hereby consents to electronic service at these email addresses.

III. REQUIREMENTS FOR INTER PARTES REVIEW

A. Payment of Fees (37 C.F.R. §42.103)

The required fees are submitted herewith. If any additional fees are due at any time, the Office is authorized to charge such fees to Deposit Account No. 502387.

B. Grounds for Standing (37 C.F.R. §42.104(a))

Petitioner certifies pursuant to 37 C.F.R. §42.104(a) that the patent for which review is sought is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review.

C. Identification of Challenge and Precise Relief Requested (37 C.F.R. §42.104(b)(1)-(2))

Petitioner requests *inter partes* review and cancellation of Claims 1-6 and 8 as obvious under 35 U.S.C. §103(a), on the following grounds:

Ground 1: Claims 1-2, 4-6, and 8 are obvious over Roger Y. Tsien et al., WO 91/06678 A1 (published May 16, 1991) ("Tsien"), Ex. 1003, in combination with PROTECTIVE GROUPS IN ORGANIC SYNTHESIS (Theodora W. Greene & Peter G.M. Wuts eds., 3rd ed. 1999) ("Greene & Wuts"), Ex. 1005, and Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications*, TETRAHEDRON LETTERS 32:7593-96 (1991) ("Zavgorodny"), Ex. 1008.

Ground 2: Claim 3 is obvious over Tsien, Ex. 1003, in combination with

Greene & Wuts, Ex. 1005, and Zavgorodny, Ex. 1008, in further combination with James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, SCIENCE 238:336-41 (1987) ("Prober"), Ex. 1007.

IV. THE '537 PATENT AND PRIOR PROCEEDINGS

A. The '537 Patent

The '537 patent, titled "Labelled Nucleotides," was filed as a divisional of application No. 10/227,131, which was filed on August 23, 2002. Ex. 1001. The '537 patent claims priority to an earlier foreign application (GB0129012.1), but the challenged claims are not entitled to an earlier priority date because the recited azido or azidomethyl protecting groups were not disclosed. Ex. 1002, 5 (GB0129012.1); Ex. 1092, 4 (conceding August 2002 priority date).

Claims 1 and 6 are of primary significance to this petition. Claim 1 recites:

> 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***.

Ex. 1001, 19:49-59 (emphasis added). Dependent claim 6 recites "[t]he method according to claim 1, wherein the protecting group is CH_2N_3," *i.e.*, an "azidomethyl" group. *Id.*, 20:3-4. Illumina has conceded that each of the limitations were previously disclosed in Tsien with the exception of the use of an azido or azidomethyl protecting group. Ex. 1094, 7-18; 821 F.3d at 1363-65.

The words "azido" and "azidomethyl" do not appear in the '537 specification. Such protecting groups are only disclosed in Figure 3 as one of 20 different substituted protecting groups (annotated version below), where R_1 and R_2, are "each selected from H, OH, or any group than can be transformed into an OH, including a carbonyl." Ex.1001, Fig.3.

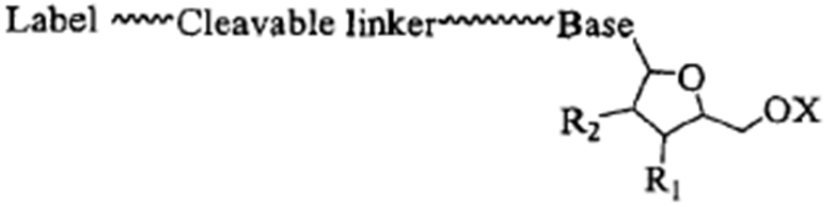
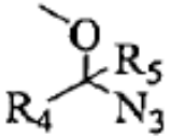


Figure 3 further states that R_1 and R_2 groups may include the following group,



which is azidomethyl when R_4 and R_5 are both hydrogen. *Id.*

The '537 patent does not identify any benefit of using an azido protecting group; does not mention any difficulty selecting conditions for incorporating an azido group with a polymerase or removing it to reveal a 3′-OH; and does not describe any unexpected results arising from the use of an azido-containing

protecting group. In fact, the only place where "azido" or "CH_2N_3" (azidomethyl) appears in the '537 patent is in the limitations of the claims, which were added in amendments submitted August 16, 2007— nearly 5 years after the patent's earliest claimed priority date. Ex. 1002, 103.

The lack of detail regarding the azido protecting group is not surprising given that the alleged point of novelty described in the specification was that "[i]n the present invention, a nucleoside or nucleotide molecule is linked to a detectable label *via a cleavable linker group attached to the base*[.]" Ex. 1001, 2:3-5 (emphasis added). The specification emphasized that "[t]he molecules of the present invention are in contrast to the prior art, where the label is attached to the ribose or deoxyribose sugar, or where the label is attached via a non-cleavable linker." *Id.*, 2:15-18, 7:54-57.

In contrast to this detailed discussion of the linker for the label, the '537 specification describes the selection of a protecting group and the conditions for deblocking as known within the art. *See id*., 7:57-67 ("The skilled person will appreciate how to attach a suitable protecting group to the ribose ring to block interactions with the 3′-OH…. Suitable protecting groups will be apparent to the skilled person, and can be formed from ***any suitable protecting group disclosed in Greene and Wuts***, supra." (emphasis added)), 9:49-10:3, 8:59-9:10; *see also* Part VI, *infra*.

Finally, the claimed method recited in claim 1 only requires a single step of "incorporating" the reversibly blocked, labelled nucleotide or nucleoside "into the

nucleic acid molecule." *Id.*, 19:49-50. Claim 1 does not require removal of the protecting group; it only requires that "said protecting group *can be* modified or removed to expose a 3′ OH group." *Id.*, 19:57-58 (emphasis added). Thus, while the claimed labeling method could certainly be used for SBS, claim 1 requires no more than a single incorporation step. Ex. 1094, 7; 821 F.3d at 1367. With only one or a few incorporated labeled nucleotides, the method of claims 1-6 and 8 could also be useful to detect polymorphisms, such as Single Nucleotide Polymorphisms (SNPs), small-scale insertions/deletions (INDELs), and multi-nucleotide mutations. Ex. 1101, ¶¶88-89. Indeed, the '537 patent itself teaches that the disclosed method is useful where only a single incorporation event occurs, and only a single round of incorporation is required by the challenged claims. *See, e.g.*, Ex. 1001, 2:7-9.

B. Impact of Prior Proceedings Regarding the '537 Patent

The '537 patent was previously challenged by IBS in two petitions. IPR2013-00517 and -00518. In IPR2013-00518, claims 7 and 11-14 were cancelled in response to Illumina's request for adverse judgment. Exs. 1088 & 1089. Therefore, Illumina is "precluded from taking any action inconsistent with the adverse judgment…." 37 C.F.R. §42.73(d)(3). Cancelled claim 7 has the same limitations of claim 1, except that where claim 1 recites that "the protecting group comprises an azido group," claim 7 recites "the protecting group and cleavable linker are removable under identical conditions." Additionally, the limitations of cancelled dependent claims 11-14 (which depend from claim 7) are identical to challenged dependent claims 2-5 (which depend from claim 1). Thus, Illumina's concession

that claims 7 and 11-14 are not patentable should preclude Illumina from advancing any patentability argument that is not related to the azido or azidomethyl limitations of claims 1 or 6. *See id*.

Due to the findings in IPR2013-00517 and the Federal Circuit decision thereon, Illumina cannot reasonably contest the following facts:

(1) all of the limitations of claims 1-2, 4-6 and 8[1] of the '537 patent are disclosed in Tsien except the azido and azidomethyl protecting groups (821 F.3d at 1363-64);

(2) Zavgorodny discloses an azidomethyl protecting group for the 3′-OH of nucleosides (*id.*,1364-65);

(3) Greene & Wuts discloses an azidomethyl protecting group (*id.*, 1368);

(4) a POSITA would have had a reasonable expectation of success in combining the teachings of Tsien with the azidomethyl protecting group of Zavgorodny 1991 to arrive at the challenged claims (*id.*, 1367); and

(5) none of the challenged claims require removal of the protecting group (*i.e.*, deblocking), much less quantitative deblocking. *Id.*, 1367.

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[1] Claim 3 further recites a deazapurine base, which the Board found was disclosed by Prober (Ex. 1091, 12; *see also* Part IX.F *infra*), and which Illumina itself has previously asserted was both disclosed in Prober and well-known in the art. Ex. 1092, 42-43; Ex. 1104, 12-15.

V. DEFINITION OF A PERSON OF ORDINARY SKILL IN THE ART

Factors that may be considered in determining the level of ordinary skill in the art include: (1) the "type of problems encountered in the art;" (2) "prior art solutions to those problems;" (3) "rapidity with which innovations are made;" (4) "sophistication of the technology; and" (5) "educational level of active workers in the field." *In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Based on these factors, Petitioner proposes the following definition of a POSITA:

> A POSITA at the time of the invention would have been a member of a team of scientists working on the research and development of DNA analysis and sequencing techniques. Such a person would have held a doctoral degree related to bioorganic chemistry, biological chemistry or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience directed toward the research and development of DNA analysis and sequencing technologies.

See Ex. 1101, ¶53.[2]

The "Summary of the Invention" of the '537 patent describes how the claimed invention would be useful for a wide variety of techniques for the analysis of DNA (or RNA), including "sequencing reactions, polynucleotide synthesis,

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[2] This definition is substantially similar to the definition proposed by Illumina in the prior IPR of the '537 Patent. Ex. 1092, 9-10. The Board did not address the level of ordinary skill in the art in the prior proceeding. Exs. 1091 & 1094.

nucleic acid amplification, nucleic acid hybridization assays, [SNP] studies, and other techniques using enzymes ….” Ex. 1001, 2:7-14. In 2002, DNA sequencing-related art was rapidly evolving and combined a variety of disciplines, including chemistry, engineering, biology, and computer science. Ex. 1038, 1:22-26; Ex. 1101, ¶60; *see also* Part VI, *infra*. A POSITA would have necessarily had a high level of education and experience to understand and utilize the full scope of the claimed inventions for these applications. Ex. 1101, ¶60. “Active workers” in the field usually had doctoral degrees and substantial laboratory experience, as evidenced by the backgrounds of the inventors and the authors of prior art in the field. Ex. 1101, ¶¶57-58; Exs. 1160-1168.

