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On behalf of **Illumina Cambridge Ltd.**

By: Kerry S. Taylor

Michael L. Fuller

Nathanael R. Luman

KNOBBE, MARTENS, OLSON & BEAR, LLP

2040 Main Street, 14th Floor

Irvine, CA 92614

Tel.: 858-707-4000

Email: BoxIllumina2@knobbe.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLETE GENOMICS, INC.

Petitioner

v.

ILLUMINA CAMBRIDGE LTD.

Patent Owner

IPR2017-02172

Patent 7,566,537

**PRELIMINARY RESPONSE OF PATENT OWNER
ILLUMINA CAMBRIDGE LTD.**

Columbia Exhibit 2026

Illumina, Inc. v. The Trustees of Columbia
University in the City of New York

IPR2018-00322

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Pursuant to 35 U.S.C. § 313, 37 C.F.R. § 42.107, and the Notice of Filing Date Accorded to Petition (Paper 3), Patent Owner Illumina Cambridge Ltd. (“Illumina”) submits its Preliminary Response to the Petition for *Inter Partes* Review filed by Complete Genomics, Inc. and its real party-in-interest, BGI Shenzhen Co., Ltd. (collectively “BGI”).

I. INTRODUCTION

BGI’s attempt to challenge the ’537 Patent is a prime example of a repetitive challenge to a repeatedly-upheld patent that should be denied. Further investment of scarce judicial resources is unwarranted, especially given the low probability of success implied by the past outcomes upholding the patent. Even beyond that, Patent Owner deserves repose after expending so much time, effort and attention successfully defending its duly issued and legally valid patent.

The ’537 Patent has been battle tested in the crucible of district court and PTAB litigation based on the very same Tsien prior art reference that is the centerpiece of this petition along with the same secondary references Greene & Wuts, Zavgorodny and Prober. *Seven* judges have considered and rejected this prior art attack. This includes a three judge PTAB panel, a three judge Federal Circuit panel and Judge Alsup of the Northern District of California.

Judge Alsup specifically addressed the validity of the ’537 Patent in granting a preliminary injunction and concluded that it was unlikely to be invalidated given

the weakness of the prior art, including Tsien modified by Greene & Wuts. *Illumina, Inc. v. Qiagen N.V.*, 207 F.Supp.3d 1081, 1088-1090 (N.D. Cal. 2016). He found a “weak” showing of a motivation to combine the prior art to show the claimed inventions and a low likelihood of success even if one were motivated to modify the Tsien reference. *Id.* Given the high stakes in an injunction proceeding, it is safe to conclude that the enjoined infringer had full motivation to make the best prior art argument it could based on Tsien. Yet, its obviousness attack on the ’537 Patent was soundly rejected. *Id.* After this loss, the infringer ultimately agreed to a consent decree enjoining it from infringing the ’537 Patent, further underlining the proven validity of the patent.

Beyond that, all claims challenged by BGI’s petition withstood a full trial in IPR2013-00517. The previous petition was filed by Intelligent Bio-Systems and its parent company, Qiagen, a sophisticated, multinational company based in Germany with offices throughout the U.S. The Board issued a final written decision upholding the patentability of all challenged claims over the prior art Tsien reference in view of the Zavgorodny reference. Green & Wuts and Prober were considered too. The Federal Circuit panel unanimously affirmed the Board’s decision. *Intelligent Bio-Systems, Inc. (“IBS”) v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016). The Federal Circuit considered all the same references relied on in the pending petition and confirmed that the PTAB properly

rejected the prior art challenge. *Id.* at 1366-69 (evaluating Tsien, Zavgorodny, and Greene & Wuts).

BGI has been in the sequencing business for years, including, but not limited to, in the U.S. through its subsidiary CGI. BGI failed to file this petition during the pendency of the prior IPR even though it addresses the same prior art as BGI pursues now. Nor did it seek to join the prior proceeding. BGI sat on the sidelines and apparently wanted to reap the benefit of the previous petitioner's potential success or wait to stage its own follow-on attack to take advantage of the Board and Federal Circuit's responses to the arguments and evidence presented in the first IPR. The Board ruled in favor of Illumina in the original IPR. BGI's belated rehash of prior arguments based on the same prior art should not be rewarded. Instituting another IPR proceeding would not "secure the just, speedy, and inexpensive resolution of every proceeding." 37 C.F.R. § 42.1(b).

The Board has put petitioners on notice that follow-on petitions will be heavily scrutinized under 35 U.S.C. §§ 314(a) and 325(d) even if there are no district court decisions upholding the invalidity of the patent or Federal Circuit decisions addressing the same prior art. The Board has issued informative and precedential decisions directing follow-on petitioners to explain why Board and Patent Owner resources should be expended on their secondary petitions. In the

face of 314(a) or 325(d), BGI does not even attempt to justify its belated secondary petition on the same prior art and should be rejected outright.

Illumina is a U.S. company that began as a technology-driven start-up company in the biotechnology hotbed of San Diego, California, and merged with a similarly driven company out of Cambridge, UK – Solexa – to jointly deliver ground-breaking and highly popular sequencing technology. Today, Illumina has become the leading innovator in the DNA sequencing industry, employing approximately 5,500 workers. The challenged claims of '537 patent protect Illumina's highly successful sequencing products that use labeled nucleotides having a reversible 3'-O-azidomethyl protecting group. Both BGI and Qiagen have been developing DNA sequencers but, to-date, they have been unable to develop an alternative technology to effectively compete against Illumina's reversible 3'-O-azidomethyl terminator technology in the United States.

The current petitioner, BGI, and the original failed petitioner, Qiagen, are not strangers. They have business ties and an aligned interest in gaining free access to the valuable inventions protected by the '537 patent as soon as they can. BGI's follow-on petition seeks to abuse the IPR process by retreading even though Qiagen lost.

BGI's retread petition fails to establish a prima facie case of obviousness for the same reasons that the Board determined Qiagen's earlier petition failed, the

Federal Circuit affirmed that decision and Judge Alsup enjoined their infringement. BGI relies on Tsien as the primary reference in its obviousness challenge. Tsien provides three distinct criteria for selecting a 3'-blocking group from the literature:

- (1) the ability of a polymerase enzyme to accurately and efficiently incorporate dNTPs carrying the 3'-blocking group into DNA,
- (2) the availability of mild conditions for rapid and quantitative deblocking, and
- (3) the ability of a polymerase enzyme to reinitiate DNA synthesis subsequent to deblocking.

BGI's petition, however, fails to establish that an azidomethyl protecting group would have been known to meet any of these criteria. A person of ordinary skill in the art ("POSITA") therefore would not have been motivated to use an azidomethyl group as Tsien's 3'-blocking group.

Not only does BGI's follow-on petition fail to establish a prima facie case of obviousness, it also fails to rebut Illumina's significant evidence of secondary considerations of non-obviousness. In the previous IPR, Illumina raised significant evidence of secondary considerations of nonobviousness, including long-felt but unmet need, unexpected results, and evidence of copying. BGI fails to substantively address this evidence, and thus fails to carry its burden of demonstrating obviousness. BGI's desire to gain access the claimed technology by

attacking the patent that covers it only strengthens those secondary considerations. For all of these reasons, the Board should deny institution of BGI's follow-on petition.

II. ILLUMINA'S CLAIMED INVENTION INCLUDES A NOVEL AND NONOBVIOUS 3'-OH PROTECTING GROUP FOR DNA SEQUENCING

Illumina is the undisputed innovative leader in the DNA sequencing industry. Illumina has been referred to as the “smartest company in the world” because it “commercializes a truly innovative technology” and causes competitors “to refine or rethink their strategies.” Ex-2001 at 27-29. Illumina's novel and successful methods of labeling nucleic acid molecules use a reversible 3'-O-azidomethyl ether protecting group in its DNA sequencing instruments. Illumina's successful sequencing instruments “account[] for the largest market share for sequencing instruments compared to other platforms.” Ex-2002 at 337. “Illumina's highly successful suite of instruments have been the juggernaut of NGS [next generation DNA sequencing], relegating technologies that could not keep pace to niche applications or outright dissolution.” *Id.* at 348. Indeed, where Illumina has succeeded, Complete Genomics (“CGI”) and BGI¹ have failed. For example, CGI and BGI instruments attempted to sequence DNA using the

¹ BGI, formerly Beijing Genomics Institute, is a Chinese company that acquired CGI in March of 2013. Ex-2003 at 1. BGI is a real party-in-interest. Petition at 4.

“combinatorial probe-anchor ligation (cPAL)” technology, which CGI marketed under the name “Revelocity.” *Id.* at 335. The Revelocity sequencing technology was not commercially viable and could not compete with Illumina’s 3’-O-azidomethyl nucleotides. *Id.* at 348 (“The casualties of the NGS arms race have included... the Revelocity system from Complete Genomics.”), *id.* at 337 (“although the cPAL-based Revelocity system [from CGI] was intended to compete with the Illumina HiSeq² in terms of cost and throughput, its launch was suspended in 2016 and it is now only available as a service platform for human WGS [whole genome sequencing]”).

