

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COMPLETE GENOMICS, INC.,  
Petitioner,

v.

ILLUMINA CAMBRIDGE LTD.,  
Patent Owner.

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Case IPR2017-02172  
Patent 7,566,537 B2

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Before ERICA A. FRANKLIN, ZHENYU YANG, and  
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION  
Denying Institution of *Inter Partes* Review  
37 C.F.R. § 42.108

ILLUMINA EX. 1096 ILLUMINA V. COLUMBIA IPR2018-00291, -00318, -00322, -00385, and -00797
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## I. INTRODUCTION

Complete Genomics, Inc. (“CGI” or “Petitioner”), on October 5, 2017, filed a Petition to institute *inter partes* review of claims 1–6 and 8 of U.S. Patent No. 7,566,537 B2 (“the ’537 patent”). Paper 1 (“Pet.”).<sup>1</sup> Illumina Cambridge Ltd. (“Patent Owner”), on January 23, 2018, filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”).

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless the Petition “shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Institution of *inter partes* review is, however, discretionary. *See* 35 U.S.C. § 314(a); 35 U.S.C. § 325(d); 37 C.F.R. § 42.108(a). Based on the particular circumstances of this case, as explained below, we exercise our discretion under § 325(d) and deny the Petition.

## II. BACKGROUND

### A. *Related Matters*

Petitioner identifies other proceedings related to the ’537 patent. Pet. 4–7. The identified proceedings include, *inter alia*, the following:

- 1) IPR2013-00517 (petition for *inter partes* review by Intelligent Bio-Systems, Inc. (“IBS”));
- 2) IPR2013-00518 (petition for *inter partes* review by IBS);
- 3) *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) (appeal of IPR2013-00517);
- 4) *Illumina, Inc. v. Qiagen, N.V.*, 207 F.Supp.3d 1081 (N.D.

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<sup>1</sup> Petitioner identifies BGI Shenzhen Co., Ltd. (and other BGI companies) as a real party-in-interest to these proceedings. Pet. 4.

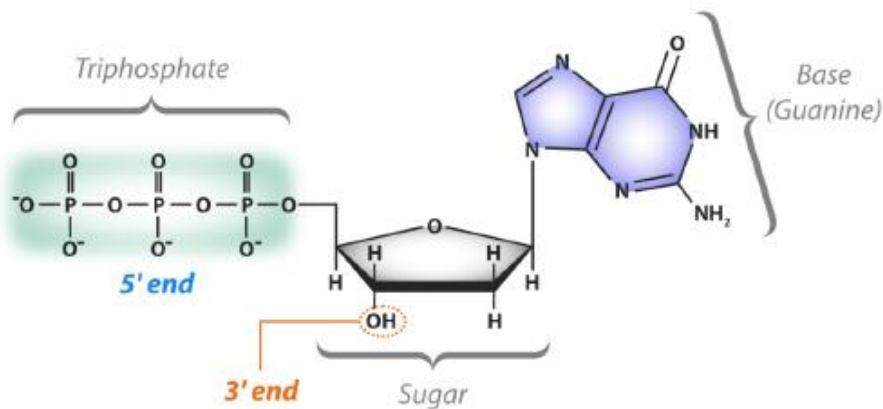
- Cal. 2016) (involving assertion of the '537 patent against Qiagen and its subsidiary, IBS);
- 5) *The Trustees of Columbia University v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.) (involving assertion of patents against Illumina, and assertion of the '537 patent against IBS, Columbia's licensee of the accused technology); and
- 6) IPR2017-02174 (petition for *inter partes* review by CGI, filed concurrent with the present Petition).

Pet. 4–7. We describe these proceedings in more detail in Section II.E. below.

*B. Background Technology and the '537 Patent*

The '537 patent relates generally to labeled nucleotides and nucleosides, and to methods of using such molecules in, for example, nucleic acid sequencing reactions. Ex. 1001, 2:1–7.

A “nucleotide” consists of a nitrogenous base, a sugar, and one or more phosphate groups. *Id.* at 4:48–49. An illustrative depiction of a deoxyribonucleotide triphosphate is provided below.