This high level of skill in the art is further demonstrated by the numerous highly technical choices that the ’537 patent (and the prior art) describe as being within the ordinary skill of a POSITA at the time. For example, a POSITA would have known how to select a suitable reversible blocking group, select an enzyme for incorporating the modified nucleotide, utilize methods to label and detect the modified nucleotide, select deblocking conditions, and optimize reaction conditions such as temperature, pH, and time for each step. Ex. 1101, ¶60; *see also* Part VI.B, *infra*.

VI. THE STATE OF THE ART

A. Advances in DNA Science

Natural DNA is composed of two strands, arranged in a double helical

structure.[3] Each strand is made up of a series of nucleotides, which are composed of three distinct chemical components: a nucleobase (or "base"), sugar, and a phosphate group. DNA polymerase catalyzes strand extension by formation of a new phosphodiester bond between the 5′ carbon of each additional nucleotide and the 3′-OH group of the last nucleotide in the strand. *See* Ex. 1101, ¶¶8-13.

One significant use for DNA technology is sequencing, which typically requires labeled nucleotides to detect and identify the bases in the sequence. Early methods used radioactive labeling and gel electrophoresis to separate fragments by size. *See, e.g.*, Exs. 1018 & 1019. One such method was Sanger's dideoxy chain termination method, published in 1977, in which nucleotide analogues without hydroxyl groups on the 2′ and 3′ positions of the sugar ("dideoxynucleotides") terminated the extension activity of DNA polymerase after their incorporation. Ex. 1020; Ex. 1101, ¶14. However, the use of radioisotopes and electrophoresis, which are labor intensive, time consuming, and expensive, were substantial drawbacks to the method. Ex. 1003, 3:1-8; Ex. 1004, 2:19-39; Ex. 1101, ¶¶14-15. These problems led the industry to look for "next-generation" sequencing methods to reduce the cost of whole-genome sequencing.

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[3] Petitioner assumes that the Board is familiar with many of the basic scientific principles underlying the structure and function of DNA. However, out of an abundance of caution, the declaration of Dr. Sutherland reviews the principles that are necessary background for this Petition. *See* Ex. 1101, ¶¶8-12.

During the late 1980s and 1990s, many research groups continued working toward the development of "next-generation" sequencing methods. One major breakthrough came in 1987 with Prober's disclosure of terminators that incorporated a fluorophore label so as to avoid the use of radioactivity. Ex. 1101, ¶16. Other next-generation sequencing methods developed in this time period include, for example, sequencing by hybridization. *See* Ex. 1022, 7:41-58.

By 1990, at least two independent groups filed patents that taught the use of reversibly blocked and labeled nucleotides to achieve SBS. Tsien, Ex. 1003; Dower, Ex. 1004. These references disclose the use of terminators with reversible blocking groups to protect the 3′-OH, a label attached to the base via a cleavable linker, and cycles of incorporation and deprotection to add and detect a single labeled nucleotide, one at a time, to a growing strand of DNA that is complementary to a template strand of an unknown sequence. Ex. 1003, 10-14; Ex. 1004, 4:44-5:6. Tsien and Dower both demonstrate that a POSITA would have known how to select a 3′-OH blocking group, label, linker, incorporation and deblocking conditions, and would have been optimistic that a 3′-OH blocked, labeled nucleotide would be incorporated by DNA polymerase into DNA. Ex. 1003, 22-25; Ex. 1004, 18:1-20; Ex. 1101, ¶¶17-25.

Before August 2002, nucleotide analog chemistry was a focus of significant scientific and commercial resources. Rapid development was driven by immense market pressure to acquire genetic information and translate it into novel, effective therapies, including technologies such as next-generation sequencing, gene therapy,

and small-interfering RNA. Ex. 1101, ¶¶60, 90. The use of organic chemistry that was compatible with biological systems was also expanding and was of enormous interest to scientists in these rapidly developing fields. Ex. 1029; Ex. 1051; Ex. 1101, ¶¶33-34, 90.

B. Knowledge of a POSITA Relating to SBS

The prior art references and admissions in the '537 patent demonstrate that well before the priority date of the '537 patent, a POSITA would have been familiar with techniques for SBS, as well as use of labelled nucleotides in methods such as the detection of polymorphisms, that do not require more than a few cycles of nucleotide addition, detection and deblocking. Moreover, these sources establish that a POSITA would have known how to select a reversible 3′-OH protecting group for nucleotides and conditions for incorporation and deblocking of such nucleotides. A POSITA also would have known techniques for optimizing SBS processes independent of the chosen protecting group. Ex. 1101, ¶¶73-83.

1. **Use of the solid phase was well known in the art.**

As a starting point, a POSITA would have known that SBS would take place in the solid phase, typically with the template and growing DNA strands attached to a solid support. Ex. 1101, ¶¶22, 44, 74; Ex. 1003, 10:16-18:34, 32:9-34:34; Ex. 1004, Figs.8A-B, 1:21-25; Ex. 1038, 4:4-10, 4:21-65. The '537 patent admits that the incorporation is "preferably carried out with the target polynucleotide arrayed on a solid support," and states that "[m]ethods for immobilizing polynucleotides on a solid support are well known in the art[.]" Ex. 1001, 9:1-2, 9:9-17.

Use of the solid phase typically results in significantly higher yield and lower reaction time compared to the same reaction performed with all reactants in the liquid phase. Ex. 1101, ¶¶22, 44, 74, 111-116. This is because solid phase permits use of excess reactants to drive a reaction to completion, while avoiding the reduction in yield that would be caused by the purification of liquid products from the excess of reactants in a liquid phase reaction. Ex. 1101, ¶¶22, 44, 74; Ex. 1003, 20:18-20; Ex. 1004, 23:34-37. There would be no loss of material during the purification process because any impurities, cleavage products, or excess reagents are simply washed away from the immobilized product. Ex. 1101, ¶¶74, 110-111. For reversible cleavage reactions, the removal of cleavage products also prevents the reverse reaction from occurring. Ex. 1101, ¶74. A POSITA would therefore have appreciated that the anticipated yield at each step in the solid phase with a substantial excess of reactants would be substantially higher than if the same reaction were performed in the liquid phase. *Id*.; Ex. 1003, 20:18-22; Ex. 1004, 8:19-21; Ex. 1014, 341. For example, as detailed in Part IX.D.4, *infra*, a POSITA would have appreciated that the pure isolated product yields reported for Loubinoux's liquid phase reactions would substantially under-estimate the yields that would be achieved for the deprotection of immobilized azidomethyl-blocked nucleotides in the solid phase. Ex. 1101, ¶¶44, 74, 108-112. Loubinoux's reported yields would have actually encouraged a POSITA to use an azidomethyl protecting group. *Id.*

A POSITA would also have known that the solid phase permits the use of a

multitude of identical copies of the subject DNA so that numerous copies of the complementary molecule can be synthesized simultaneously. *See* Ex. 1003, 6:34-7:9; Ex. 1004, 7:51-63; Ex. 1055, 3:14-47, 5:44-47. A POSITA would have understood that an advantage of solid phase methods using multiple DNA copies was that the sequence can continue to be determined even if the yield from the incorporation or deprotection steps is not 100%. Ex. 1101, ¶¶22, 74, 80-83; Ex. 1004, 10:36-39; Ex. 1055, 7:29-47.

2. **Labels and linkers were well known in the art.**

The prior art demonstrates that a variety of labels and linkers were well-known by the priority date of the '537 patent. *See, e.g.*, Ex. 1003, 26:28-30, 28:19-29:2; Ex. 1038, 2:50-64.

The '537 patent admits that "[t]he present invention can make use of conventional detectable labels. Detection can be carried out by any suitable method …. Although fluorescent labels are preferred, other forms of detectable labels will be apparent as useful to those of ordinary skill." Ex. 1001, 5:19-44. The '537 patent also admits that "[c]leavable linkers are known in the art" and "can be adapted from standard chemical protecting groups, as disclosed in Greene & Wuts …." Ex. 1001, 6:9-19.

3. **Enzymes capable of incorporation and conditions for their use were well known in the art.**

Prior art to the '537 patent demonstrates that enzymes suitable for incorporation of nucleotide analogs were known and readily available. *See* Ex. 1003, 19:3-18; Ex. 1004, 18:21-32. Illumina admitted this fact in the '537 patent:

"Many different polymerase enzymes exist, and it will be evident to the person of ordinary skill which is most appropriate to use." Ex. 1001, 8:62-64.

The prior art further acknowledges that "appropriate reaction conditions" for the incorporation reaction were "those used for conventional sequencing reactions with the respective polymerases. The conditions are then modified in the usual ways to obtain the optimal conditions for the particular terminator compound[.]" Ex. 1004, 17:25-27, 25:4-14; Ex. 1003, 19:19-23. The '537 patent admits the same: "Other conditions necessary for carrying out the polymerase reaction, including temperature, pH, buffer compositions etc., will be apparent to those skilled in the art. This polymerization step is allowed to proceed for a time sufficient to allow incorporation of a nucleotide." Ex. 1001, 9:49-10:12.