BGI abandoned cPAL due to inferior read lengths, and instead adopted Illumina’s polymerase-based sequencing-by-synthesis (“SBS”) approach. BGI refers to its copycat polymerase approach as “combinatorial probe-anchor synthesis (cPAS).” BGI asserts cPAS provides “longer reads ... compared to the previously described combinatorial probe-anchor ligation (cPAL) chemistry.” Ex-2004 at 2. BGI’s cPAS-based BGISEQ-500 platform “is limited to mainland China” (Ex-2002 at 337), apparently due to “patent issues” excluding BGI from other markets. Ex-2005 at 2. BGI’s present petition seeking cancellation of the

² The HiSeq instrument is one of Illumina’s flagship DNA sequencing instruments and, like all of Illumina’s sequencing instruments, uses 3’-O-azidomethyl protected nucleotides.

'537 patent claims that protect Illumina's labeling methods and reversible 3'-O-azidomethyl terminator technology is a strong signal that BGI wants to send its infringing sequencers into the U.S.

BGI's petition alleges that Claims 1-6 and 8 of the '537 patent would have been obvious to a POSITA based on a combination of Tsien, Greene & Wuts, and Zavgorodny. Tsien was published in 1991 and identified several criteria for a 3'-protecting group to be used in DNA sequencing methods. Ex-1003 at 20:28-21:3, 23:27-24:5. With Tsien's publication as a guide, researchers immediately set forth searching for nucleotide 3'-protecting groups compatible with the identified criteria. By August of 2002, at least 11 separate research teams had tried to identify 3'-protecting groups that were effective for use in DNA sequencing:

(1) Tsien investigated at least 3'-O-allyl and various other groups (Ex-1003 at 21:20-31);

(2) Dower (Affymax) contemplated at least "acetyl, tBOC, NBOC, and NVOC" 3'-OH protecting groups (Ex-1004 at 25:47-51);

(3) Metzker investigated 3'-O-methyl, 3'-O-acetyl, 3'-O-allyl, 3'-O-tetrahydropyran, 3'-O-4-nitrobenzoyl, 3'-O-2-aminobenzoyl, and 3'-O-2-nitrobenzyl groups (Ex-1041 at 4263);

(4) Canard investigated at least 3'-O-anthranyloyl and 3'-O-anthranyl derivatives (Ex-1042 at 10859);

(5) Stemple (ASM Scientific) investigated at least 3'-O-(2-nitrobenzyl) groups (Ex-2006 at 13:18-20);

(6) Odedra (Amersham Pharmacia) investigated at least acetyl and phenylacetamide groups (Ex-2007 at Figs. 2 & 11);

(7) Cheeseman (Beckman Instruments) investigated at least 3'-O-succinyl and 3'-O-anhydride derivatives (Ex-1055 at 4:50-63);

(8) Kwiatkowski (Helicos BioSciences) investigated at least 3'-O-hydrocarbyldithiomethyl and 3'-O-"functionalized acetal" groups (Ex-2008 at 2:40-60; Ex-2009 at 15:11-16:24);

(9) Rosenthal investigated 3'-blocking groups that "generate a 3' hydroxyl group" (Ex-2010 at 11:3-10);

(10) Rabani investigated at least a 3'-O-(4-benzoyl)benzoyl group (Ex-2011 at 2:15-21); and

(11) Ju investigated at least 3'-O-allyl and 3'-O-methoxymethyl groups (Ex-1038 at Fig. 7).

None of these researchers investigated or even suggested a protecting group comprising an azido group that can be modified or removed to expose a 3'-OH group. These research efforts showed that Tsien's 3'-O-allyl group was a reversible protecting group that could be incorporated effectively by polymerases. Ex-1003 at 24:29; Ex-1041 at 4263; Ex-1038 at 3:7-22.

Despite the numerous research efforts by multiple teams, only Illumina identified the azidomethyl group as a protecting group for DNA sequencing. Ex-1001 at 19:49-20:4. Illumina found that the azidomethyl protecting group was incorporated by polymerases and was surprisingly cleaved in rapid and quantitative yield under conditions that permit polymerase incorporation for DNA sequencing. This resulted in sequencing successes unachievable with other 3'-OH protecting groups. These properties were not known in the prior art at the time the '537 patent was filed, and no knowledge in the art would have led a POSITA to expect that an azidomethyl group could be successful. To date, Illumina's 3'-O-azidomethyl group remains the industry-leading reversible terminator technology for sequencing even though 15 years have passed since the '537 patent was filed.

The present petition asserts unpatentability of the same '537 patent claims using the same references and arguments over which the Board and Federal Circuit previously upheld patentability in IPR213-00517. The Board should deny Petitioner's request to re-litigate patentability of Illumina's claims for the same reasons it upheld Illumina's claims in the previous IPR. A summary of the previous IPR proceeding and Federal Circuit affirmance is provided in the following section.

**III. THE BOARD, FEDERAL CIRCUIT, AND DISTRICT COURT
PREVIOUSLY UPHELD PATENTABILITY OF THE
CHALLENGED CLAIMS**

A. The Board previously upheld the same claims over the same art and arguments in IPR2013-00517

On August 19, 2013, Intelligent Bio-Systems and its parent company, Qiagen,³ filed a petition for IPR of Claims 1-6 and 8 of the '537 patent in IPR2013-00517. On August 30, 2013, they filed a revised petition. Ex-1090 at 2, 49. The revised petition challenged Claims 1-6 and 8 based on the following grounds:

Ground	Claim(s)	Obviousness Challenge
1a	1-6 and 8	Ju and Zavgorodny
1b	1-6 and 8	Ju and Greene & Wuts
1c	1-6 and 8	Tsien and Zavgorodny
1d	1-6 and 8	Tsien and Greene & Wuts
2a	3	Tsien, Zavgorodny, and Prober
2b	3	Tsien, Greene & Wuts, and Prober

Ex-1090 at 6-8. Grounds 1c-2b of the revised petition raised the same art against the same claims as BGI's follow-on petition. Petition at 8-9.

³ Qiagen acquired IBS in June of 2012. Ex-1092 at 1.

Qiagen argued that “one of ordinary skill in the art, in order to improve the efficiency, reliability, and robustness of the sequencing by synthesis [SBS] method taught in Tsien, would have been motivated to use other protecting groups that meet the criteria of Tsien, such as the azidomethyl group taught by Zavgorodny.” Ex-1090 at 38. BGI’s follow-on petition relies on the same SBS motivation. Petition at 21.

The Board instituted trial on Grounds 1a, 1c, and 2a, and denied grounds 1b and 2b as redundant. Ex-1091 at 15.

In its Patent Owner response, Illumina argued, *inter alia*, that Claims 1-6 and 8 were nonobvious because a POSITA would not have been motivated to combine Tsien or Ju with the azidomethyl group disclosed by Zavgorodny. Ex-1092 at 12-42. Illumina supported its arguments by analyzing Greene & Wuts, Loubinoux, and several other relevant references, along with the expert testimony of Dr. Romesberg and Dr. Burgess. *Id.* Illumina further presented significant evidence of secondary considerations of nonobviousness. *Id.* at 43-60.

On February 11, 2015, the Board issued its final written decision upholding the patentability of Claims 1-6 and 8. Ex-1094 at 24. Significant resources were expended by the Board and Illumina in reaching this decision, including analyzing over 200 exhibits, 90 papers, 4 expert witnesses, and conducting an oral hearing.

In the final written decision, the Board “agree[d] with Patent Owner that Petitioner has not shown, by a preponderance of the evidence, that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl group as the 3’ hydroxyl protecting group in Tsien’s processes.” *Id.* at 9. The Board explained:

the prior art suggests that an ordinary artisan would not have expected Zavgorodny’s azidomethyl group to be removed quantitatively, as Tsien requires. We, therefore, agree with Patent Owner that Petitioner has not shown that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl protecting group in Tsien’s sequencing methods.

Id. at 14. The Board also found that Illumina presented “evidence that an ordinary artisan would not have considered Zavgorodny’s conditions suitably mild for Tsien’s sequencing purposes.” *Id.*

The Board considered Greene & Wuts and Loubinoux, and found “Loubinoux describes only a 60–80% removal efficiency of azidomethyl groups from phenols, and Greene and Wuts suggests that removal from simple aliphatic alcohols, such as that present at the 3’ position of nucleotides, would be less efficient, because phenol is a better leaving group.” *Id.* at 21. The Board rejected Qiagen’s arguments regarding Loubinoux as follows:

Petitioner advances evidence that Loubinoux’s pure product yields of 60 to 80 percent would have been viewed as a poor proxy for actual

reaction efficiency. The fact that pure product yields might be a poor indicator of actual reaction efficiency does not substitute, however, for evidence showing that an ordinary artisan would have expected Zavgorodny's azidomethyl group to be removed quantitatively under conditions suitable for performing Tsien's sequencing processes.

Id. at 16-17.

BGI's petition argues that the Board did not consider the Reply arguments submitted during the previous IPR in its final decision. Petition at 2, 6-7. BGI is incorrect. The Board considered the Reply arguments and found they were not persuasive. Ex-1094 at 16 ("Further, even if we were to overlook the procedural infirmities in Petitioner's Reply arguments, we would not find them persuasive.");⁴ *id.* at 21 ("For the reasons discussed above, we do not find Petitioner's [Reply] arguments persuasive.").

B. The Federal Circuit affirmed the Board's decision from IPR2013-00517

The Board's final written decision from IPR2013-00517 was appealed to the Federal Circuit. BGI's petition makes it seem like Illumina lost on appeal. To the contrary, **the Federal Circuit unanimously affirmed the Board's decision and upheld the patentability of Claims 1-6 and 8.** *IBS*, 821 F.3d at 1370.

⁴ Emphasis supplied unless otherwise noted.