Ex. 1101, ¶ 8. The depiction above shows, *inter alia*, the 3'-hydroxyl(3'-OH) group of the deoxyribose sugar; the sugar of a DNA nucleotide is a 2'

deoxyribose, meaning the 2' carbon lacks a bond to an oxygen atom. *Id.*

¶ 10 (depicting 2-deoxyribose and ribose); Ex. 1001, 4:49–51 (“In RNA, the sugar is a ribose, and in DNA is a deoxyribose, i.e., a sugar lacking a hydroxyl group that is present in ribose [at the 2' carbon]”).

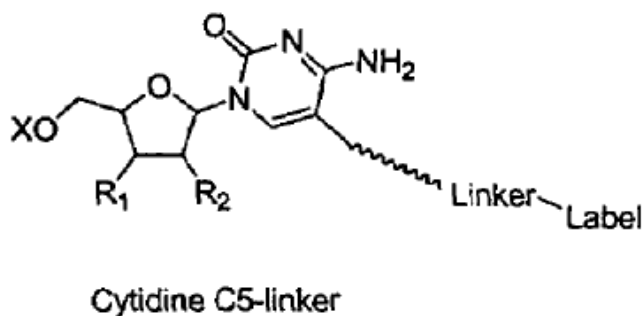
Nucleotides, such as depicted above, are building blocks of DNA and, through complementary base-pairing, form molecules of DNA that consist of two associated nucleic acid strands and a double-helical structure that resembles a twisting ladder. Ex. 1101, ¶¶ 8–9. Natural DNA contains four bases: the base may include a purine or pyrimidine, such as the purines adenosine (A) and guanine (G), and the pyrimidines cytosine (C) and thymine (T). Ex. 1001, 4:51–54. The sequence of these bases in DNA provides genetic information, and ultimately encodes the traits in living organisms. *Intelligent Bio-Systems*, 821 F.3d at 1362.

A base of one DNA strand bonds with the complementary base on the opposing strand in a known pattern: A pairs with T, and G pairs with C. Ex. 1101, ¶ 9. Because of this pattern of base pairing, if the sequence of one strand is known, the other strand’s sequence can be deduced. *Id.* In addition, enzymes (e.g., DNA polymerase) may cause the strand to be extended with the phosphate group on the 5' carbon of each additional nucleotide attaching to the 3'-OH of the last nucleotide in the strand via a new phosphodiester bond. *Id.* ¶ 11. The added nucleotide is one that, as explained above, bonds with its complementary base of the nucleotide at a corresponding position on the opposing nucleic acid strand. *Id.* ¶ 9; Ex. 1001, 2:50–53.

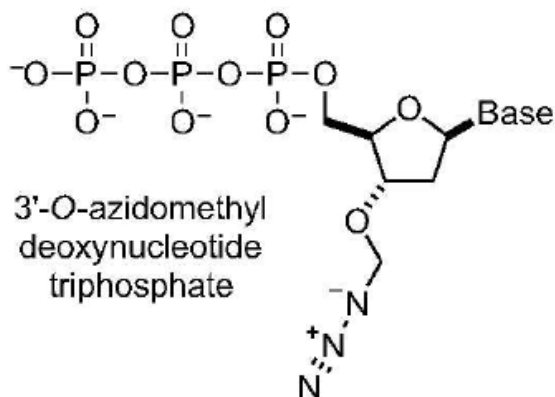
As described in the '537 patent, “[t]he invention features a nucleotide or nucleoside molecule, having a base that is linked to a detectable label via a cleavable linker.” Ex. 1001, 2:23–24. The label may be, for example, a

fluorophore that is detectable by fluorescence spectroscopy. *Id.* at 5:20–25. The nucleotide also includes a ribose or deoxyribose sugar, which “sugar can include a protecting group attached via the 2' or 3' oxygen atom,” and the protecting group “can be removed to expose a 3'-OH.” *Id.* at 2:25–28.

The '537 patent depicts several exemplary labeled nucleotide structures, such as shown below.



Ex. 1001, Fig. 1 (partial). Figure 1 (partial) above shows a nucleotide having a base (here cytidine) attached to a label via a linker. *Id.* The '537 patent explains that “X” in this molecule can be, for example, a triphosphate, and that R<sub>1</sub> and R<sub>2</sub> may be selected from H, OH, or any group that can be transformed into an OH. *Id.* at 4:7–11. Among the “suitable hydroxyl protecting groups” that can be transformed into an OH, the '537 patent identifies azidomethyl (CH<sub>2</sub>N<sub>3</sub>). *Id.* at Fig. 3. A further representation of an azidomethyl protecting group is shown below.