4. A POSITA would have known how to select a suitable protecting group and deblocking conditions.

A POSITA would have focused on three primary issues when selecting a reversible 3′-OH protecting group to use with SBS methods: (1) ability of a polymerase to incorporate the modified nucleotide with the protecting group, (2) selection of deblocking conditions that do not harm the DNA, and (3) that the incorporation and deblocking steps result in a yield that is reasonable for the desired application. Ex. 1101, ¶¶79-80.

As described in the prior art, the ability of a polymerase to incorporate protected nucleotides is dependent on the size of the protecting group. Ex. 1038, 2:50-57, 3:1-3:5; Ex. 1101, ¶95 (citing Exs. 1003, 1026-27, 1024, 1038 & 1041-42).

With respect to the deblocking conditions, the prior art taught that "[o]ptimally, the blocking agent should be removable under mild conditions … thereby allowing for further elongation of the primer strand with next synthetic cycle." Ex. 1004, 18:3-8; Ex. 1003, 20:33-34 ("availability of mild conditions for rapid and quantitative deblocking"). In this context, a POSITA would have appreciated that "mild conditions" are those that would not "degrade the DNA template moiety" or interfere with enzyme function. Ex. 1038, 26:25-27. Ex. 1101, ¶86. Notably, like the incorporation step, a POSITA would have expected the substantial excess of deblocking reagents that may be used in solid phase methods to achieve nearly quantitative deblocking in reduced time (as compared to solution phase chemistry followed by purification). Ex. 1101, ¶¶78-81; *see also* Ex. 1038, 26:27-30.

The '537 patent also admits that "[s]uitable protecting groups ***will be apparent to the skilled person,*** and can be formed from ***any suitable protecting group disclosed in Greene & Wuts***, supra." Ex. 1001, 7:65-8:1 (emphasis added). "The protecting group should be removable (or modifiable) to produce a 3′-OH group. The process used to obtain the 3′-OH group can be any suitable chemical or enzymic reaction." *Id.*, 8:1-4. Thus, the selection of a protecting group and deblocking conditions from the literature was within the skill of a POSITA.

5. **A POSITA would have known other methods to optimize the SBS process.**

A POSITA would have also appreciated that reaction conditions are easily

modified and additional steps could be employed to optimize the sequencing process. For example, Tsien explicitly mentions non-chemical assistance to improve deblocking. *See* Ex. 1003, 25:26-30. Additional optimization steps were known in the art, including the use of a capping step, which irreversibly blocks any remaining unblocked 3′-OH groups after the incorporation step, thereby reducing errors associated with subsequent nucleotide misincorporation and improving the signal-to-noise ratio, as well as performing detection cycles both before and after the deblocking step, and only considering sequence data when both incorporation and deblocking steps were successful. Ex. 1038, 21:42-53; Ex. 1004, 26:13-18; Ex. 1085, 15:17-40; Ex. 1101, ¶¶81-83.

In sum, the optimization of all of the foregoing variables—(1) the use of solid phase DNA synthesis; (2) the selection of appropriate labels and linkers; (3) the selection or engineering of a polymerase for the incorporation of nucleotides and the optimization of incorporation conditions; (4) the selection of a suitable protecting group and optimization of deblocking conditions; and (5) the manipulation of additional variables to further optimize the SBS process— are described in the prior art and admitted in the ’537 as being within the knowledge and skill of a POSITA.

C. A POSITA Would Have Appreciated Multiple Uses for Modified Nucleotides

While many SBS-practitioners seek to optimize the length of the available “read” (*i.e.*, the number of sequential bases read), modified nucleotides were also

useful for methods that did not require many cycles of incorporation, detection, and deblocking, such as the detection of SNPs, INDELs, and multi-nucleotide mutations. *See* Ex. 1101, ¶¶88-89 (citing Exs. 1073-75). As the '537 patent admits, the modified nucleotides may also be useful in "sequencing reactions, polynucleotide synthesis, nucleic acid amplification, nucleic acid hybridization studies, [SNP] studies, and other techniques using enzymes…." Ex. 1001, 2:7-14. As one example, Tsien's method could be combined with the azidomethyl group to modify the Arrayed Primer Extension (APEX) technique, allowing it to be used for the characterization of multi-nucleotide polymorphisms, many of which were known to correlate to disease. Ex. 1101, ¶89; Ex. 1074, 250. Several potential applications would require identification of only 1 or a few bases and would not require many (or any) steps of repetition. Ex. 1101, ¶¶88-89.

VII. CLAIM CONSTRUCTION

Claim 1 should be construed according to the Board's prior Final Written Decision, *i.e.*, "as encompassing the use of any protecting group attached via the 2′ or 3′ oxygen atom of a [sugar] moiety, in which the protecting group can be modified or removed to expose a 3′ OH group." Ex. 1094, 6. In addition, the claims require that "the protecting group comprises an azido group." Ex. 1001, 19:58-9; 821 F.3d at 1363. This construction was not contested by Illumina and was accordingly relied on by the Federal Circuit. 821 F.3d at 1364.

Additionally, consistent with the Federal Circuit's decision, Claim 1 must be

construed such that it "'does not require removal of the protecting group to allow subsequent nucleotide incorporation,' let alone quantitative removal." *Id*. at 1364, 1367 ("removal is simply not required by the claim of the '537 patent"); *see also* Ex. 1001, 19:48-20:18.

VIII. ALL THE LIMITATIONS OF CLAIMS 1-6 & 8 WERE DISCLOSED IN THE PRIOR ART

A. The "Azido" and "Azidomethyl" Protecting Groups of Claims 1 and 6 Were Disclosed in Zavgorodny and Greene & Wuts.

Claim 1 recites that "the protecting group comprises an azido group." Claim 6 recites that the protecting group is CH_3N_3," which is azidomethyl.

1. Greene & Wuts discloses "azido" and "azidomethyl" protecting groups

Greene & Wuts, a widely known reference text for the selection of protecting groups, discloses the use of an azidomethyl protecting group with an aryl alcohol (phenol):

Azidomethyl Ether: N_3CH_2OAr

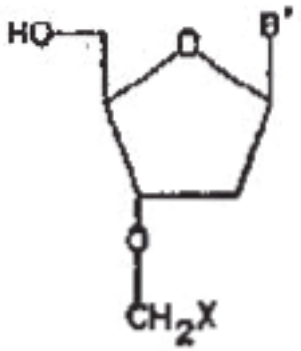
The azidomethyl ether, used to protect phenols and prepared by the displacement of azide on the chloromethylene group, is cleaved reductively with $LiAH_4$ or by hydrogenolysis (Pd–C, H_2). It is stable to strong acids, permanganate, and free-radical brominations.[1]

1. B. Loubinoux, S. Tabbache, P. Gerardin, and J. Miazimbakana, *Tetrahedron*, **44**, 6055 (1988).

Ex. 1005, 260; *see also* Ex. 1101, ¶¶94-95.

2. Zavgorodny discloses the "azido" and "azidomethyl" protecting groups of Claims 1 and 6, respectively.

Zavgorodny discloses a substituted nucleoside (formula 5, excerpted below), where X can be N_3. Ex. 1008, 7594-95.



5 B' = Thy, Cyt, Ade, Guo

When X is N_3, the 3′-OH of the sugar moiety is protected by azidomethyl, $–CH_2N_3$, as recited in claim 6. Ex. 1101, ¶72. Zavgorodny further teaches that "[t]he compounds discussed above 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." Ex. 1008, 7595.

B. Tsien Discloses Each Limitation of Claims 1-2, 4-6, and 8 Except the Azido and Azidomethyl Protecting Groups.

As described below, and detailed in Dr. Sutherland's declaration (Ex. 1101, ¶72), each limitation of claims 1-2, 4-6, and 8 is disclosed in Tsien, with the exception of the azido protecting group. Moreover, the Board previously found that Tsien discloses each of these limitations. Ex. 1094, 10-11. This finding was affirmed by the Federal Circuit:

> Both Ju and Tsien disclose a method of sequencing unknown DNA involving the SBS method, including the labeling of nucleotides for detection and the use of a protecting group at the 3′-OH position of the

> nucleotide. Neither Ju nor Tsien disclose a protecting group that comprises an azido group, however.

821 F.3d at 1363-64; *see also* 620 Fed.Appx. at 923, 925 ("[T]he prior art discloses labels attached to the base, cleavable tethers, and reversibly capped 3′-OH groups.").

Illumina also requested adverse judgment against claim 7, which is identical to claim 1 except that it recites that the "protecting group and cleavable linker are removable under identical conditions," instead of "the protecting group comprises an azido group," as in claim 1. Thus, Illumina is precluded from arguing that these limitations were not disclosed in the prior art. *See* 37 C.F.R. §42.73(d)(3).

The preamble and first limitation of claim 1 recite "A method of labeling a nucleic acid molecule the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule …." Tsien describes how "the polymerase and the four labeled dNTPs are added to the reaction zone 14 under conditions adequate to permit the enzyme to bring about addition of the one, and only the one, of the four labeled blocked dNTPs which is complementary to the first available template nucleotide following the primer," where a "dNTP" is defined as a "**deoxy**nucleotide triphosphate[]." Ex. 1003, 12:22-27, 9:35-10:1 (emphasis added). Thus, Tsien discloses the labeling of a nucleic acid molecule by incorporating one of the four labeled blocked dNTPs into the growing chain.

Claim 1 next recites "wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker …." Although

the ’537 specification states this was the alleged point of novelty, Tsien discloses a detectable label linked to a base by a cleavable “spacer or tether”:

> One method involves the use of a fluorescent tag attached to the base moiety. The tag may be chemically cleaved (either separately from or simultaneously with the deblocking step) and measured either in the reaction zone before deblocking or in the reaction eluant after cleavage. . . . [The] label can be attached to the dNTP through a spacer or tether. The tether can be cleavable if desired to release the fluorophore or other label on demand.