1. The Federal Circuit affirmed that there was no motivation

The Federal Circuit determined the Board “was justified in finding that, despite having acknowledged the quantitative deblocking requirement in Tsien, the Petition did not provide a specific or credible explanation why an ordinary artisan would have expected Zavgorodny's azidomethyl protecting group to meet Tsien's quantitative deblocking requirement under conditions suitable for use in Tsien's sequencing methods.” *Id.* at 1368. The Federal Circuit agreed that Loubinoux does not support a finding that an azidomethyl group would meet Tsien’s sequencing methods:

Prior art of record, however, demonstrates that an ordinary artisan would have expected Zavgorodny’s azidomethyl group to be removed at a much lower efficiency than required by Tsien’s methods. That prior art reference is known as Loubinoux. Loubinoux reports a 60-80% removal efficiency for azidomethyl groups from phenols using triphenylphosphine. 60-80% removal is not quantitative removal within the meaning of Tsien or Ju.

Id. at 1364-65. The Federal Circuit further agreed that both Loubinoux and Greene & Wuts would not have been expected to meet Tsien’s sequencing methods:

In its decision the Board acknowledged two background references presented by Illumina: Loubinoux, which teaches that azidomethyl methyl groups are removed from phenols with modest efficiency (60-80% yield), and Greene & Wuts, which teaches that removal of an azidomethyl methyl group from the 3' hydroxyl position of a

deoxyribonucleotide moiety is likely to proceed with even lower efficiency. These references support a conclusion that the claimed efficiency that allegedly motivated the combination would not be achieved and that a person of ordinary skill in this field would not have been motivated to use the azidomethyl group of Zavgorodny as a ‘protecting group [that] can be modified or removed to expose a 3’ [hydroxyl] group’ of a nucleic acid molecule, as the claim requires. This is so because the azidomethyl group would have been expected to perform inefficiently in that role.

Id. at 1368-69.

The Federal Circuit determined the Board’s finding that a POSITA “would not have had reason to combine Tsien or Ju with Zavgorodny to achieve the claimed invention” was supported by the record and affirmed the Board’s decision.

Id. at 1368.

2. Reasonable expectation of success is measured by the claims

The Federal Circuit determined that the reasonable expectation of success must be measured against the claimed invention. *Id.* at 1367 (“one must have a motivation to combine accompanied by a reasonable expectation of success in achieving what is claimed in the patent-at-issue”). The Federal Circuit agreed with the Board that Illumina’s claims do not require a particular cleavage efficiency. *Id.* The Federal Circuit therefore explained that cleavage efficiency is not relevant to whether a POSITA had a reasonable expectation of success, but cleavage

efficiency is relevant to whether a POSITA had a motivation to combine. *Id.* at 1367-68.

BGI incorrectly asserts that the Federal Circuit's opinion precludes Illumina from contesting that "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." Petition at 13. BGI's assertion overlooks that Claim 1 requires "incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule." Ex-1001 at 19:50-51. BGI's petition must therefore demonstrate that there was a reasonable expectation of success in arriving at a method in which a nucleotide having a 3'-OH azido protecting group is incorporated into a nucleic acid molecule. *IBS*, 821 F.3d at 1367.

C. The Northern District of California upheld the same claims over the same art and arguments

After the Federal Circuit upheld the Board's final written decision, Qiagen argued in the Northern District of California that the '537 patent was obvious over the prior art, including Tsien modified by Greene & Wuts. *Illumina*, 207 F.Supp.3d at 1088. Judge Alsup found a "weak" showing of a motivation to combine the prior art and a low likelihood of success even if one would have been motivated to modify Tsien. *Id.* at 1090. He concluded that the '537 Patent was unlikely to be invalidated given the weakness of the prior art. *Id.* After this loss,

Qiagen ultimately agreed to a consent decree enjoining it from infringing the '537 Patent, further underlining the proven validity of the patent.

IV. BGI PROVIDES NO JUSTIFICATION FOR ITS REQUEST TO RELITIGATE PATENTABILITY OF THE CHALLENGED CLAIMS

BGI's follow-on petition challenges the same claims upheld by the Board after a full IPR trial in IPR2013-00517, and which the Federal Circuit affirmed. Specifically, BGI's follow on petition challenges Claims 1-6 and 8 of the '537 patent based on the following grounds:

Ground	Claim(s)	Obviousness Challenge
1	1-2, 4-6 and 8	Tsien, Greene & Wuts, and Zavgorodny
2	3	Tsien, Greene & Wuts, Zavgorodny, and Prober

Petition at 8-9. As discussed in the previous section, the Board and Federal Circuit considered each of these references and determined that Illumina's claims are nonobvious over the references. *Supra* Section III.

BGI and the first petitioner (Qiagen) have an aligned interest in selling sequencers that rely on Illumina's innovation of superior labeling methods and reversible azido terminator technology. Both companies are developing sequencers but, to-date, neither has been able to develop a technology comparable to Illumina's innovative technology without copying Illumina's reversible 3'-O-azidomethyl protecting groups. Ex-2002 at 348. BGI and Qiagen have joined forces in developing DNA sequencing technology—they have had a business

relationship since at least 2014 (including during the pendency of IPR2013-00517 and its appeal). For example, on July 29, 2014, BGI and Qiagen “announced that they have entered into a distribution and service agreement” for analyzing DNA sequences. Ex-2012 at 1. On May 4, 2015, “Qiagen announced today that it has expanded its relationship with BGI, the world’s largest genomics organization, to provide Qiagen’s Ingenuity Variant Analysis in integrated bioinformatics for all customers of BGI’s sequencing services.” Ex-2013 at 1.

After the previous IPR trial and appeal, the district court prevented Qiagen’s efforts to “usurp Illumina’s position in [the DNA sequencing] market with pirated technology” by enjoining Qiagen from entering the U.S. market. *Illumina*, 207 F.Supp.3d at 1093. BGI’s follow-on petition should not be allowed to pick up where Qiagen’s IPR petition left off. IPRs were not intended as an iterative tool for industry competitors to gang up on an innovative patent owner by passing the role of petitioner like a baton from one entity to another, allowing each petitioner to retool and refine the previous petitioner’s arguments. BGI’s follow-on petition is exactly the kind of excess and abuse of IPRs that Congress empowered the Board to combat when it enacted Sections 314(a) and 325(d). These sections provide an appropriate mechanism for the Board to police the waste of Board resources, as well as the inequities and prejudices to patent owners, caused by follow-on petitions.

The Board has issued numerous decisions (including informative and precedential decisions) notifying petitioners that follow-on petitions will be scrutinized under 35 U.S.C. §§ 314(a) and 325(d), including the following exemplary decisions:

- *General Plastic Industrial Co. Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 15-16 (P.T.A.B. 2017) (Precedential for § 314(a));
- *NVIDIA Corp. v. Samsung Elec. Co.*, IPR2016-00134, Paper 9 at 6-7, (P.T.A.B. 2016) (Regarding § 314(a));
- *LG Elecs. Inc. v. Core Wireless Licensing S.A.R.L.*, IPR2016-00986, Paper 12 at 6-7 (P.T.A.B. 2016) (Regarding § 314(a));
- *Medtronic, Inc. v. Nuvasive, Inc.*, IPR2014-00487, Paper 8 at 7 (P.T.A.B. 2014) (Informative for § 325(d));
- *Unified Patents, Inc. v. Personal Web Technologies, LLC*, IPR2014-00702, Paper 13 at 7-8 (P.T.A.B. 2014) (Informative for § 325(d)); and
- *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, IPR2013-00324, Paper 19 at 4-7 (P.T.A.B. 2013) (Informative for § 325(d)).

The continuing theme in these and other decisions is clear: follow-on petitions must articulate reasons why the Board should deviate from the normal policy of denying follow-on petitions. Despite the Board's numerous warnings, BGI makes no attempt to justify why the Board and Illumina's time, effort, and resources

should be expended on its follow-on petition under § 314(a) or § 325(d). It is not surprising that BGI declines to address these sections because the Board's decisions on § 314(a) or § 325(d) demonstrate that BGI's follow-on petition should be denied.

V. BGI'S PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 314(a)

The Board's *General Plastic* decision provides notice to petitioners that the Board will evaluate seven factors when exercising its discretion to deny institution of follow-on petitions under 35 U.S.C. § 314(a). *General Plastic*, Paper 19 at 15-16 (Precedential). The seven factors are:

1. Whether the same petitioner previously filed a petition directed to the same claims of the same patent;
2. Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;
3. Whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;

4. The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;
5. Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;
6. The finite resources of the Board; and
7. The requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review. *Id.*

The Board “need not weight all of these factors equally and not all of the factors need to weigh against institution for [the Board] to exercise [its] discretion” in denying institution. *Starbucks Corp. v. Ameranth, Inc.*, CBM2017-00053, Paper 7 at 18 (P.T.A.B. 2017).

BGI filed its petition on October 5, 2017. The *General Plastic* decision was designated as “Informative” on September 18, 2017, and as “Precedential” on October 18, 2017. The Board has consistently applied these factors to follow on petitions for over 1.5 years. *See, e.g., NVIDIA*, IPR2016-00134, Paper 9 at 6-7; *LG Elecs.*, IPR2016-00986, Paper 12 at 6-7; *Xactware Solutions, Inc. v. Eagle View Techs. Inc.*, IPR2017-00034, Paper 9 at 7-8 (P.T.A.B. 2017). BGI was therefore

on notice that it should have addressed the Board's § 314(a) factors in its follow-on petition. There is no excuse for BGI's failure to address the Board's discretionary denial factors. The *General Plastic* factors weigh against institution and totality of the factors compels denial of institution.