Ex. 1101, ¶ 95. The representation above shows a 3'-O-azidomethyl deoxynucleotide triphosphate, where the azidomethyl group is attached to the 3' oxygen atom of the deoxyribose sugar moiety, thereby, protecting a nascent 3'-OH.

The '537 patent describes methods of labeling nucleic acids, in which an enzyme is used to incorporate a labeled nucleotide into the nucleic acid molecule. Ex. 1001, 2:32–38. The '537 patent also describes methods of using labeled and blocked nucleotides to determine the sequence of a target single-stranded polynucleotide. *Id.* at 2:50–57. More specifically, the '537 patent explains that this method

can be carried out by contacting the target polynucleotide separately with the different nucleotides to form the complement to that of the target polynucleotide, and detecting the incorporation of the nucleotides. Such a method makes use of polymerisation, whereby a polymerase enzyme extends the complementary strand by incorporating the correct nucleotide complementary to that on the target. The polymerisation reaction also requires a specific primer to initiate polymerisation.

*Id.* at 8:50–58. Because the 3'-OH of the nucleotide(s) to be added is protected by a protecting group, the enzyme incorporates only one nucleotide at a time into the complementary strand, thus providing a controlled sequencing reaction. *Id.* at 7:51–54. The detectable label uniquely identifies the particular type of nucleotide (e.g., containing a base “G”) that was incorporated into the growing complementary strand. *Id.* at 2:55–57, 5:20–24, 10:4–9. The label and protecting group are then removed, thus exposing a 3'-OH on the previously added nucleotide, and the process repeats with the addition of the next labeled and blocked nucleotide(s). *Id.* at 2:55–3:16, 7:43–8:14. By detecting, one-by-one, the type of nucleotides

that are added to the complementary strand, the sequence of the entire target polynucleotide chain can be determined. *Id.* at 2:50–3:3.

*C. Illustrative Claims*

Petitioner challenges claims 1–6 and 8. Claim 1, the only challenged independent claim, and dependent claim 6 are reproduced below:

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

6. The method according to claim 1, wherein the protecting group is CH<sub>2</sub>N<sub>3</sub> [*i.e.*, azidomethyl].

Ex. 1001, 19:48–59, 20:3–4.

*D. The Asserted Grounds of Unpatentability*

Petitioner contends claims 1–6 and 8 are unpatentable under 35 U.S.C. § 103 based on the following grounds. Pet. 8–9.

Ground	References	Basis	Claims
1	Tsien, <sup>2</sup> Greene & Wuts, <sup>3</sup> and Zavgorodny <sup>4</sup>	§ 103	1, 2, 4–6, and 8

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<sup>2</sup> Tsien, WO 91/06678 A1, published May 16, 1991. Ex. 1003.

<sup>3</sup> Theodora W. Greene & Peter G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 1–5, 14–23, 246–60 (John Wiley & Sons, Inc., 3<sup>rd</sup> ed. 1999). Ex. 1005.

<sup>4</sup> Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in*

2	Tsien, Greene & Wuts, Zavgorodny, and Prober <sup>5</sup>	§ 103	3
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Petitioner also relies on the Declaration of John D. Sutherland, D. Phil. (Ex. 1101), and cites to several ancillary references.

*E. History of the '537 Patent at the U.S. Patent Office and in Other Legal Proceedings*

i) Relevant Prosecution History

The '537 patent issued on July 28, 2009 from U.S. Application No. 11/301,578, filed December 13, 2005. Ex. 1001.<sup>6</sup> Claim 9 (which later issued as claim 1) did not recite a “protecting group” or a “protecting group [that] comprises an azido group” when that claim was originally filed. Ex. 1002, 71. At the time the application was filed, the applicants disclosed Zavgorodny '00<sup>7</sup> in an Information Disclosure Statement (IDS) along with

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*Nucleoside Chemistry*, 32 TETRAHEDRON LETTERS 7593–96 (1991). Ex. 1008.

<sup>5</sup> James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCIENCE 336–41 (1987). Ex. 1007.

<sup>6</sup> This application is a divisional of U.S. Application No. 10/227,131, filed on August 23, 2002 and which issued as U.S. 7,057,026 B2 on June 6, 2006.