Id., 28:5-10, 19-23.

Claim 1 next recites that “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….” Tsien discloses that the “blocking group present on the 3′-hydroxyl position of the added dNTP prevents inadvertent multiple additions[].” *Id*., 12:27-29; 20:25-27.

Claim 1 next recites that “said protecting group can be modified or removed to expose a 3′ OH group ….” Tsien discloses this limitation as well:

> After successfully incorporating a 3′-blocked nucleotide into the DNA chain, the sequencing scheme requires the blocking group to be removed to yield a viable 3′-OH site for continued chain synthesis.

Id., 23:28-31, Fig.3.

Dependent Claim 2 further recites “wherein said incorporating is accomplished via a terminal transferase, a polymerase or a reverse transcriptase.”

Tsien discloses that its coupling process is an "enzyme moderated process," and that "Sequenase™ enzyme (an enzyme derived from bacteriophage T_7 DNA polymerase …)" or "other polymerases" can be used. *Id.*, 19:4-18.

Dependent claim 4 further recites that "the nucleotide is a deoxyribonucleotide triphosphate." Similarly, Tsien discloses that the "synthesis is carried out using deoxyribonucleotide triphosphates (dNTP) …." *Id.*, 7:3-4.

Dependent claim 5 further recites that "the label is a fluorophore." Tsien explicitly discloses a method that "involves the use of a fluorescent tag attached to the base moiety." *Id.*, 28:5-6.

Dependent claim 8 further recites the steps of "detecting the detectable label and cleaving the cleavable linker." Tsien explicitly discloses these limitations. First, Tsien teaches detection: "As part of this invention, the incorporation of each dNTP into the complementary chain is noted by detecting a label or reporter group present in or associated with the incorporated dNTP." *Id.*, 26:2-5. Tsien further teaches that the "dNTP can be incorporated and the fluorescence measured and removed according to the methods described below." *Id.*, 28:3-4. With regard to a cleavable linker, Tsien teaches:

> In another type of remote labeling the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The tether can be cleavable if desired to release the fluorophore or other label on demand.

Id., 28:19-23.

IX. THE CHALLENGED CLAIMS ARE OBVIOUS OVER THE PRIOR ART

A. Legal Standards for Obviousness

KSR identifies numerous rationales that support an obviousness conclusion, including:

> (B) Simple substitution of one known element for another to obtain predictable results; …
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

MPEP §2143; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). A finding of obviousness requires "a motivation to combine the prior art to achieve the claimed invention and … a reasonable expectation of success in doing so." *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). With regard to the "reasonable expectation of success," the POSITA need only have a reasonable expectation of success of developing the claimed invention, as opposed to an expectation of success of developing commercial products or methods containing elements in addition to those embodied in the claims. 821 F.3d at 1367.

The person of ordinary skill in the art is "presumed to be aware of all the pertinent prior art," including secondary references and background knowledge. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). The person of ordinary skill in the art is also expected to utilize his common sense

ordinary creativity, and is not merely an automaton. *KSR*, 550 U.S. at 414, 420-21. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.*, 420. Optimization is considered routine. *See Pfizer Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007).

For the purposes of an invalidity analysis, lack of disclosure within a patent specification may be evidence of that a person of skill in the art would have been expected to know the necessary details or processes required to implement the claimed invention. *See In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (noting how the fact that a patent's specification does not provide the detail Patent Owner contends must be present in the prior art supports a finding that a POSITA would have known how to implement the features at issue).

B. The Crux of this Petition is the Rationale for a "Motivation to Combine"

As discussed in Parts IV.B and VIII.B, *supra*, the Federal Circuit previously affirmed the Board's decision that all the limitations of claims 1-2, 4-6, and 8 were disclosed in Tsien and Zavgorodny. Moreover, the Federal Circuit decided that a POSITA would have had a reasonable expectation of success in combining them to arrive at the claimed invention of the '537 patent. 821 F.3d at 1367 ("The Board's reliance on the absence of a reasonable expectation of success was, thus, improper[.]"). Therefore, the only remaining question is whether a POSITA would have been motivated to combine the azidomethyl protecting group disclosed in

Greene & Wuts and Zavgorodny with the sequencing methods disclosed in Tsien.

As detailed below, a POSITA would have been motivated to combine these references based on at least two rationales: (1) "teaching, suggestion, or motivation in the prior art" and (2) azidomethyl as a "simple substitution of one known element for another," *i.e.*, the 3′-OH protecting groups disclosed in Tsien.

C. Tsien's Disclosure Must Be Considered from the Perspective of a POSITA

Tsien, published in 1991 (over a decade before the priority date), describes a method and apparatus for SBS, including the incorporation, detection, and deblocking of modified nucleotides. Ex. 1003. These steps are repeated, as necessary, to determine the identity of each nucleotide in the target DNA. *Id*. Tsien teaches several important features that would be considered by a POSITA when selecting a potential 3′-blocking group: (1) the target single-stranded DNA are immobilized on a solid surface in a reaction chamber; (2) numerous copies of the "subject primed single stranded DNA are immobilized on this surface"; and (3) the addition and removal of reactants such as enzymes, nucleotides, and deblocking reagents, as well as rinsing steps, can all occur automatically and with appropriate adjustments to conditions to allow the reactions to run to completion. Ex. 1003, 11:34-36, 13:16-24, 14:1-3; Ex. 1101, ¶¶17-22, 73-81.

Tsien discloses several exemplary 3′-OH blocking groups, noting that "[t]he most common 3′ hydroxyl blocking groups are esters and ethers." Ex. 1003 21:12-13. Tsien states that "presently preferred embodiments" include "ether blocking

groups such as alkyl ethers." *Id*., 21:24-25. Tsien further teaches that cleavable ethers would be preferred over esters because esters are typically deblocked by base hydrolysis, which was known to result in "premature deblocking." *Id*., 21:24-25, 24:5-7, 24:29-25:3. Therefore, a POSITA would have read Tsien as suggesting the use of ethers over esters, and particularly ethers that can be removed "only when the specific deblocking reagent is present." *Id*., 25:1-2; Ex. 1101, ¶¶92-93.

Next, Tsien teaches that there are a "wide variety of hydroxyl blocking groups" that possess the advantages of selective chemical cleavage and directs the POSITA to the literature to find acceptable substitutes. *Id*., 24:34-25, 21:32-34 ("These blocking materials in their fundamental forms have all been described in the literature as has their use as blockers in chemical DNA synthesis settings."). A POSITA, reading Tsien in 2002—over a decade after Tsien's publication— would have known that significant advances had been made in protecting group chemistry since 1991 and would have been motivated to exploit those advances. Ex. 1101, ¶90; *see e.g.*, Ex. 1051.

Finally, Tsien teaches the POSITA how to select suitable "blocking groups and methods of incorporation" from the literature:

> The criteria for the successful use of 3 '-blocking groups include: (l) 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.

Ex. 1003, 20:28-21:3. Tsien also teaches that "[a]fter successfully incorporating a 3′-blocked nucleotide into the DNA chain, the sequencing scheme requires the blocking group to be removed to yield a viable 3′-OH site for continued chain synthesis," and that:

> The deblocking method should: (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, (d) the exact deblocking chemistry selected will, of course, depend to a large extent upon the blocking group employed.

Id., 23:31-24:5. A POSITA would have appreciated that this second set of criteria are substantially duplicative of the second and third criteria listed above for selecting a blocking group. Ex. 1101, ¶¶18-20, 79.

Thus, Tsien's criteria for selecting a blocking group, methods of incorporation, and methods of deblocking can be summarized as: (1) "the ability of a polymerase enzyme to accurately and efficiently incorporate the dNTPs carrying the 3′-blocking groups into the cDNA chain"; (2) mild deblocking conditions that do not interfere with future enzyme function, for example by irreversible denaturation of the DNA; (3) a high (ideally approaching quantitative) yield of de-

blocked 3′-OH groups;[4] and (4) "rapid" deblocking. *Id*. A POSITA would have also appreciated that these "criteria" are to be viewed in the context of optimizing the overall procedure of nucleotide incorporation, detection and deblocking; each step is not optimized in a vacuum, but rather adjusted so that the overall process operates at peak efficiency. A person of ordinary skill would have been extremely comfortable with such an optimization process, and it would amount to nothing more than routine optimization. Ex. 1101, ¶¶77-81.

Tsien recognizes that the disclosed SBS method has the "obvious potential shortcoming" that "it employs a long sequence of serial reactions," and that "[e]ven if the efficiency and yield of each of those reactions are relatively high, the overall yield becomes the product of a large number of numbers, each of which is somewhat less than 1.00, and thus can become unacceptably low. For example if the yield of a given addition step is 98% and the deblocking is 98% as well, the overall yield after 15 additions is 48%, after 30 additions it is 23% and after 60

[4] A POSITA would have appreciated that "efficiency" typically refers to the percent conversion of reactants to products, whereas "yield" refers to the percent of products recovered following isolation or purification. A reaction's conversion "efficiency" will therefore typically be greater than the "yield," since product is typically lost during isolation and purification steps. Ex. 1101, ¶¶108, 110-112.

additions it is 5.3%." Ex. 1003, 16:21-30.[5] A POSITA would therefore have appreciated that, the fewer base pairs that require sequencing for the intended application, the less important a high yield is. Ex. 1101, ¶¶79-81, 88-89. In addition, a POSITA would have known that the acceptable overall yield would ultimately depend on the sensitivity of label detection (*i.e.*, the ability to detect the signal of the incorporated nucleotide versus the noise). Ex. 1101, ¶80. If detection was more sensitive, the process would tolerate a lower yield. *Id.*

Tsien further teaches that "[t]his limitation can be alleviated by periodically halting the DNA molecule growth to externally recreate a portion of the molecule which can then be used as a primer for renewed DNA fabrication." *Id.*, 16:31-35. "This restarting of the growth can be carried out as often as needed to assure a strong consistent label signal." Ex. 1003, 18:31-33; 7:34-8:7. Tsien goes on to describe an automated process for doing so. Ex. 1003, 17:1-18:14, 8:35-9:3, Fig.4. Thus, a POSITA would have recognized from Tsien that, in practice, the incorporation and deblocking steps will not necessarily be achieved in a quantitative yield, and that the SBS method can nevertheless be used as long as a sufficiently "strong consistent label signal" is maintained throughout the required number of

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[5] Tsien's reported overall yields are slightly incorrect. At a 98% yield per step, the overall yield would be 55% after 15 addition/deblocking steps (not 48%), 29.8% after 30 addition/deblocking steps (not 23%), and 8.9% after 60 addition/deblocking steps (not 5.3%). *See* Ex. 1101, ¶19.

detection cycles. Ex. 1101, ¶80. Obviously, higher yields is one factor that will allow longer sequencing runs, which is a desirable goal, but Tsien itself teaches that SBS reactions can work with lower yields. Ex. 1101, ¶¶81-83.