A. Factor 1: Whether the same petitioner previously filed a petition directed to the same claims of the same patent

Although BGI did not file the first petition, the Board's "discretion under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a) is not limited to situations where the same party files multiple petitions, and [the Board] find[s] that the *General Plastic* factors provide a useful framework for analyzing the facts and circumstances present in this case, in which a different petitioner filed a petition challenging a patent that had been challenged already by previous petitions." *NetApp Inc. v. Realtime Data LLC*, IPR2017-01195, Paper 9 at 10 (P.T.A.B. 2017). The importance of whether the same petitioner filed the follow-on petition is reduced when there is a high degree of similarity between a second petitioner's petition and the first petition. *Samsung Electronics Co., Ltd. v. ELM 3DS Innovations, LLC*, IPR2017-01305, Paper 11 at 19 (P.T.A.B. 2017) ("Moreover, the high degree of similarity of Samsung's instant Petition with the prior petitions by Petitioners Micron and Hynix in the 703 and 706 proceedings, as discussed above, reduces the weight we accord this factor.").

As previously discussed, BGI and Qiagen have business ties with aligned interests in bringing infringing sequencers into the U.S. *Supra* Section IV. BGI is not a small player in the sequencing industry. BGI is a sophisticated sequencing company that has long touted itself as the “world’s largest genomics organization.” Ex-2013 at 2. BGI was familiar with, and publicly endorsed the benefits of, Illumina’s sequencing technology long before the first petition was filed. Ex-1045 at 113 (In 2010, “[t]he biggest endorsement of the [Illumina] technology came from BGI, which immediately placed an order for a staggering 128 [HiSeq2000] machines”).

BGI is generally familiar with and cites Illumina’s patent portfolio in its own patent filings. *See, e.g.*, Ex-2018 at 5-6; Ex-2019 at 7-8; Ex-2020 at 7-8; Ex-2021 at 3. Despite BGI’s familiarity with Illumina’s intellectual property, it did not file a motion for joinder in the previous IPR proceeding, nor did it attempt to file its own petition during the pendency of the previous proceedings. Instead, BGI was a spectator, seeking to benefit from (1) a potential final written decision holding Illumina’s claims unpatentable from the first proceeding, or (2) a roadmap provided by the Board, Federal Circuit, and Illumina to guide its follow-on petition. BGI appears to have spent years studying the previous proceedings, yet the best challenge it could muster is simply a copycat petition based on the same art, arguments and positions from the first-filed IPR.

The Board has previously denied institution of a similar copycat petition, explaining “[i]t is wasteful of the Board’s finite resources, and frustrates the purpose of *inter partes* review as providing a quick and cost effective alternative to litigation, when a Petitioner files what is, essentially, a copy of another party’s petition, without any indication it performed its own analysis or conducted a search to identify additional art and arguments.” *Viptela, Inc. v. Fatpipe Networks Private Ltd.*, IPR2017-01125, Paper 9 at 14 (P.T.A.B. 2017). In an Informative Decision, the Board denied institution where, like here, a follow-on petition filed by a second petitioner raised the same prior art and arguments raised by the first petitioner. *Unified Patents, Inc. v. Personal Web Technologies, LLC*, IPR2014-00702, Paper 13 at 7-8 (P.T.A.B. 2014) (Informative). The Board has denied several other follow-on petitions filed by different petitioners. *See, e.g., NetApp Inc. v. Realtime Data LLC*, IPR2017-01196, Paper 10 at 10 (P.T.A.B. 2017) (denying institution where different petitioner copied a petition and “all but stepped into the shoes of the petitioners in the [previous] IPR.”); *NetApp Inc. v. Realtime Data LLC*, IPR2017-01354, Paper 16 at 10 (P.T.A.B. 2017). Instituting BGI’s follow-on petition would encourage other would-be petitioners to sit on the sidelines, wait for the Board and Federal Circuit to decide patentability, and then use those decisions as a foil to try to inject uncertainty into the previous decisions. Any such tactics should be discouraged, not rewarded with a duplicate trial that

increases expense, complication and delay. This factor weighs in favor of denying institution.

B. Factor 2: Whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it

BGI relies on Tsien, Greene & Wuts, Zavgorodny, and Prober. Petition at 8-9. BGI knew or should have known of each of these references. Tsien, Greene & Wuts, and Zavgorodny are cited on the face of the '537 patent, which issued on July 28, 2009. Ex-1001 at 1-3. Prober is cited by the '537 patent. Ex-1001 at 5:30-31. The Examiner cited Tsien and Greene & Wuts during prosecution of the '537 patent. Ex-1002 at 64. Each of BGI's asserted references were asserted in the first-filed petition. Ex-1090 at 7-8. Any reasonably diligent search by BGI would have uncovered the asserted references at least by the time the first petition was filed. BGI makes no argument and presents no evidence to show there was any barrier to it presenting arguments based on the asserted references during the pendency of the first-filed petition. This factor weighs in favor of denying institution.

C. Factor 3: Whether the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition

BGI's follow-on petition received the benefit of a full IPR trial and Federal Circuit appeal. BGI availed itself of the Board's institution and final written

decisions, the Federal Circuit’s decision, Illumina’s patent owner response, expert declarations, motion for observations on cross examination, oral hearing transcript, appellate briefing, and all related evidence made of record during the previous proceedings. BGI admits, and explains how, it strategically staged the arguments in this follow-on petition in an attempt to re-litigate issues previously settled by the Board and Federal Circuit. *See, e.g.,* Petition at 1-4. BGI’s hindsight-driven petition should be rejected because it has been guided by, and has received the benefit of, seeing the Board and Federal Circuit’s decisions addressing the same grounds. *NetApp Inc. v. Crossroads Systems, Inc.*, IPR2015-00776, Paper 13 at 8 (P.T.A.B. 2015) (“Thus, the Petition makes clear that this case [has] been guided by, and has received the benefit of, seeing the decision addressing the same grounds in the [previous] proceeding. Absent a good reason, a subsequently filed petition that only corrects defects identified by a Board decision in a prior petition is not typically granted.”).

The Board has explained “[t]he absence of any restrictions on follow-on petitions would allow petitioners the opportunity to strategically stage their prior art and arguments in multiple petitions, using our decisions as a roadmap, until a ground is found that results in the grant of review. All other factors aside, this is unfair to patent owners and is an inefficient use of the *inter partes* review process and other post-grant review processes.” *General Plastic*, Paper 19 at 17-18. BGI’s

follow-on petition openly admits it used the previous Board and Federal Circuit decisions as a roadmap. *See, e.g.*, Petition at 1-4. The follow-on petition is essentially a 14,000 word request for rehearing of the previous decisions. All other factors aside, BGI's admitted use of the previous proceedings to retool the first-filed petition should not be rewarded and justifies denial of institution.

D. Factor 4: The length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition

BGI makes no claim that it recently learned of the asserted references. As discussed above, BGI should have known about the references as of the July 28, 2009 issue date of the '537 patent, and it certainly should have known about the references based on the publicly available first-filed petition as of August 19, 2013. Several years elapsed between when BGI should have learned of the asserted references and when it finally filed its belated petition. This factor weighs in favor of denying institution.

E. Factor 5: Whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent

It took BGI at least 1.5 years to stage this follow-on attack. The first petition in IPR2013-00517 was filed on August 19, 2013. The Board issued its final written decision on February 11, 2015. The Federal Circuit affirmed the Board's decision on May 9, 2016. BGI waited to file its follow-on petition until October 5,

2017. BGI provides no explanation for this delay. Illumina has not asserted the '537 patent against BGI. The amount of time that elapsed between the Federal Circuit's decision and BGI's belated filings provided ample time to take advantage of the decisions, arguments, and evidence presented in the previous proceedings. Thus, BGI's follow-on petition seeks to "force[] the Board and Patent Owner to address yet another challenge to [the same patent] while allowing Petitioner to game the IPR process by waiting for and responding to Patent Owner's and the Board's positions in the initial IPR petition (as well as other prior IPR petitions)." *R.J. Reynolds Vapor Co. v. Fontem Holdings 1 B.V.*, IPR2017-01117, Paper 10 at 10-11 (P.T.A.B. 2017). There is no evidence that BGI was unable to file its petitions during pendency of the first-filed petition or at some earlier date. BGI's belated follow-on petition goes against the Board's guiding principle to "secure the just, speedy, and inexpensive resolution of every proceeding." 37 C.F.R. § 42.1(b). This factor weighs in favor of denying institution.

F. Factor 6: The finite resources of the Board

The Board has explained to follow-on petitioners that "multiple, staggered petition filings, such as those here, are an inefficient use of the *inter partes* review process and the Board's resources." *General Plastic*, Paper 19 at 21. Further, "the Board's resources would be more fairly expended on first petitions, rather than on a follow-on petition like the Petition in this case." *LG Electronics*, Paper 12 at 12.

Thus, the Board's resources would be better spent addressing initial petitions, rather than BGI's belated attempt to challenge the same claims for a second time with the same art. This factor weighs in favor of denying institution.