<sup>7</sup> S.G. Zavgorodny et al., *S,X-Acetals In Nucleoside Chemistry. III. Synthesis of 2'- and 3'-O-Azidomethyl Derivatives of Ribonucleosides*, 19 NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS 1977–91 (2000) (“Zavgorodny '00”). Ex. 1009. Zavgorodny '00 was not expressly relied upon as part of the prior art combination in IPR2013-00517 or the prior art combinations proposed in the pending IPRs (IPR2017-02172 and IPR2017-02174). Zavgorodny '00 includes similar disclosures related to azidomethyl blocking groups that are relied upon from Zavgorodny (Ex. 1008) in the presently pending Petition, and that were relied upon in IPR2013-00517. Compare Ex. 1009, 7494–95 with Ex. 1008, 1980–81 (disclosing an



roughly twenty other references. *Id.* at 197–99. On June 25, 2007, the applicants filed an IDS disclosing Tsien, along with four other references. *Id.* at 115–16. Greene & Wuts and Prober are identified in the body of the '537 patent's specification. Ex. 1001, 5:30–31, 6:14–17.

On October 30, 2007, the Examiner entered a rejection of claim 9 as anticipated by Ju.<sup>8</sup> Ex. 1002, 84. In response, on February 1, 2008, the applicants amended claim 9, adding the limitation:

and the nucleoside 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 atoms, and said protecting group can be modified or removed to expose a 3' OH group *and the protecting group comprises an azido group.*

*Id.* at 71 (underlining omitted and emphasis added). The applicants also added, *inter alia*, new claim 34, which was substantially the same as claim 9 except that it recited “the protecting group comprises an allyl moiety.” *Id.* at 72. The applicants responded to the Examiner's rejection, explaining the addition of the azido group to claim 9, and arguing the amended and newly presented claims were not taught or suggested by the prior art. *Id.* at 77–78.

The Examiner responded on May 16, 2008 with a rejection of claim 34 as obvious over Tsien and Greene & Wuts.<sup>9</sup> *Id.* at 64. The Examiner

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azidomethyl group can be removed under specific and mild conditions (triphenylphosphine in aqueous pyridine at ~ 20°C)). Zavgorodny was disclosed and appears in the references cited portion of the '537 patent. Ex. 1001, 3 (right col.).

<sup>8</sup> Ju et al., US 6,664,079 B2, issued Dec. 16, 2003. Ex. 1038.

<sup>9</sup> The Examiner appears to have relied on a prior edition of Greene & Wuts (Theodora W. Greene & Peter G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS (John Wiley & Sons, Inc., 1991) to the third edition relied upon in the present Petition and in IPR2013-00517. Ex. 1002, 64, 67. The 1999

determined the 3'-OH allyl protecting group was implicitly disclosed in Tsien and also obvious in view of Greene & Wuts and “the Patent Owner’s admission that all of the protecting groups are known in the prior art.” *Id.* at 65. As to claim 9 (reciting an azido protecting group) and claim 28 (reciting an azidomethyl (CH<sub>2</sub>N<sub>3</sub>) protecting group), the Examiner, without further comment, noted those claims were allowed. *Id.* On August 21, 2008, the applicants canceled claim 34 and its dependent claims, and requested allowance of the other pending claims. *Id.* at 59. Claims 9 and 28 later issued in the ’537 patent as claims 1 and 6, respectively. *Id.* at 25.

ii) Prior Petitions for *Inter Partes* Review

In IPR2013-00518, IBS challenged claims 7 and 11–14 of the ’537 patent, which claims were canceled based on Patent Owner’s disclaimer and request for adverse judgment. Pet. 6; Exs. 1088 and 1089.

In IPR2013-00517, IBS challenged claims 1–6 and 8 of the ’537 patent on multiple obviousness grounds. Pet. 6; Ex. 1090, 6–7 (Rev. Petition dated Aug. 3, 2013, Paper 7). The specific grounds are below:

Ground	References	Basis	Claims
1a	Ju and Zavgorodny	§ 103	1–6 and 8
1b	Ju and Greene & Wuts	§ 103	1–6 and 8
1c	Tsien and Zavgorodny	§ 103	1–6 and 8
1d	Tsien and Greene & Wuts	§ 103	1–6 and 8
2a	Tsien, Zavgorodny, and Prober	§ 103	3

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third edition of Greene & Wuts (Ex. 1005) appears in the references cited portion of the ’537 patent. Ex. 1001, 3 (right col.).