The POSITA would have also understood from Tsien that there were additional ways to compensate for non-quantitative deblocking and therefore, one can tolerate some loss of growing strands. *Id*. For example, by sequencing a large population of homogeneous strands, as suggested in Tsien, the signal-to-noise ratio of the label signal would be improved so as to permit longer reads than would be otherwise possible with a given chemistry. Ex. 1003, 6:34-7:35, 11:34-36; Ex. 1101, ¶81. Tsien teaches that other factors can be adjusted to improve the strength of the signal, including the number of different nucleotides added to a reaction zone, whether they were all labeled, and whether the labels were the same or different on each type of nucleotide. Ex. 1003, 7:25-35.

Tsien also mentions the desire for "rapid" deblocking without defining that term. While a POSITA may have generally understood "rapid" in the reaction rate context as being on the order of minutes, the meaning of rapid in the sequencing context was not well-defined at the relevant time. Ex. 1101, ¶¶84-85. For example, Illumina's first commercial sequencer, which was sold in 2006, well after the priority date, was reported as sequencing 18 bases in 2 days, which amounts to 2.7 hours per incorporation-detection-deblocking cycle. *Id*. Thus, a POSITA would likely have considered deblocking on the order of many minutes as being "rapid," but if higher yield is essential to a desired application, then a POSITA would

consider several hours to be sufficiently "rapid." *Id*.

D. Tsien's Incorporation and Deblocking Criteria Would Have Led a POSITA to Modify Tsien's SBS Method by Using the Azidomethyl Protecting Group of Zavgorodny and Greene & Wuts

Obviousness may be supported by a finding that the combination arises from "some teaching, suggestion, or motivation in the prior art" that would have led a POSITA to modify or combine the prior art reference(s) to arrive at the claimed invention, and a finding that there was a reasonable expectation of success. *DyStar*, 464 F.3d at 1360. The "teaching, suggestion, or motivation" can be from "references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP §2143(G); *see also DyStar*, 464 F.3d at 1367.

1. A POSITA would have appreciated that each of Tsien's incorporation and deblocking criteria suggest that azidomethyl would be a suitable alternative protecting group for use with Tsien's SBS method and would therefore have been motivated to use an azidomethyl protecting group.

i. The ability of a polymerase enzyme to accurately and efficiently incorporate the dNTPs carrying the 3′-blocking groups

A POSITA at the relevant time would have been aware that the structure of DNA polymerase leads it to discriminate against incorporation of nucleotide analogues with large protecting groups attached at the 3′ position of the sugar group. Ex. 1101, ¶¶76, 95; *see also* Ex. 1026, 1621; Ex. 1038, 2:46-59; Ex. 1027, 212-13. Thus, a POSITA would have favored small protecting groups that will not interfere with incorporation of the labeled nucleotide. Ex. 1101, ¶¶76, 95. Because azidomethyl is very small compared to some groups that had been successfully

incorporated, a POSITA would have expected it to exhibit less steric interference during incorporation than bulkier protecting groups. *Id*. A POSITA would have also appreciated that the linear shape of the azido group allows it to adopt "rotameric states" that project the linear azide group away from the active site of the polymerase and therefore lessens steric interference. Ex. 1101, ¶95.

Furthermore, a POSITA would have expected azides (*i.e.*, molecules with an azido group) to be compatible with the polymerase because by 2002, azides were well-known to be unreactive towards biological systems (*i.e.*, bio-orthogonal). Ex. 1101, ¶¶33-34, 99; Ex. 1029, 2007 (describing azides as "abiotic and chemically orthogonal to native cellular components."). For this reason, by 2002 azides were used as protecting groups, moieties on pharmaceutical molecules, and as reactive centers for bio-orthogonal reactions. Ex. 1101, ¶90. Since the stability of azides to biological nucleophiles was firmly established in the art, a POSITA would have expected the azidomethyl group to be unreactive with respect to the polymerase and would therefore have considered it a highly-desirable protecting group. Ex. 1101, ¶¶90, 96-100; Ex. 1029, 2007.

Illumina's argument in the prior IPR that the "electrophilic characteristics of Zavgorodny's azidomethyl group would likely react with strong nucleophiles within the polymerase active site, thereby preventing polymerase activity" (Ex. 1092, 15), is scientifically inaccurate and would not have deterred a POSITA from substituting Tsien's protecting groups with azidomethyl. Ex. 1101, ¶99. Illumina argued that ketone and carbonyl groups were reported as disfavored due to the electrophilic

nature of their central carbon atom, but this report would have had no impact on a POSITA's view of azidomethyl as a favorable protecting group due to known differences in the reactivity of azides and esters. *Id.* The fallacy of Illumina's argument is further demonstrated by the fact that the '537 itself identifies several carbonyl-containing groups as potential protecting groups for the 3′-OH. Ex. 1001, 4:17-22, Fig.3.

In fact, it was demonstrated in the art that azides were unreactive towards polymerases. *See* Ex. 1101, ¶¶96-98; Ex. 1015, 21459. This understanding is consistent with Tsien's listing of $-N_3$ as a "blocking modification to the 3′-OH position." Ex. 1003, 21:13-15. Indeed, Tsien cites Kraevskii as showing incorporation of such blocked nucleotides (*id.*, 21:17-19), and both Kraevskii and Copeland show that azido groups coupled to the 3′-C can be incorporated. Ex. 1076, 28; Ex. 1015, 21462; Ex. 1101, ¶¶96-98. Thus, a POSITA would not have expected a removable blocking group comprising an azide (such as azidomethyl) to interfere with incorporation by polymerases. Ex. 1101, ¶¶96-98.

A POSITA would have been motivated to use the azidomethyl protecting group because of known benefits of using ether protecting groups, the small size and biocompatibility azido groups, and the fact that the incorporation of azido groups by polymerases had already been demonstrated. For the foregoing reasons, a POSITA also would have had a "reasonable expectation of success" in arriving at the claimed invention, the incorporation of azidomethyl-protected nucleotides into DNA, as previously stated by the Federal Circuit. 821 F.3d at 1367; Ex. 1101, ¶43.

ii. Reinitiation of DNA synthesis

Illumina previously argued that a POSITA would expect an azidomethyl group to hinder re-initiation of DNA synthesis. This argument was based on Ju's teaching that an ***ester*** group may interfere with DNA polymerase. Ex. 1092, 31; Ex. 1098, ¶58. This argument is inapposite since the azidomethyl protecting group taught by Zavgorodny and Greene & Wuts/Loubinoux forms an ether — not an ester — when bound to the 3′-OH of the nucleotide. Ex. 1101, ¶100. Further, for the reasons discussed *supra* in Part IX.D.1, a POSITA would not have expected the azidomethyl ether to hinder reinitiation of DNA synthesis. *See, e.g.*, Ex. 1101, ¶¶96-98.

iii. Mild deblocking conditions

The first of Tsien's "deblocking" criteria is the availability of mild deblocking conditions. In this context, a POSITA would have understood "mild" conditions as meaning that they do not denature the DNA or interfere with future enzyme function. Ex. 1101, ¶86. As discussed in Part VI.B.4, *supra*, Tsien and the '537 patent both confirm that choosing appropriate deblocking chemistry for a particular blocking group was within the ordinary skill in the art.

A POSITA would have appreciated that the deblocking conditions for the azidomethyl group disclosed in either Zavgorodny or Loubinoux would have been sufficiently "mild" for use with Tsien's SBS methods. In addition, a POSITA would also have appreciated that those deblocking conditions were simply variations on the well-known Staudinger reaction and therefore, the azidomethyl

could be removed with other phosphine deblocking reagents, such that a POSITA was not necessarily limited to the deblocking conditions disclosed in Zavgorodny or Greene & Wuts. Ex. 1101, ¶¶103-104, 115-118.

a. Zavgorodny's deblocking conditions are sufficiently "mild"

A POSITA would have appreciated that the deblocking conditions disclosed in Zavgorodny were sufficiently mild for use with DNA sequencing. Zavgorodny explicitly discloses the azidomethyl group as a protecting group for the 3′-OH of nucleosides. Ex. 1008, 7594. Zavgorodny also teaches that the "[a]zidomethyl 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.*, 7595. In addition, because Zavgorodny's conditions were sufficiently mild for use with nucleosides, one skilled in the art would have not expected those conditions to degrade the nucleobase or ribose moieties of nucleotides that had been incorporated into a DNA strand. Ex. 1101, ¶¶119-120.