G. Factor 7: The requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review

BGI's long delay eliminated the possibility of the Board joining, consolidating, or coordinating the follow-on petition with the previous proceeding. Instituting BGI's follow-on petition would require an entirely separate proceeding to re-litigate patentability of the same claims that were previously considered and upheld by the Board and affirmed by the Federal Circuit. Instituting a new trial on BGI's petition would result in significant prejudice to Illumina, which already spent significant time, effort, and resources confirming patentability of the same claims. This factor weighs in favor of denying institution.

In sum, the totality of the Board's § 314(a) factors compel denial of BGI's follow-on petition. BGI does not even attempt to justify why its belated petition should be instituted over the Board's § 314(a) factors, even though the Board has issued numerous decisions specifically instructing follow-on petitioners to address these factors. The issues of fairness, economy, and efficiency favor denial of BGI's follow-on petition.

VI. THE PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d)

It is beyond reasonable dispute that Tsien, Greene & Wuts, and Zavgorodny were previously presented to, and considered by, the Board (Ex-1094 at 2, 13, 21) and the Federal Circuit. *IBS*, 821 F.3d at 1368. Section 325(d) provides that “[i]n determining whether to institute or order a proceeding ... 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) “does not contain any recitation regarding the identity of the party that previously presented the prior art.... [t]hus, § 325(d) is not limited to instances where the petitioner is the party who previously brought the prior art to the Office’s attention.” *TCL Corp. v. Lexington Luminance LLC*, IPR2017-01780, Paper 8 at 8 (P.T.A.B. 2018).

BGI acknowledges that the same art and arguments were considered in the previous IPR. Petition at 1-2. “On that basis alone, [the Board] may exercise [its] discretion and decline to institute”. *Travelocity.com L.P. v. Cronos Techs., LLC*, CBM2015-00047, Paper 7 at 10 (P.T.A.B. 2015). The Board issued an Informative decision cautioning that follow-on petitioners presenting the same or substantially the same arguments must provide “persuasive reasoning as to why [the Board] should institute *inter partes* review over the same or substantially the same prior art or argument’s that were presented [previously].” *Medtronic, Inc. v.*

Nuvasive, Inc., IPR2014-00487, Paper 8 at 7 (P.T.A.B. 2014) (Informative). BGI, however, provides none. There are ample reasons why the Board should exercise its discretion to deny institution under § 325(d). Instituting BGI's follow-on petition would waste time, effort, and resources on re-litigating the same issues the Board and Federal Circuit have previously considered. Congress implemented § 325(d) to empower the Board to ensure that follow-on petitions, such as BGI's follow-on petition, are not used as tools for harassment "through repeated litigation and administrative attacks on the validity of a patent." H.R. Rep. No. 112098, part 1, at 48 (2011). The Board should deny institution under § 325(d).

VII. THE PERSON OF ORDINARY SKILL

Illumina previously submitted its definition for a POSITA in IPR2013-00517 involving the same claims from the same patent. Ex-1092 at 9-10. BGI concedes its proposed definition is "substantially similar to the definition proposed by Illumina in the prior IPR." Petition at 14, n.2. Thus, there is no reason to deviate from Illumina's definition.

VIII. NEW CLAIM CONSTRUCTION IS UNNECESSARY

The Board previously construed Claim 1. Ex-1094 at 6-7. No additional claim construction is required at this stage.

IX. THE LAW OF NONOBVIOUSNESS

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior

art.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). As the petitioner, it is BGI’s “burden to demonstrate both that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *IBS*, 821 F.3d at 1367-68.

X. THERE WAS NO MOTIVATION TO COMBINE TSIEN WITH GREENE & WUTS OR ZAVGORODNY

The Board, Federal Circuit, and Northern District of California previously considered Tsien’s sequencing method and the alleged azidomethyl disclosures of Greene & Wuts and Zavgorodny, and all concluded there was no motivation to combine Tsien’s method with an azidomethyl protecting group. *Supra* Section III.

A. Introduction to Tsien, Greene & Wuts, and Zavgorodny

Tsien discloses DNA sequencing methods that use nucleotides having a 3’-OH protecting group.⁵ Tsien does not disclose a removable 3’-OH azido protecting group. Ex-1101 ¶92, n.3; Ex-1092 at 11-12. BGI’s petition admits that Tsien sets forth three criteria “teach[ing] 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:

⁵ A 3’-OH protecting group is a type of 3’-blocking group that can be removed or “deblocked” to regenerate a 3’-OH moiety. Ex-1090 at 9-10.

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

Petition at 33-34; Ex-1003 at 20:28-21:3. BGI's petition concedes that Tsien's second criteria includes the following requirements: (i) “mild deblocking conditions” (Petition at 41-46) and (ii) quantitative deblocking (*id.* at 46-50).

Greene & Wuts provides an encyclopedia-like listing of protecting groups “for five major functional groups: -OH, -NH, -SH, -COOH, and >C=O.” Ex-1005 at ix. Greene & Wuts is a “mammoth” book. Ex-2022 at ix. “In total, 1050 protecting groups are covered, with 5350 references.” Ex-1025 at 426. Greene & Wuts discloses two different classes of protecting groups for -OH functional groups in two separate chapters: Chapter 2 discloses protecting groups for aliphatic hydroxyl groups (such as those found at the 3' OH position of nucleotides), while Chapter 3 discloses protecting groups for aromatic phenols and catechols. Ex-1005 at 17-23, 246-248; Ex-1098 ¶49. The azidomethyl protecting group is disclosed in Chapter 3, along with 60 other protecting groups for aromatic phenols. *Id.* at 246-247. Greene & Wuts does not disclose that the azidomethyl protecting group is acceptable for aliphatic -OH groups. *Id.* at 17-23. The 3'-OH

group on Tsien's nucleotides is an aliphatic -OH group; it is not an aromatic phenol. Ex-1098 ¶48.

Zavgorodny is a synthetic organic chemistry paper. Zavgorodny discloses over 180 compounds that are described as "useful specifically blocked synthons." Ex-1008 at 7595. One of these 180 compounds contains an azidomethyl protecting group. Zavgorodny's compounds have no specified use or intended purpose. Ex-2023 at 105:23-106:3, 104:10-14. Although "synthon" is a term normally associated with a synthetic, chemical synthesis of nucleotides, rather than the biological (enzymatic) approach used in Tsien's sequencing method. Zavgorodny does not disclose DNA sequencing methods.

Illumina previously submitted extensive arguments and evidence demonstrating that a POSITA would not have been motivated to use an azidomethyl group in Tsien's methods because an azidomethyl group would not have been expected to meet any of Tsien's three criteria for a reversible 3'-OH nucleotide blocking group. Ex-1092 at 12-32. The Board and Federal Circuit agreed there was no such motivation. *Supra* Section III. In the next sections, Illumina will explain, for a second time, why a POSITA would not have been motivated to use an azidomethyl group in Tsien's methods.

B. Criteria 1: A POSITA would not have expected a 3'-O-azidomethyl group to be efficiently and accurately incorporated by a polymerase

Illumina previously explained and presented evidence that a POSITA would not have been motivated to use an azidomethyl moiety because it would not have been expected that a 3'-O-azidomethyl group would be efficiently and accurately incorporated by a polymerase. Ex-1092 at 14-17. The Board considered all the arguments and evidence presented in the previous IPR and ultimately agreed that a POSITA would not have “considered it obvious to use Zavgorodny’s azidomethyl group as the 3’ hydroxyl protecting group in Tsien’s processes.” Ex-1094 at 9.

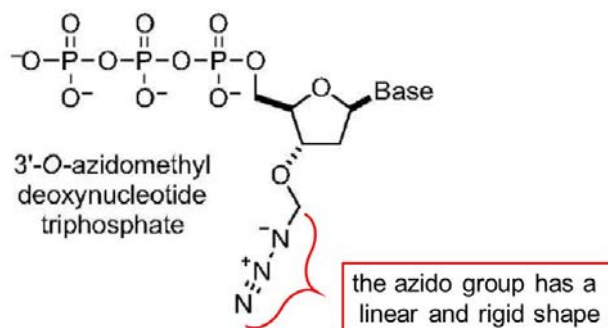
1. There was no motivation to use an azidomethyl group in Tsien’s sequencing methods because there was no expectation of efficient and accurate polymerase incorporation

BGI argues that nucleotides bearing a 3'-O-azidomethyl group would have been expected to be incorporated because this group “is very small compared to some groups that had been successfully incorporated” and “would have expected it to exhibit less steric interference” than the other incorporated groups. Petition at 38-39 (citing Ex-1101 ¶¶76, 95).

BGI’s argument overlooks important differences in the shape, steric bulk, and polarity of the azidomethyl group as compared to the other 3’-groups that had been incorporated.