2b	Tsien, Greene & Wuts, and Prober	§ 103	3
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Ex. 1090, 7–8.

Patent Owner waived the filing of a preliminary response and, on February 13, 2014, the Board instituted *inter partes* review on claims 1–6 and 8 over Tsien (or Ju) in combination with Zavgorodny (grounds 1a and 1c in the table above). Ex. 1091, 2, 15. The Board further instituted review of claim 3 based on the combination of Tsien, Zavgorodny, and Prober (ground 2a). *Id.* The Board concluded that the challenges to claims 1–6 and 8 based on the combination of Tsien (or Ju) and Greene & Wuts were “redundant” to the grounds for which institution was ordered. *Id.* at 5, 15. On May 5, 2014, Illumina filed its Patent Owner Response. Ex. 1092. And, on July 28, 2014, IBS filed its Reply. Ex. 1093.

The Board held a full trial and issued a Final Written Decision dated February 11, 2015. Ex. 1094. The Board determined that the preponderance of the evidence did not support a conclusion that claims 1–6 and 8 were unpatentable. *Id.* at 3–4. Among other things, the Board “agree[d] with Patent Owner that Petitioner [had] not shown . . . that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl group as the 3' hydroxyl protecting group in Tsien’s processes.” *Id.* at 9. The Board further found that “the prior art suggests that an ordinary artisan would not have expected Zavgorodny’s azidomethyl group to be removed quantitatively, as Tsien requires.” *Id.* at 14. As explained by the Board, Tsien’s requirement for quantitative deblocking “mean[s] essentially 100% removal of the protecting group.” *Id.* at 12.

In reaching its conclusion, the Board also relied on Greene & Wuts and Loubinoux,<sup>10</sup> which together disclose removal of an azidomethyl protecting group from phenols (as distinct from simple aliphatic alcohols like the 3' hydroxyl of a deoxyribonucleotide). *Id.* at 13. Based on the reported yields (60–80%) of deprotected phenols in Loubinoux, and Greene & Wuts' teaching that a phenol is a better leaving group (i.e., is more easily cleaved) than a simple alcohol, the Board found that the ordinary artisan would have expected *inefficient* removal/deblocking of an azidomethyl moiety in Tsien's methods. *Id.* at 13–14; Ex. 1005, 248. Thus, contrary to IBS's contentions, the Board determined the ordinarily skilled person would not have been motivated to use an azidomethyl group to meet Tsien's sequencing criteria — especially the requirement for quantitative deblocking. *Id.* at 7, 18.<sup>11</sup> Although the Board also criticized IBS's Reply as introducing new evidence and lines of reasoning to support the challenge, the Board nevertheless determined the Reply was unpersuasive. *Id.* at 16 (“[E]ven if we were to overlook the procedural infirmities in Petitioner's Reply arguments, we would not find them persuasive”).<sup>12</sup>

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<sup>10</sup> Bernard Loubinoux et al., *PROTECTION OF PHENOLS BY THE AZIDOMETHYLENE GROUP APPLICATION TO THE SYNTHESIS OF UNSTABLE Phenols*, 44 TETRAHEDRON 6055–64 (1988) (as translated). Ex. 1006. Greene & Wuts cites Loubinoux for the use of an azidomethyl group to protect phenols. Ex. 1005, 260.

<sup>11</sup> The Board made similar findings and reached a similar conclusion with respect to the challenge based on Ju and Zavgorodny. Ex. 1094, 18–22.

<sup>12</sup> For example, the Board considered but rejected IBS's contention that it would have been obvious and a matter of ordinary creativity to use deblocking conditions other than those reported in Zavgorodny (e.g., using different removal agents and/or higher concentrations of reagents to drive the reaction rapidly to completion). Ex. 1094, 14–18.

iii) Proceedings Before the Federal Circuit

On May 9, 2016, the Federal Circuit affirmed the Board's determination in IPR2013-00517 that claims 1–6 and 8 had not been shown to be obvious. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016). The court analyzed the prior art combination of Tsien and Zavgorodny. *Id.* at 1363–64. And, like the Board, the court accepted that Tsien required quantitative deblocking for successful use of 3' blocking groups in Tsien's DNA sequencing methods and that, "for the deblocking (i.e., the removal of the protecting group) to be quantitative, it must take place at 100% or near-100% efficiency." *Id.* at 1364.