Illumina previously asserted that the conditions described by Zavgorodny for removing its azidomethyl group would not have been considered sufficiently mild for use in Tsien's sequencing methods because the pyridine used in removing Zavgorodny's azidomethyl protecting group allegedly was known to denature DNA. Ex. 1092, 19-23; Ex. 1094, 8. However, Illumina overstated the conclusion that use of aqueous pyridine would denature DNA. Ex. 1101, ¶¶119-122. Neither of the references previously relied on by Illumina for the proposition that pyridine

denatures DNA (Ex. 1092, 20-21 (citing Kit, Ex. 1033; Lee, Ex. 1034)) shows that aqueous pyridine would denature DNA under Zavgorodny's deblocking conditions (temperature and concentration), and a POSITA would not have expected those conditions to do so. Ex. 1101, ¶¶119-122. Furthermore, Levine, a paper referenced by Lee, teaches that the denaturant capacity of pyridine is similar to that of phenol (Ex. 1036, 171, Table II), which is a medium routinely used in microbiology to extract DNA solutions without denaturing the DNA. *See, e.g.*, Exs. 1082-1083; *see also* Ex. 1101, ¶120. Thus, Illumina's assertion is unwarranted and contrary to the common understanding of a POSITA at the time. A POSITA would not have expected denaturation to be caused by a reagent with the approximate denaturing effect of phenol, especially when mixed with a substantial amount of water, such as the *aqueous* pyridine suggested in Zavgorodny. Ex. 1101, ¶120.

Even if a POSITA would have thought that pyridine might destabilize or denature DNA at the temperatures used in the reaction, they would have been well aware of options to counter this, such as the use of a hairpin loop primer to allow DNA strands to re-hybridize. *Id.*, ¶124; Ex. 1038, 3:51-58;. Annealing (or re-hybridizing) after denaturing was a common practice in 2002, and was the basis of the technology utilized in hybridization assays at the time. *See, e.g.*, Ex. 1021; Ex. 1101, ¶124.

b. Greene & Wuts refers to Loubinoux, which provides alternative "mild" deblocking conditions

Greene & Wuts' disclosure of an azidomethyl protecting group is based on

Loubinoux, which teaches the use of azidomethyl as a protecting group for the synthesis of unstable phenols. Exs. 1005-1006. Loubinoux describes how the disclosed reaction conditions were chosen: "we used the two methods of the literature which, because of their gentleness, appeared the most appropriate: [1] the treatment with triphenylphosphine and then with water, in tetrahydrofuran at 25°C,[4] and [2] the treatment with hydrogen in the presence of palladium on carbon, at 25°C and at atmospheric pressure." Ex. 1006, 4-5. Footnote 4 of Loubinoux cites Vaultier, which further provides that triphenylphosphine and water may also be used in a single step. Ex. 1056, 764, n.6. A POSITA would have appreciated that treatment with triphenylphosphine in water and tetrahydrofuran at 25°C would be a potential alternative for Zavgorodny's removal conditions,[6] essentially changing only the co-solvent from pyridine to tetrahydrofuran (THF). Ex. 1101, ¶122. A POSITA would have readily understood that, unlike the phosphine and water, the co-solvent plays no active role in the mechanism of the Staudinger reaction and can be substituted with another suitable co-solvent—or omitted entirely if the all the reactive species are water-soluble. *See* Ex. 1101, ¶109; Ex. 1029, 2007-08, Fig.2A.

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[6]A POSITA considering using Tsien's SBS method would have known that Loubinoux's second removal method is not compatible with SBS because it requires a solid catalyst (palladium on carbon), which would be in a distinct solid phase and therefore difficult to contact with immobilized DNA. Ex. 1101, ¶107.

c. A POSITA would have known that alternative "mild" conditions could be used to deblock an azidomethyl protecting group

Regardless of the specific phosphine deblocking reagent and co-solvent used in Zavgorodny or Greene & Wuts/Loubinoux, a POSITA would have readily appreciated that an azidomethyl group could be reduced and hydrolyzed to recover the 3′-OH with any suitable phosphine reagent and water; the choice of phosphine and co-solvent could be readily adapted to any particular application. Ex. 1101, ¶¶114-116; *see also* Exs. 1028 & 1029. The reported removal conditions would have been understood by a POSITA to utilize the well-known Staudinger reaction, which was first taught in 1919. Ex. 1028, 1354. A POSITA would have known that the Staudinger reaction was not limited to the use of triphenylphosphine or any particular co-solvent, but that it could be used with other phosphine reagents. Ex. 1006, 7. Thus, the specific reducing agent and co-solvents reported in Zavgorodny and Greene & Wuts/Loubinoux would not have dissuaded a POSITA from combining Tsien's SBS method with an azidomethyl protecting group because the option to use alternative deblocking reagents was well-known to a POSITA, who was capable of optimizing reaction conditions. Ex. 1101, ¶¶114-116; *see also* Part VI.B.4, *supra*.

In particular, because DNA is water-soluble, a POSITA would have appreciated the advantages of using a water-soluble phosphine, thereby avoiding the use of a co-solvent entirely. *See, e.g.*, Ex. 1029, 2007; Ex. 1101, ¶116. Indeed, one water-soluble phosphine, TCEP, had been known for over a decade by 2002 (Burns,

Ex. 1057, 2648), was commercially available since 1992 (Getz, Ex. 1078, 74), and was known to be bio-orthogonal (such that it would not damage or denature DNA). Ex. 1029, 2009; Ex. 1101, ¶118. A POSITA would therefore have known that TCEP could have been used as an alternative to the triphenylphosphine disclosed in Zavgorodny, thereby removing the azidomethyl group and restoring the 3′-OH without the need for any co-solvent. Ex. 1101, ¶¶114-116. Thus, in light of the foregoing, a POSITA would have been motivated to utilize the azidomethyl group because of the variety of mild deblocking conditions that were available at the time.

iv. **A quantitative or high yield of de-blocked 3′-OH groups**

Tsien teaches "quantitative" or "high yield" deblocking as a factor for designing an SBS process. Ex. 1003, 20:28-21:3. However, as discussed above (*see* Part IX.C, *supra*), a POSITA would have appreciated that a less than quantitative yield is to be expected in practice, and that methods such as restarting the sequencing with a new primer can alleviate that issue. Ex. 1003, 16:31-35; Ex. 1101, ¶19. Moreover, a POSITA would have been motivated to combine Tsien's method with the azidomethyl group for applications that did not require more than a few sequential nucleotide additions, including, for example, improving on the widely-used APEX method for identifying SNPs. *See* Part VI.C, *supra*; Ex. 1101, ¶¶88-89; Ex. 1074, 250.

Even if quantitative yield was desired, the POSITA would still have been motivated to utilize the azidomethyl group. Zavgorodny refers to the "very specific

and mild" conditions for deblocking, but does not specifically refer to yield. Ex. 1008, 7595. Loubinoux's reported pure isolated product yields of unstable phenols would have encouraged a POSITA to use azidomethyl as a protecting group in Tsien's SBS method because a POSITA would expect quantitative deblocking under the SBS conditions. Ex. 1101, ¶¶110-113.

A POSITA reading Loubinoux would have appreciated that there are several critical differences between the deblocking reaction to be used with Tsien's methods and those performed in Loubinoux. Most importantly, Tsien's SBS method would have been performed with the growing DNA strand immobilized on a solid surface. Ex. 1101, ¶¶22, 74; *see also* Part IX.C, *supra*. In contrast to reactions in the liquid phase (as in Loubinoux), a POSITA would have readily appreciated that by using the solid phase, the reactions can be driven to completion with excess reactants, and purification steps are unnecessary because the excess reactants and cleavage products can be washed from the immobilized DNA before the next incorporation step. Ex. 1101, ¶74. Thus, a POSITA would have known that, with sufficient time and excess reagents, the azidomethyl deblocking reaction would be driven to completion (*i.e.*, a quantitative yield). Ex. 1101, ¶¶110-113.

Loubinoux's reported "pure product yields" of 60-80% for unstable phenols would have led a POSITA reasonably to expect a significantly greater deblocking efficiency of the azidomethyl group when used with Tsien's SBS method. *Id*. This is because Loubinoux's "pure product yields" would not have been understood by a POSITA as a reasonable comparator for the "efficiency" or "yield" referred to in

Tsien. *Id*.. "Pure product yields," as used in Loubinoux, refers to the percentage recovery of the isolated unstable phenol products after purification of the products using liquid chromatography on a silica column. Ex. 1101, ¶¶30, 110; Ex. 1006, 6. A POSITA would have expected there to be a significant loss of product during Loubinoux's purification step, an issue that would not be present in Tsien's SBS method that uses the solid phase where purification is not required. Moreover, a POSITA would have expected Loubinoux's purification step to cause an inordinately large loss of product given that the phenol products were admittedly unstable. Ex. 1101, ¶¶110-111. Indeed, a POSITA would have understood that, given the loss of product to purification and the unstable nature of the phenol products, Loubinoux's reported "pure product yields" of 60-80% suggest that the reaction efficiency must actually have been very high, not excluding over 99%, or else the pure isolated product yields would have been far lower. Ex. 1101, ¶¶108, 111-113. Thus, Loubinoux's reported "pure product yields," combined with the understanding that Tsien's SBS method would be performed in the solid phase with excess reactants and no required purification, would have led a POSITA to expect that azidomethyl could be quantitatively removed when used in Tsien's method. Ex. 1101, ¶¶110-113. For these same reasons a POSITA would have actually been encouraged by many of the yields previously cited by Illumina as discouraging. *See* Ex. 1101, ¶108; Ex. 1092, 26-29; Ex. 1098, ¶50.

In fact, quantitative cleavage of an azidomethyl group had already been reported for other biological substrates that were immobilized in the solid phase.