BGI’s witness, Dr. Sutherland, admits that the shape of the 3’-OH protecting group is an important factor for incorporability. Ex-1101 ¶95 (“DNA polymerase

discriminates against nucleotide analogues based on size and shape”). An azidomethyl group has a linear shape. Petition at 39. The linear shape of an azidomethyl group is rigid along the three nitrogen atoms:



Ex-1101 ¶95 (page 69) (annotated); Ex-2024 ¶25. All three nitrogen atoms lie in essentially the same plane, as shown below:

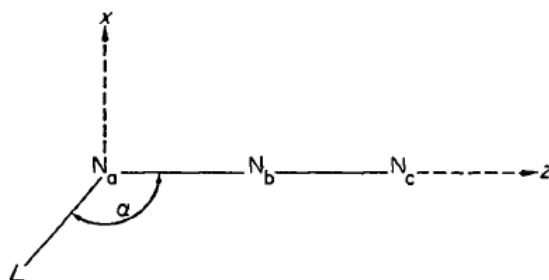


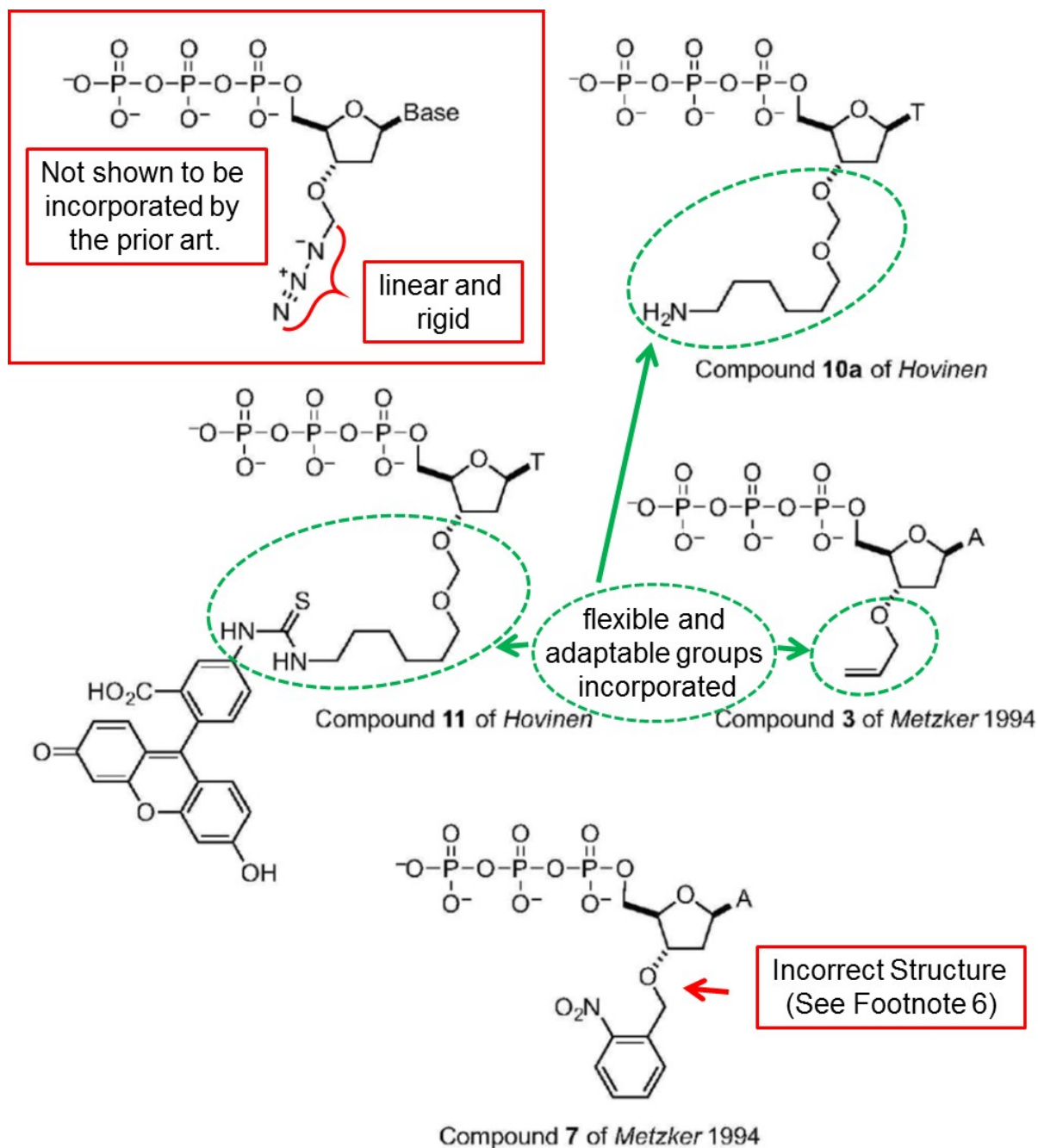
FIGURE 1. The geometry of covalent azides (L is the atom to which N_a is bound; all the nuclei lie in the xz plane).

Ex-2027 at 4. The three azido nitrogen atoms are severely restricted in their degree of freedom—the three atoms are limited to rotation about a single axis. *Id.*; Ex-2024 ¶25.

BGI argues “the linear shape of the azido group allows it to adopt rotameric states” that “lessens steric interference.” Petition at 39. The linear azido group,

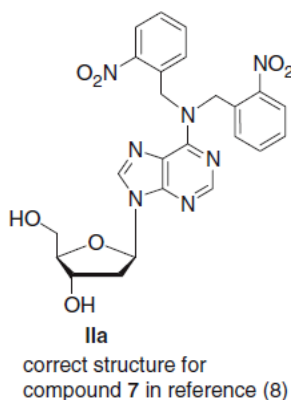
however, behaves essentially like a cylinder. Ex-2024 ¶25. This cylinder rotates along only one axis (the z-axis shown in the above Figure 1 from Ex-2027). *Id.* The linear and rigid cylindrical shape of the azido group would not be expected to allow each nitrogen atom to be independently repositioned within the active site to lessen steric hindrance. *Id.* Instead, the long and linear cylindrical shape of the azido group would occupy a large amount of space and provides significant steric bulk that must be accommodated within a polymerase active site. Ex-2028 at 71:1-8 (“I would think that with an azide -- an azide is a very long molecule. It’s a long, narrow molecule. It’s three atoms linear. That means you’ve got to have -- oh, about, I’m guessing, five angstroms of linear space; half a nanometer. For an enzyme, that’s a lot of space, and you have to have the space to accommodate that and it can’t wrap around.”).

BGI relies on 3’-moieties that Hovinen and Metzker demonstrated were incorporable to assert that the allegedly “very small” azidomethyl group would also be expected to be incorporated. Petition at 38-39 (citing Ex-1101 ¶95). The linear and rigid shape of an azido group is very different from the flexible and adaptable 3’-moieties that Hovinen and Metzker demonstrated were incorporated by polymerases. These differences are as shown in the following annotated figure:



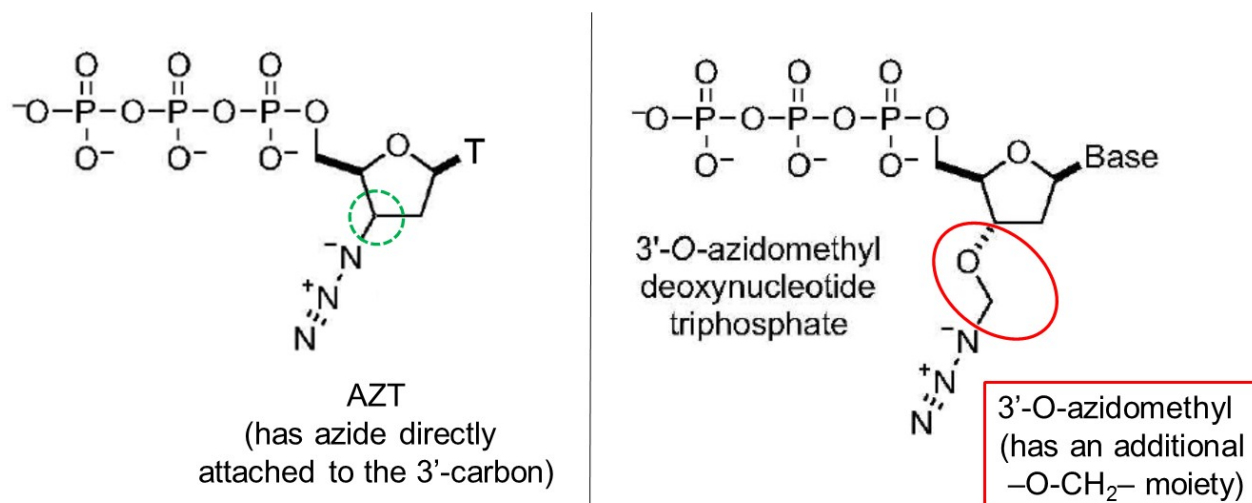
Ex-1101 ¶95⁶ (page 69) (annotated); Ex-2024 ¶26. Hovinen explains that it specifically selected “a long flexible acetal arm” for two reasons: “(i) the reporter groups may be kept distant from the catalytic center of the polymerase, and (ii) the flexible arm would not severely restrict the conformational motion that the sugar ring undergoes on binding to enzyme.” Ex-1027 at 212-13. The Hovinen and Metzker 3’-moieties have significant flexibility and adaptability to adopt configurations compatible within the internal geometry of the polymerase active site relative to the azidomethyl group. The incorporability of these 3’-moieties would not lead a POSITA to look to the linear and rigid azidomethyl group as a similarly suitable polymerase substrate. Ex-2024 ¶27.

⁶ Ex-1101 ¶95 on page 69 shows an incorrect structure for Compound 7. BGI omits that the structure of Compound 7 was later corrected to be:



which does not have a 3’-OH protecting group. Ex-2029 at 6339-40. Thus, if a POSITA had pursued Compound 7, it would not have worked in Tsien’s SBS method because it lacks a 3’-blocking group.