According to the Federal Circuit, although the challenged claims of the '537 patent do not require quantitative deblocking, the expectation (or lack thereof) of high efficiency deblocking "is central to a finding of no motivation to combine." *Id.* at 1368. That is so, the court explained, because the petitioner argued the skilled artisan would have been motivated to use Zavgorodny's azidomethyl group with Tsien's SBS (sequencing-by-synthesis) method to meet Tsien's criteria. *Id.*<sup>13</sup> Analyzing *Greene & Wuts* and *Loubinoux*, the court further concluded there was "substantial evidence to support a finding that a person of ordinary skill would not have had a reason to combine Tsien or Ju with Zavgorodny to achieve the claimed invention." *Id.* at 1368–69 ("These references [*Greene & Wuts* and

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<sup>13</sup> As noted by the Federal Circuit, "IBS argued that an ordinary artisan, to improve the efficiency, reliability, and robustness of the sequencing by synthesis method taught by Tsien, would have been motivated to use other protecting groups that meet the criteria of Tsien, such as the azidomethyl group taught by Zavgorodny." *Intelligent Bio-Systems*, 821 F.3d at 1364 (internal quotation marks and citation omitted); *see also* Ex. 1094, 7.

Loubinoux] support a conclusion that the claimed efficiency that allegedly motivated the combination would not be achieved.”). Indeed, as the court held, “[t]his is so because the azidomethyl group would have been expected to perform inefficiently in that role [as a protecting group that can be removed to expose a 3'-OH group of a nucleotide].” *Id.* at 1369.

iv) Proceedings Before the District Courts

After the Federal Circuit’s decision, Patent Owner sued Qiagen N.V. and several of its subsidiaries (including IBS) in the Northern District of California, alleging infringement of the ’537 patent. *Illumina*, 207 F.Supp.3d at 1083, 1086. Patent Owner also moved for a preliminary injunction against Qiagen. *Id.* Qiagen did not deny that its accused DNA sequencing products were covered by claims 1–6 and 8 of the ’537 patent, and instead argued the claims would have been obvious over Tsien, Ju, and Greene & Wuts. *Id.* at 1087–88.<sup>14</sup>

In its decision and order dated September 9, 2016, the district court found “Qiagen’s obviousness argument [was] unpersuasive” and “weak,” and held that Patent Owner “has shown it is *likely* to defeat Qiagen’s invalidity arguments.” *Id.* at 1088–90. The court determined, among other things, that “Greene & Wuts is an extensive treatise covering thousands of protecting groups for various purposes,” and that, while “Greene & Wuts does teach the use of azidomethyl . . . [,] that reference is in a chapter

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<sup>14</sup> As the Federal Circuit explains, on a motion for preliminary injunction, the district court should “weigh the evidence both for and against validity” then assess whether a “substantial question” exists related to the patent’s validity, “meaning that the alleged infringer has presented an invalidity defense that the patentee has not shown lacks substantial merit.” *Titan Tire Corp., v. Case New Holland, Inc.*, 566 F.3d 1372, 1379 (Fed. Cir. 2009).

directed at phenols, which are hydroxyl groups [] of a different type than the hydroxyl group that appears in nucleotides or nucleosides.” *Id.* at 1089.

Also, the court found, “Greene & Wuts offers an entirely separate chapter on aliphatic alcohols, which include the types of hydroxyl groups that appear in nucleotides and nucleosides . . . [but] makes no mention of azido groups” in that chapter. *Id.* The court pointed to testimony from Qiagen’s expert, acknowledging that the removal conditions for azidomethyl disclosed in Greene & Wuts would be inappropriate for use with nucleotides and would alter DNA structures. *Id.* And, the court cited to the earlier decisions by the Board and Federal Circuit related to IPR2013-00517 and their analysis of Tsien and Greene & Wuts. *Id.* at 1090 n.2. In so doing, the court agreed that Greene & Wuts “would have indicated a low likelihood of success in using azidomethyl in the process taught by Tsien.” *Id.* at 1090.

After analyzing Qiagen’s invalidity defenses, the district court addressed other factors relevant to the request for a preliminary injunction (e.g., irreparable harm, etc.) and ultimately granted the injunction in Patent Owner’s favor. *Id.* at 1093–94. According to Patent Owner, after the injunction was granted Qiagen agreed to a consent judgment and the case ended. Prelim. Resp. 2, 17–18; Paper 17, 4.