See Young, Ex. 1051, 68 ("cleavage of the dipeptide from the resin followed by proton NMR spectroscopy confirmed the expected structure and the quantitative cleavage of the Azm [(azidomethyl)] group").[7] Young stated that "[a]zide reduction can be accomplished through the action of numerous mild reducing agents," and choose azidomethyl as a "minimalist design approach." *See id.*, 52-55. Young also reported that a search of the literature, specifically including Loubinoux, provided "encouragement" to use azidomethyl. *Id.*, 52-53. Thus, Young serves as a clear example of how a POSITA would have adopted the azidomethyl protecting group from the literature, apply it to a solid phase synthesis, and achieve quantitative cleavage. *Id*. This disclosure would have strongly motivated a POSITA to utilize the azidomethyl group in the SBS method disclosed by Tsien. Ex. 1101, ¶¶108, 110-113.

In the prior IPR, Illumina argued that Loubinoux's reported yields would have led a POSITA to expect that azidomethyl would not cleave quantitatively, and therefore would not be an attractive protecting group. Ex. 1092, 24-25. But Illumina misrepresented the overall yields described in Loubinoux as corresponding to the "removal *efficiency* for phenolic azidomethyl groups." *Id*., 24 (emphasis

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[7] *See also* Exs. 1048-1052 (demonstrating public availability of Young thesis prior to August 2002 via University of Wisconsin-Madison Library catalog (Exs. 1048-49), inclusion in WorldCat catalog (*id.*), availability for sale from ProQuest/UMI (Ex. 1050-52), and publication and circulation of the abstract in DAI (Exs. 1050-52).

added). As described above, Loubinoux actually reports pure product ***yields*** of an unstable phenol product as between 60 and 80% after purification, ***not*** only the "efficiency" of the removal. Ex. 1101, ¶¶110-112. A POSITA would have readily understood this distinction — and given the expectation that much of the lost yield would have been due to purification of the unstable products — would have known that the reported yields in Loubinoux should be considered encouraging that azidomethyl could be deblocked in high yield on the solid phase. *Id*. Knowing that the azidomethyl group was compatible with solid phase synthesis and cognizant of the yield that solid phase reactions would offer, a POSITA would have been motivated by Loubinoux to use azidomethyl, as evidenced by Young (Ex. 1051).

v. **Rapid deblocking**

In the prior IPR, Illumina also claimed that the prior art indicates that the reduction of azido to amino would not proceed rapidly, without defining what "rapid" means within the context of the claimed invention, and without considering the kinetics of the reduction reaction. Ex. 1092, 29. A POSITA would have appreciated that use of the Staudinger reaction, such as that disclosed in Zavgorodny or Greene & Wuts/Loubinoux, would have likely resulted in rapid deblocking: "The phosphine and the azide react with each other rapidly in water at room temperature in high yield. Both are abiotic and essentially unreactive toward biomolecules inside or on the surfaces of cells." *See* Ex. 1029, 2007. The same result would have been expected if an alternative phosphine reagent, such as TCEP, was chosen. Ex. 1101, ¶116.

Furthermore, Illumina's argument that the literature indicates it takes a long time (between 3 to 72 hours) "for nucleoside-related compounds bearing an azido group to be converted to an amino group using triphenylphosphine in pyridine and water" is misleading. *See*, Ex. 1092, 29. First, Illumina's argument that Loubinoux reports a reaction time of 7-10 hours for triphenylphosphine in pyridine and water is simply incorrect; that reported time is for the treatment with hydrogen in the presence of palladium on carbon, not the method using triphenylphosphine. Ex. 1006, 4-7. Second, none of Illumina's cited references utilized solid-phase synthesis and therefore their authors were unable to use significant molar excesses of reducing agents. *See* Ex. 1098, ¶50. Accordingly, a POSITA would have expected to achieve significantly faster reaction times than those reported. Ex. 1101, ¶¶105-106.

As discussed above, rapid deblocking is a relative term and its definition would be dependent on what a POSITA sought to use the deblocking reaction for. Ex. 1105, ¶84. However, given the state of the art in 2002, a deblocking reaction on the order of many minutes to several hours could reasonably be considered to be rapid by a POSITA for most applications. *Id*.

As noted above, a POSITA would have been sufficiently knowledgeable and skilled to optimize reported reactions to improve the speed of deblocking. For example, the POSITA would have been able to select an alternative deblocking reagent, such as TCEP, which was known to be water-soluble, bio-orthogonal, and to react rapidly with azides. Ex. 1029, 2007; Ex. 1105, ¶¶77, 114-117.

Furthermore, it was known in the art that the speed of the reactions, such as the cleavage of the azidomethyl group, could be improved by using a higher concentration of reducing reagents, higher temperatures, as well as optimized salt concentrations and pH conditions. Ex. 1105, ¶60, 74. Given these options, a POSITA would have been motivated to select an azidomethyl protecting group and thereby achieve rapid and high-yielding deblocking.

2. The obviousness of combining azidomethyl with Tsien's SBS methods is further supported by the '537 Patent and Illumina's statements in other proceedings

As demonstrated above, Tsien's incorporation and deblocking criteria would have suggested to a POSITA that azidomethyl would be a suitable protecting group for use with Tsien's SBS methods. The fallacy of Illumina's counter-arguments from the prior IPR is highlighted by the contradiction between Illumina's non-obviousness and written description/enablement arguments in prior litigation. On the one hand, Illumina has asserted that an azidomethyl protecting group is sufficiently described and enabled to a POSITA based solely on its disclosure of azidomethyl as one of 20+ different blocking groups in Figure 3 (Ex. 1097, 15:15-25), despite the complete absence of disclosure of appropriate deblocking reagents or conditions, much less how to achieve a high yield from the deblocking reaction. Ex. 1001. Yet, on the other hand, when faced with Zavgorodny's disclosure of azidomethyl as being used as a protecting group for nucleosides that is capable of being removed under "very mild and specific" conditions with "triphenylphosphine and aqueous pyridine," Illumina argues not only that a POSITA would be dissuaded

from using azidomethyl because these conditions would allegedly denature DNA and not result in a quantitative yield, but that these alleged deleterious effects would actually occur. Ex. 1092, 19-21. If that were true, certainly Illumina would have needed to include additional disclosure regarding suitable deblocking reagents and conditions for azidomethyl in order to sufficiently describe and enable the claimed reversible azidomethyl protecting group. 32 F.3d at 1568. Illumina cannot have it both ways.

As established by the foregoing, there was ample teaching in the prior art to motivate a POSITA to combine Tsien's method with the azidomethyl group from Zavgorodny and Greene & Wuts. As a POSITA would also have had a reasonable expectation of success (*see* 821 F.3d at 1367), the challenged claims are obvious.

E. A POSITA Would Have Recognized Azidomethyl As a Known Element That Could Be Simply Substituted Into Tsien's SBS Method to Yield Predictable Results

Obviousness may be supported by a finding that the combination arises from "simple substitution of one known element for another to obtain predictable results." MPEP §2143; *KSR*, 550 U.S. at 416. This rationale is supported by "(1) the finding that the prior art contained a [method] which differed from the claimed [method] by the substitution of some components (step, element, etc.) with other components; (2) a finding that the substituted components and their functions were known in the art; [and] (3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable …." MPEP §2143. Absolute predictability is not required;

only a reasonable expectation of success. *See Pfizer*, 480 F.3d at 1364.

As discussed above, the only difference between the nucleotides used in Tsien's SBS method and claimed method is the use of an azidomethyl protecting group. *See* Part VIII, *supra*; Ex. 1105, ¶72. Moreover, a POSITA would have recognized that azidomethyl satisfied all of Tsien's criteria for a blocking group for SBS. *See* Part IX.D, *supra*.

The azidomethyl protecting group and its function were known in the art. Zavgorodny not only disclosed the use of an azidomethyl protecting group, but did so for the same function as claimed in '537 claim 1, *i.e.*, to protect the 3′-OH on the sugar of a nucleoside. Ex. 1008, 7594. Moreover, Greene & Wuts, the go-to reference book for identifying protecting groups for organic synthesis, also disclosed azidomethyl as a protecting group for a hydroxyl group. Ex. 1005, 260; Ex. 1105, ¶¶28-29, 94. Indeed, the '537 patent acknowledges that a POSITA could select a suitable protecting group from Greene & Wuts. Ex. 1001, 7:65-9:4. A POSITA would also have known of azidomethyl and its function as a hydroxyl protecting group from other prior references. *See* Loubinoux, Ex. 1006 (protecting hydroxyl group during synthesis of unstable phenols); Young, Ex. 1051 (protecting hydroxyl group during synthesis of sulfated peptides). In each of these references, azidomethyl served as a protecting group (*i.e.*, reversible blocking group) for a hydroxyl group, such that both the group itself and its function as a protecting group were necessarily known in the art.

Moreover, as discussed above, a POSITA could have substituted the

azidomethyl protecting group of Zavgorodny and/or Greene & Wuts for the reversible blocking groups disclosed by Tsien, such as the "presently preferred" alkyl ethers, to arrive at the claimed nucleotide labeling method. *See* Part IX.C, *supra*. Since the claimed invention only requires incorporation of the nucleotide (not deblocking or subsequent incorporation steps), a POSITA would have readily appreciated that a nucleotide with an azidomethyl protecting group on the 3′-OH could be substituted for the protecting groups in Tsien due to its small size, conformational flexibility, and likely ability to be incorporated by polymerase due to its reported use in bio-orthogonal chemistry and prior reports of azide-bearing nucleotides being successfully incorporated by polymerases. *See* Part IX.C-D, *supra*; Ex. 1105, ¶¶95-102. Indeed, the Federal Circuit already declared that a POSITA would have a reasonable expectation of success at arriving at the claimed invention based on the combination of Tsien and Zavgorodny. 821 F.3d at 1367. Moreover, even though not required by the claims, due to the known properties of azidomethyl as a protecting group, a POSITA would also have known that it could be substituted in an SBS process with multiple incorporation-deblocking cycles. *See* Part IX.D.iv; Ex. 1105, ¶¶95-102, 113-124. Accordingly, it would have been obvious to simply substitute any of Tsien's protecting groups with the azidomethyl group.