BGI argues that incorporation of nucleotides bearing a 3'-azido (-N-N≡N) group, such as 3'-azido thymidine (AZT), would lead a POSITA to expect a nucleotide bearing the larger 3'-O-azidomethyl (-O-CH₂-N-N≡N) group would also be incorporated. Petition at 40 (citing Ex-1015 & Ex-1076); Ex-1015 at 21462 (discussing AZT incorporation); Ex-1076 at 28 (discussing 3'-N₃ dNTP incorporation). The structures of a 3'-azido nucleotide, AZT, and a nucleotide having a 3'-O-azidomethyl group are shown below:



Ex-2024 ¶28. The 3'-O-azidomethyl protecting group contains an extra oxygen atom, an extra carbon atom, and two extra hydrogen atoms than the 3'-azido group of AZT.

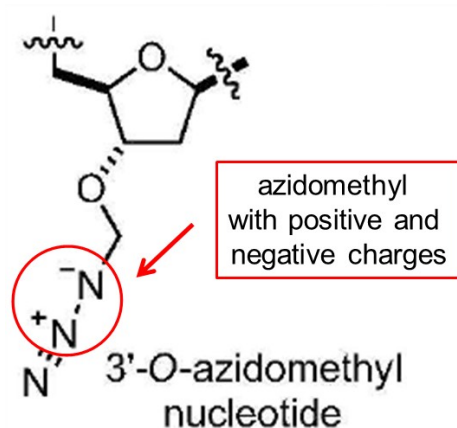
In 2001, Boyer studied the incorporation and positioning of AZT within the polymerase active site. Ex-2030 at 4832; Ex-2024 ¶29. Boyer determined that when the 3'-azido group of AZT is incorporated, it occupies the entire available space within the polymerase active site. Boyer reported, “when AZT is

incorporated, the AZT interferes with the formation of the closed ternary complex [of the polymerase]. We believe that the problem is steric and that the large azido group interferes with the ability of AZT to occupy the P [portion of the active] site, or the ability of the incoming dNTP to enter the N [portion of the active] site, or both.” Ex-2030 at 4833. Boyer explains that incorporation of AZT results in “the distance between D185 and the first and second azido nitrogens [to be] less than the sum of the van der Waals radii.” *Id.* at 4838. Thus, AZT incorporation essentially overstuffs the polymerase active site with the steric bulk of the linear and rigid 3'-azido group.

Dr. Sutherland admits “polymerases were known to be sensitive to steric bulk on the sugar.” Ex-1101 ¶95 (page 67); Ex-2024 ¶30. A 3'-O-azidomethyl group has greater steric bulk on the sugar than the 3'-azido group of AZT because the 3'-O-azidomethyl has an extra oxygen atom, an extra carbon atom, and two extra hydrogen atoms. Dr. Sutherland concedes that polymerases distinguish between nucleotides “based on the difference in steric bulk on each respective sugar” and that adding a single oxygen atom to the sugar can be the difference between incorporation and non-incorporation. Ex-1101 ¶95 (citing Ex-1026). BGI does not explain where within the active site the extra oxygen atom, carbon atom, and two hydrogen atoms would be expected to fit.

BGI asserts that an azidomethyl group would have been expected to be incorporated because it has a “small” size. Petition at 38-39. As discussed above, the incorporation of 3'-groups within the polymerase active site is dependent on size, as well as shape and flexibility. Metzker demonstrated that a small 3'-O-acyl group was not incorporated, while a small 3'-O-allyl group was incorporated. Ex-1041 at 4263, 4265; Ex-2024 ¶31. Thus, selecting a 3'-protecting group that is small is insufficient, by itself, to support an expectation of incorporation.

The ability of a polymerase enzyme to successfully incorporate a nucleotide substrate is influenced not only by the shape and size of the substrate, but also its polarity. Ex-2024 ¶32. BGI's petition fails to account for the polarity of the azidomethyl group. An azidomethyl group is highly polar. The significant polarity of an azidomethyl group is shown on page 81 of Dr. Sutherland's declaration (the relevant portion of his declaration is reproduced below):



Ex-1101 ¶109 (page 81) (annotated). Dr. Sutherland correctly concedes that the azidomethyl group contains positive and negative charges on the nitrogen atoms,

which imparts a large amount of polarity to the azidomethyl group. *Id.*; Ex-2024 ¶32. But Dr. Sutherland never accounts for this polarity in reaching his conclusion that a POSITA would have been motivated to use an azidomethyl moiety. Dr. Sutherland relies upon Hovinen's and Metzker's reported incorporation of non-polar groups. *Id.* Dr. Sutherland does not explain why a POSITA would take the leap from using non-polar-substituted nucleotides to using a highly polar 3'-azidomethyl-substituted nucleotide. BGI's petition is similarly silent. A POSITA would not have considered the non-polar substrates cited by BGI to provide a reason for using Zavgorodny's polar azidomethyl group.

For all of these reasons, BGI has not demonstrated that a POSITA would have been motivated to use a 3'-O-azidomethyl group as a substrate to be incorporated by a polymerase. BGI has therefore failed to demonstrate that a POSITA have been motivated to use a 3'-O-azidomethyl group in Tsien's sequencing methods.

2. BGI has not shown there was a reasonable expectation of success in arriving at the claimed "incorporation"

BGI admits that Claim 1 of the '537 patent requires "incorporation." Petition at 11-12 (Claim 1 "requires a single step of 'incorporating'"); Ex-1001 at 19:50-51. It was therefore necessary for BGI to demonstrate that a POSITA would have had a reasonable expectation of success in arriving at this claim element. *IBS*, 821 F.3d at 1367-68 (It is petitioner's "burden to demonstrate both that a

skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.”); *supra* Section III.B.2. But BGI fails to address the expectation of success of the claimed “incorporation” anywhere in its petition, and thus fails to demonstrate a *prima facie* case of obviousness. The Board should deny the petition for at least this reason.

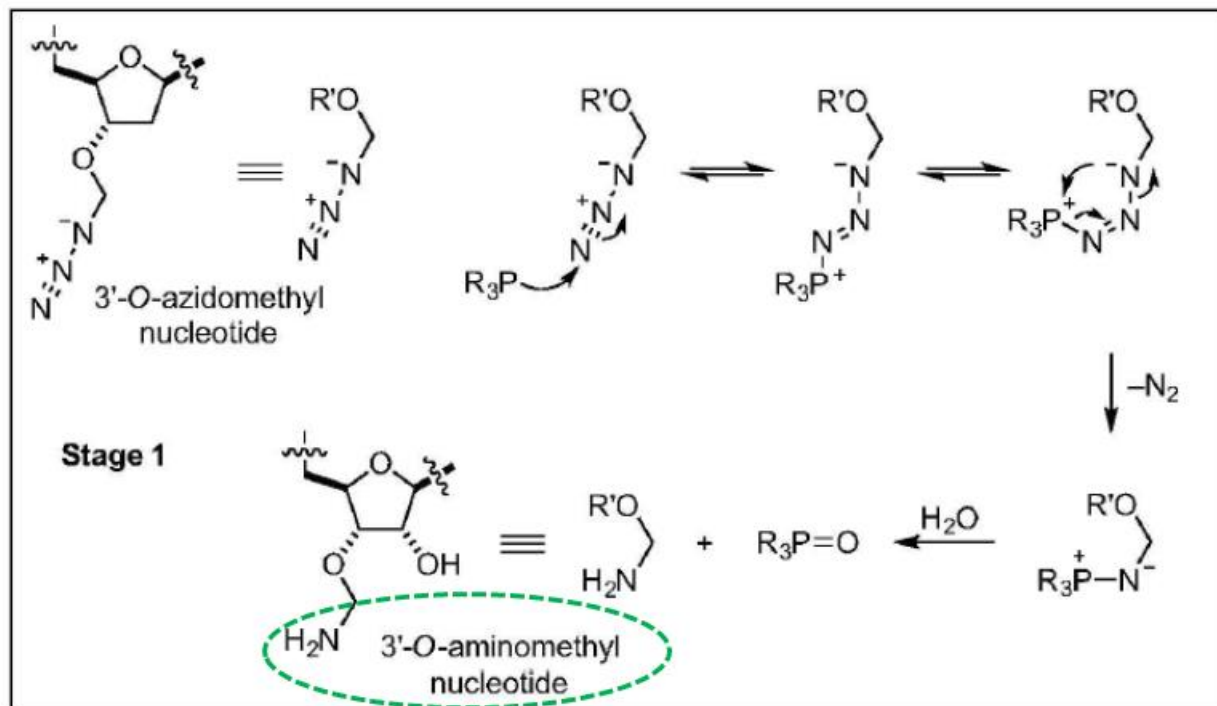
C. Criteria 2(i): A POSITA would not have expected azidomethyl removal conditions to be “mild” for Tsien’s DNA sequencing method

In the previous IPR, the Board found that Illumina presented “evidence that an ordinary artisan would not have considered Zavgorodny’s conditions suitably mild for Tsien’s sequencing purposes.” Ex-1094 at 14; *id.* at 8 (considering Illumina’s arguments and evidence that “the pyridine used in removing Zavgorodny’s azidomethyl protecting group was known in the art to denature DNA”). The Board found there was no indication that an azidomethyl protecting group would be deblocked “under conditions suitable for use in Tsien’s sequencing methods.” *Id.* at 14. The Federal Circuit determined that the Board was justified in finding that there was no motivation to use azidomethyl because a POSITA would not have expected “Zavgorodny’s azidomethyl protecting group to meet Tsien’s quantitative deblocking requirement under conditions suitable for use in Tsien’s sequencing methods.” *IBS*, 821 F.3d at 1368.