In other, earlier-filed district court proceedings in Delaware, IBS sued Patent Owner for infringement of five DNA sequencing-by-synthesis related patents, and Patent Owner responded by asserting the ’537 patent (and two other patents) against IBS. Pet. 5. *The Trustees of Columbia University v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.). This litigation was stayed based on eight requests for *inter partes* review (including IPR2013-00517). Pet. 5. According to Petitioner, although all the challenged claims in seven of the eight IPRs were canceled, “certain claims of the ’537 patent

survived.” Pet. 5–6. The Delaware litigation ended via order of dismissal dated August 2, 2017, apparently based on the parties’ “negotiated settlement.” *See The Trustees of Columbia University*, 1:12-cv-00376-GMS (document 132 (Stipulation and Order of Dismissal)).

CGI filed the present petitions for *inter partes* review (IPR2017-02172 and IPR2017-02174) on October 5, 2017.

### III. ANALYSIS

#### A. *Discretionary Non-Institution*

##### i) Discretionary Non-Institution under § 314(a)

Patent Owner argues we should exercise our discretion and deny the Petition under 35 U.S.C. § 314(a). *See, e.g.*, Prelim. Resp. 21, 30. We are, as explained below, denying institution based on the Board’s discretion under § 325(d). *See* Section III.A.ii. Accordingly, we decline to reach Patent Owner’s arguments related to whether discretionary denial under § 314(a) is appropriate based on the circumstances presented here.

##### ii) Discretionary Non-Institution under 35 U.S.C. § 325(d)

Patent Owner argues the Board should deny institution under § 325(d) because “Tsien, Greene & Wuts, and Zavgorodny were previously presented to, and considered by, the Board . . . and the Federal Circuit.” Prelim. Resp. 31. According to Patent Owner, “Section 325(d) ‘does not contain any recitation regarding the identity of the party that previously presented the prior art. . . . Thus, § 325(d) is not limited to instances where the petitioner is the party who previously brought the prior art to the Office’s attention.’” *Id.* (quoting *TCL Corp. v. Lexington Luminance LLC*, IPR2017-01780, slip op. at 8 (PTAB Jan. 2, 2018) (Paper 8)).



The Petition does not address § 325(d) directly but, in supplemental briefing authorized by the Board, Petitioner asserts that it is offering new arguments and evidence in support of the combination of Tsien, Greene & Wuts, and Zavgorodny. Paper 14, 7. Thus, Petitioner argues, the Board should not deny the Petition under § 325(d). *Id.*

In addition to § 314(a), the Board also has discretion to deny a petition under § 325(d). Section 325(d) provides, in pertinent part:

In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31 [related to petitions for *inter partes* review], the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

35 U.S.C. § 325(d). Section 325(d) is not specifically limited based on the identity of the party that advanced the prior art or arguments. Hence, § 325(d) applies, for example, to a follow-on petition advancing the same or substantially the same prior art even if filed by a different petitioner. *See, e.g., Unified Patents, Inc. v. PersonalWeb Techs., LLC*, IPR2014-00702 (PTAB July 24, 2014) (Paper 13) (informative); *Google LLC v. Uniloc Luxembourg S.A.*, IPR2017-02067 (PTAB Mar. 29, 2018).

As explained above, the Board already considered whether claims 1–6 and 8 would have been unpatentable as obvious based on the teachings of Tsien, Greene & Wuts, Zavgorodny, and Prober. *See supra* Section II.E.ii.<sup>15</sup>

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<sup>15</sup> Although not the focus of Patent Owner’s arguments, we observe that Tsien, Greene & Wuts, and Zavgorodny were before the Examiner during prosecution. *See supra* Section II.E.i. The Examiner, citing Tsien and Greene & Wuts and an admission (from Patent Owner) that all the protecting groups were known in the art, rejected as obvious certain claims reciting an allyl protecting group while expressly allowing the amended claims that

There is no reasonable dispute that *the same prior art* that Petitioner is now asserting should be combined was already presented to the Board, and a full trial held. Indeed, the Board issued a Final Written Decision on this matter, and the Federal Circuit affirmed that decision.