F. Ground 2: Claim 3 is Obvious Over Tsien in Combination with Greene & Wuts and Zavgorodny, In Further Combination with Prober.

Claim 3, which depends from claim 1, recites the additional limitation

"wherein the base is a deazapurine." This limitation is disclosed in Prober, published in 1987, which discloses the use of a fluorescent dye attached "to the 7 position in the 7-deazapurines" and explains that "[t]he 7-deazapurines were used to facilitate stable linker arm attachment at that site." Ex. 1007, 337, 338-40 (reporting incorporation); Ex. 1105, ¶¶16, 72, 125. Indeed, Illumina previously argued that "[d]eazapurines were part of the DNA sequencing art since the late 1980s and had become ubiquitous in the 1990s due to numerous well-known benefits of deazapurines for sequencing." Ex. 1087, 3; 620 Fed.Appx. at 925 ("There does not appear to be any dispute that the prior art discloses deazapurines.").

A POSITA would have been motivated to combine Prober's disclosure of deazapurines with Tsien because, as previously acknowledged by the Federal Circuit and admitted by Illumina, "Tsien expressly teaches using the nucleotides described in Prober, which are C7-substituted deazapurines." Ex. 1087, 22; Ex. 1003, 29:12-14. "[T]he express invitation to incorporate a 3′-blocked dNTP having a fluorescent base label using the method disclosed in Prober provides a motivation to combine Tsien with the 7-deazapurine of Prober." 620 Fed.Appx. at 927-28; Ex. 1087, 3, 16-18, 22, 31-33; Ex. 1103, 12-13; Ex. 1105, ¶¶126-127.

Additionally, as Illumina previously argued, ***"[e]ven absent this express encouragement***, a skilled artisan would be motivated to combine the disclosure of Tsien with a deazapurine base ***due to the ubiquity and well-known benefits of deazapurines for sequencing***." Ex. 1087, 22; 620 Fed.Appx. at 928; Ex. 1105,

¶¶126-129. Thus, a POSITA would have had both a motivation to combine and a reasonable expectation of success in using deazapurine with Tsien's teachings as recited in claim 3. *Id.*

X. OBJECTIVE INDICIA OF NONOBVIOUSNESS DO NOT SUPPORT THE PATENTABILITY OF THE CHALLENGED CLAIMS

Illumina will not be able to rebut the prima facie case of obviousness with evidence of secondary considerations. As detailed below, each of the arguments previously raised by Illumina is without merit because the requisite "nexus" between the challenged claims and the alleged secondary considerations cannot be met.[8] *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013).

A. No Nexus Between the Satisfaction of a Long-Felt, Unmet Need and the Claimed Azidomethyl Group

Illumina previously asserted that its invention satisfied a long-felt, unmet need for "protecting groups that could be efficiently and rapidly cleaved under conditions compatible with DNA sequencing," "a fast and efficient SBS method," and "for SBS nucleotides and methods capable of very high efficiency (quantitative or nearly quantitative) cleavage under DNA-friendly mild reaction conditions."

[8] Illumina previously made confidential arguments and cited confidential exhibits in support of secondary considerations (Ex. 1092, 47-49), and the prior Petitioner also referenced confidential information in its Reply (Ex. 1093, 11), such that Petitioner herein cannot address these issues at this time.

Ex.1092, 44-49; Ex. 1093, 10-11. However, none of these purported long-felt, unmet needs are commensurate in scope with the claims, which do not require removal of the protecting group, much less removal with a high degree of efficiency or rapidity, and have no requirements regarding reaction conditions. Thus, these purported long-felt, unmet needs are irrelevant to the obviousness inquiry.

Moreover, Illumina did not provide any evidence that its purported satisfaction of a long felt need for "fast and efficient SBS methods" was due to the claimed azidomethyl protecting group, as opposed to other factors, and thus did not establish the necessary nexus. Ex. 1105, ¶¶131-132. Illumina's argument relies on two publications, but neither article supports the proposition that the alleged success was causally linked to the azidomethyl protecting group. *See* Ex. 1092, 45-46 (discussing Bentley (Ex. 1039), Mardis (Ex. 1040), and Dr. Romesberg's discussion thereof (Ex.1098, ¶¶61-65)).

Bentley — which identifies all six of the '537's named inventors as coauthors — describes ***numerous*** factors that contributed to the alleged success described therein, including the use of an engineered polymerase to improve the efficiency of incorporation of the nucleotides, the use of a particular cleaving agent to remove the protecting group, and hardware and software improvements. Ex. 1039, 53, 58 & Supp. Info. 16, Fig.S2b; Ex. 1105, ¶¶133-137.

Similarly, Mardis does not even mention, much less credit, Illumina's claimed azidomethyl group as causing an increase in data output. Yet, Illumina relies on Mardis for the proposition that Illumina's "protected nucleotides

demonstrate long read lengths in SBS and can generate superior amounts of sequence information" and "were recognized for increasing data output by eight orders of magnitude." Ex. 1092, 46 (citing Mardis, Ex. 1040, 1999). Rather, Mardis provides an overview comparing the development of sequencing platforms between 2001 and 2011, and does not discuss any details regarding Illumina's products. Thus, Mardis simply provides no basis for concluding that the particular claimed protecting group is responsible for any alleged increase in data output. Ex. 1101, ¶¶138-139 (discussing Ex. 1040, Fig.1, Table 1).

Moreover, during the deposition of Illumina's expert in the prior IPR, Dr. Burgess admitted that numerous factors would impact the read length in a SBS process, including selection of cleaving agent, concentration of cleaving agent, the pH of the cleaving conditions, temperature, and selection of the polymerase. Ex. 1100, 49:1-24, 50:1-3, 52:14-17. Thus, any alleged success of Illumina's commercial SBS product is inseparable from these other, unclaimed, features of the product.

B. Illumina's Arguments for New and Unexpected Results Do Not Have a Sufficient Nexus to the Claims and Are Based on Hindsight Bias

Illumina's assertion that the 3′-*O*-azidomethyl group performs unexpectedly better than other protecting groups fails to account for other, unclaimed factors, such as choice of polymerase and removal conditions, and is therefore insufficient to support nonobviousness. *See* Part X.A (discussing Bentley).

Notably, Illumina alleges that Ju, Tsien, and other prior art did not suggest

that 3′-*O*-azidomethyl groups "are cleaved with surprisingly greater speed" (Ex. 1092, 51), but removal of the protecting group, much less removal at high speed, is not recited in the challenged claims. Moreover, the '537 specification says nothing about the alleged superiority of azido-containing protecting groups or the alleged "dramatically improved results relative to SBS methods in the prior art." *Id*. Rather, the '537 includes azido groups as one of a multitude of possible protecting groups that a POSITA could select, and states that such a person would be sufficiently skilled to identify suitable conditions for their use. Ex. 1001, Fig.3, 7:57-8:4. Thus, Illumina's arguments reflect a hindsight bias because what was explicitly described in the patent as being within the knowledge and skill of a POSITA is now alleged to be both nonobvious and the basis of new and unexpected results.

Illumina also further relies on experimental comparisons between 3′-*O* allyl groups and 3′-*O*-azidomethyl groups, but the details of those comparisons were filed under seal such that Petitioner cannot address them at this time. *See* Ex. 1092, 51-55 (redacted); Ex. 1098, ¶¶79-81; Ex. 1101, ¶¶140-142.

C. Evidence of Copying is Completely Absent

Illumina previously asserted that evidence of copying by the prior Petitioner "confirms the superiority of [Illumina's] 3′-*O*-azidomethyl group over other protecting groups for SBS." Ex. 1092, 55-59. This argument was partially redacted in the public filing (Ex. 1092, 58-59), such that Petitioner can only partially address this argument at this time. Ex. 1101, ¶¶143-145. However, this argument appears

to have been erroneous, as there was apparently no evidence that Dr. Ju's group attempted to replicate any specific product of Illumina (Ex. 1092, 56-58), as required for it to constitute objective evidence of nonobviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Kamada, Ltd. v. Grifols Therapeutics Inc.*, IPR2014-00899, Paper 22, 4 (Mar. 4, 2015) (Ex. 1085).

D. Praise by Others Was Likely Unrelated to the Claim Limitations

Illumina previously asserted that praise by others was a relevant secondary consideration (Ex. 1092, 59-60), but that argument was completely redacted in public filings such that Petitioner cannot address it at this time. *See* Ex. 1092, 59-60; Exs. 1098-1099. However, based on the prior petitioner's argument in reply, it appears that Illumina failed to establish the requisite "nexus" because the praise was not specifically directed to the alleged novel feature of the invention. *See* Ex. 1093, 15.

XI. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests this *inter partes* review, and cancellation of claims 1-6, and 8 of the '537 patent.

Dated: October 5, 2017

Respectfully Submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 CFR §42.24(a), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this Petition for *Inter Partes* Review, that the number of words in this Petition is 13,999. Pursuant to 37 C.F.R. § 42.24(a)(1), this word count does not include the table of contents, table of authorities, table of exhibits, mandatory notices, certificate of word count, or the certificate of service.

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§42.6(e)(4)(i) *et seq*. and 42.105(b), the undersigned Certifies that on October 5, 2017, a true and entire copy of this **PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 7,566,537 B2**, and all supporting exhibits, were served by EXPRESS MAIL to the Patent Owner by serving the correspondence address of record, indicated below.

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