Petitioner's attempt to overcome these facts by invoking allegedly new evidence and argument does not persuade us that another review of the same claims over Tsien, Greene & Wuts, and Zavgorodny is warranted. The fact remains, Petitioner is using Tsien, Greene & Wuts, and Zavgorodny in substantially the same way as those references were used in the prior challenge (and relying on substantially the same teachings in those references as well). That is, Tsien is relied upon for the basic nucleotide incorporation and sequencing methods, and Greene & Wuts and Zavgorodny are relied upon as teaching an azidomethyl protecting group that is allegedly a suitable protecting group for Tsien's processes. *Compare* Ex. 1090, 31–37 (claim chart in IPR2013-00517) *with* Ex. 1101, 36–44 (claim chart here).<sup>16</sup> Although the Board did not institute trial on any ground where Greene & Wuts was expressly used in an obviousness combination, finding those grounds redundant, the Board (and the Federal Circuit), nevertheless examined the same relevant teachings in Greene & Wuts that Petitioner cites here. Ex. 1094, 13; *Intelligent Bio-Systems*, 821 F.3d at 1368–69; Pet. 25,

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recited an azido or azidomethyl protecting group. *Id.* The Examiner's allowance of the azido/azidomethyl claims under these circumstances, especially when paired with the Board's thorough consideration of Tsien, Greene & Wuts, and Zavgorodny in IPR2013-00517 reinforces the appropriateness of exercising § 325(d) discretion here.

<sup>16</sup> Petitioner's reliance on Prober is limited to dependent claim 3 and Prober's teaching of the limitation in that claim of "wherein the base is a deazapurine." Pet. 55–57.

43–44. Both the Board and Federal Circuit determined and made clear, in their respective opinions, that those teachings reinforced that the challenged claims had not been shown to be obvious over Tsien and Zavgorodny. *See supra*, Section II.E.ii–iii.<sup>17</sup>

As to Petitioner’s “new” reasons for combining the references, those too are insufficient to avoid discretionary denial here. Pet. 31–32; *see also* Prelim. Resp. 31–32; Paper 17, 5. We are not persuaded Petitioner’s “simple substitution” theory departs materially from arguments advanced in earlier proceedings. Pet. 53–54. *Medtronic, Inc. v. Nuvasive, Inc.*, IPR2014-00487, (PTAB Sept. 11, 2014) (Paper 8) (informative) (exercising discretionary denial under § 325(d) where follow-on petition failed to provide sufficient persuasive reasoning to undertake another review over the same combination of art). The Board considered the use of an alternative protecting group, such as the azidomethyl group as in Greene & Wuts or Zavgorodny, in Tsien’s processes; and the Board concluded using an azidomethyl group in this way was neither simple nor obvious, at least inasmuch as such a change would not have been expected to meet Tsien’s requirements. *See, e.g.*, Ex. 1094, 13–14. As to Petitioner’s argument that the prior art taught or suggested the proposed modification, many of Petitioner’s assertions relate to what an ordinarily skilled person allegedly “would have appreciated,” in opposition to the Board’s earlier consideration and determinations on these matters. *See, e.g.*, Pet. 46 (“[A] POSITA would have appreciated that a less than quantitative yield is to be expected in

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<sup>17</sup> As also explained above (Section II.E.iv), after the Board’s and Federal Circuit’s decisions, a district court also determined that a § 103 challenge to the ’537 patent’s claims based on Tsien in combination with Greene & Wuts was “weak” and “unpersuasive.” *Illumina*, 207 F.Supp.3d at 1088–90.

practice”) and 47 (“A POSITA reading Loubinoux would have appreciated that there are several critical differences between the deblocking reaction to be used with Tsien’s methods”); *see, e.g.*, Ex. 1094, 8–9 (considering Tsien, Loubinoux and relevant argument and expert testimony about the same); *see also, e.g.*, Ex. 1092, 21–30. We recognize Petitioner cites its own expert’s opinions and “secondary references” to support its theories. Pet. 4. But, we are not persuaded the reasons advanced by Petitioner justify avoidance of § 325(d) when the Board and the Federal Circuit have already considered the relied upon prior art.

Thus, because the Petition presents the same or substantially the same prior art previously presented to the Office, we exercise our discretion and deny review of the Petition under 35 U.S.C. § 325(d).

#### IV. CONCLUSION

For the foregoing reasons, we exercise our discretion under 35 U.S.C. § 325(d) not to institute review in this proceeding with respect to claims 1–6 and 8 of the ’537 patent.

#### V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and that we do not institute *inter partes* review of any claim of the ’537 patent based on the grounds asserted in this Petition.

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