BGI admits Tsien requires “mild deblocking conditions” that “do not denature the DNA or interfere with future enzyme function” (Petition at 41) and “would not degrade the DNA.” *Id.* at 22. But BGI fails to carry its burden of showing a POSITA would have been motivated to use an azidomethyl group in view of the following evidence at the time that: (1) phosphine deblocking conditions produce amines, which Stanton discloses would cleave the phosphate ester backbone of DNA, (2) pyridine was a DNA denaturant, and (3) the deblocking conditions disclosed by Young would not be considered mild in Tsien’s SBS methods.

1. Phosphine deblocking conditions produce amines

BGI argues that the triphenylphosphine deblocking conditions disclosed by Zavgorodny and Loubinoux would have been appropriately “mild” for Tsien’s method. Petition at 41-44. BGI further expands the allegedly “mild” conditions to “any suitable phosphine reagent.” *Id.* at 45. Dr. Sutherland, however, admits that the reaction of a phosphine with an azidomethyl group produces an amine (Ex-1101 ¶110) and he shows the amine formation on page 81 of his declaration:



Id. at page 81 (annotated).

Evidence available at the time of Illumina's invention indicated that such amine formation would not have been expected to be mild for Tsien's method due to an intramolecular reaction that cleaves the phosphate ester backbone of DNA. For example, Stanton, an exhibit cited by BGI, explains that the amine group formed by the reaction of a phosphine with an azido group would cleave the phosphate ester backbone of DNA and degrade the DNA:

The amino group may be generated in situ from the corresponding azido sugar by treatment with tris(2-carboxyethyl)-phosphine (TCEP) after the azide-modified polynucleotide has been formed. The amino group, once formed, spontaneously attacks the phosphate ester linkage resulting in cleavage.

Ex-1046 at 85:10-13. BGI admits that degradation of DNA would not be mild. Petition at 22 (“mild conditions are those that would not degrade the DNA”). Therefore, evidence indicates that BGI’s proposed deblocking conditions using phosphines would not have been considered “mild” in Tsien’s method.

In the previous IPR, Illumina raised Stanton’s disclosures regarding DNA degradation. Ex-2031 ¶5. ***BGI, however, failed to address this evidence of DNA degradation in its petition, and this evidence therefore stands unrebutted.*** A POSITA would have been discouraged from using an azidomethyl group due to Stanton’s disclosure.

2. Pyridine was a known DNA denaturant

BGI does not appear to dispute that pyridine was known to be an “especially effective” DNA denaturant. Ex-1033 at 57-58. Instead, BGI argues that a mixture of Zavgorodny’s triphenylphosphine in pyridine and water (i.e., aqueous pyridine) would not have a denaturing effect. Petition at 42-43.

BGI ignores that triphenylphosphine is practically insoluble in water. Ex-2032 at 9815. It would therefore require significant amounts of pyridine to solubilize triphenylphosphine in a mixture of pyridine and water. Ex-1098 ¶54. The significant amounts of pyridine required to solubilize triphenylphosphine would have been expected to denature DNA and, therefore, would not have motivated a POSITA to use Zavgorodny’s deblocking conditions in Tsien’s

method. *Id.* ¶55. A POSITA would have been discouraged from using an azidomethyl group due to the expected denaturation of DNA using Zavgorodny's deblocking conditions.

3. Young's cleavage conditions were not mild

BGI relies on cleavage conditions disclosed by Young for disclosure of allegedly quantitative azidomethyl cleavage. Petition at 49. Young discloses two methods for removing an azidomethyl group: (1) $\text{SnCl}_2/\text{PhSH}/\text{Et}_3\text{N}$ (Ex-1051 at 67-68), and (2) concentrated trifluoroacetic acid ("TFA"). *Id.* at 65. BGI does not assert that Young's cleavage conditions would meet Tsien's mild deblocking criteria. In fact, Young's cleavage conditions would not have been expected to be mild because Young's cleavage conditions were expected to degrade DNA. Ex-1098 ¶47; Ex-2033 at 129; Ex-2024 ¶34; Ex-2026 at 4997; Ex-2037 at 42. Based on the foregoing, BGI has not demonstrated that a POSITA would have been motivated to use Zavgorodny's azidomethyl moiety in Tsien's methods because no evidence establishes that azidomethyl deblocking conditions would have met Tsien's "mild" criteria.

D. Criteria 2(ii): A POSITA would not have expected quantitative azidomethyl removal

The Board previously determined "the prior art suggests that an ordinary artisan would not have expected Zavgorodny's azidomethyl group to be removed quantitatively, as Tsien requires." Ex-1094 at 14. In reaching this determination,

the Board considered arguments based on Loubinoux and Greene & Wuts, and found “Loubinoux describes only a 60–80% removal efficiency of azidomethyl groups from phenols, and Greene and Wuts suggests that removal from simple aliphatic alcohols, such as that present at the 3’ position of nucleotides, would be less efficient, because phenol is a better leaving group.” *Id.* at 21. The Federal Circuit agreed with the Board that the “[p]rior art of record, however, demonstrates that an ordinary artisan would have expected Zavgorodny’s azidomethyl group to be removed at a much lower efficiency than required by Tsien’s methods.” *IBS*, 821 F.3d at 1364-65.

BGI’s petition concedes that “a POSITA would have appreciated that a less than quantitative yield is to be expected in practice.” Petition at 46. This direct concession confirms that a POSITA would not have been motivated to use Zavgorodny’s azidomethyl group in Tsien’s methods and should result in denial of BGI’s follow-on petition.

BGI argues that Loubinoux’s reported “pure product yields” of 60-80% “would not have been understood by a POSITA as a reasonable comparator for the ‘efficiency’ or ‘yield’ referred to in Tsien.” Petition at 47-48. According to BGI, a POSITA would have ignored Loubinoux’s reported yields, and would instead conclude that Loubinoux’s actual (but non-reported) reaction efficiency “must

have been very high.” Petition at 48. The Board considered and rejected this same argument in the previous IPRs as follows:

Petitioner advances evidence that Loubinoux’s pure product yields of 60 to 80 percent would have been viewed as a poor proxy for actual reaction efficiency. The fact that pure product yields might be a poor indicator of actual reaction efficiency does not substitute, however, for evidence showing that an ordinary artisan would have expected Zavgorodny’s azidomethyl group to be removed quantitatively under conditions suitable for performing Tsien’s sequencing processes.

Ex-1094 at 16-17. The Federal Circuit analyzed Loubinoux and Greene & Wuts and determined that these references support the Board’s decision:

In its decision the Board acknowledged two background references presented by Illumina: Loubinoux, which teaches that azidomethyl methyl groups are removed from phenols with modest efficiency (60-80% yield), and Greene & Wuts, which teaches that removal of an azidomethyl methyl group from the 3' hydroxyl position of a deoxyribonucleotide moiety is likely to proceed with even lower efficiency. These references support a conclusion that the claimed efficiency that allegedly motivated the combination would not be achieved and that a person of ordinary skill in this field would not have been motivated to use the azidomethyl group of Zavgorodny as a protecting group that can be modified or removed to expose a 3' hydroxyl group of a nucleic acid molecule, as the claim requires. This is so because the azidomethyl group would have been expected to perform inefficiently in that role.

IBS, 821 F.3d at 1368-69.

BGI argues that Young would have provided an expectation of quantitative azidomethyl cleavage. Petition at 49. Young discloses two methods for reducing an azidomethyl group: (1) $\text{SnCl}_2/\text{PhSH}/\text{Et}_3\text{N}$ (Ex-1051 at 67-68), and (2) concentrated trifluoroacetic acid (“TFA”). *Id.* at 65. These methods would not have motivated a POSITA to use an azidomethyl protecting group in Tsien’s methods because Young’s cleavage methods would have been expected to degrade DNA. *Supra* Section X.C.3; Ex-1098 ¶47; Ex-2024 ¶34. BGI has not demonstrated that the Board should reverse its previous determination that a POSITA would not have been motivated to use Zavgorodny’s azidomethyl group in Tsien’s methods. The Board should deny BGI’s follow-on petition for the same reasons that the Board previously determined that a POSITA would not have considered it obvious to use an azidomethyl protecting group in Tsien’s methods.

E. Criteria 3: A POSITA would not have expected an azidomethyl ether to permit a polymerase to reinitiate synthesis subsequent to deblocking

Illumina previously explained and presented evidence that a POSITA would not have been motivated to use a 3’-O-azidomethyl group in Tsien’s methods because there was no evidence that a polymerase would reinitiate synthesis after deblocking the 3’-O-azidomethyl group. Ex-1092 at 31-33, 15-16. The Board considered the arguments and evidence, and ultimately agreed a POSITA would not have “considered it obvious to use Zavgorodny’s azidomethyl group as the 3’

hydroxyl protecting group in Tsien's processes." Ex-1094 at 9. The Federal Circuit affirmed. *IBS*, 821 F.3d at 1370.

BGI argues that 3'-azidonucleotides, such as 3'-azido thymidine phosphate (AZT), would lead to an expectation that an azidomethyl would not hinder a polymerase from reinitiating synthesis. Petition at 41 (citing Part IX.D.1 of the Petition). BGI ignores, however, that 3'-azidonucleotides were used to treat HIV *precisely because* they prevent a polymerase from reinitiating synthesis after incorporation. Ex-1015 at 21462; Ex-2030 at 4832; Ex-2034 at 44:9-45:6. BGI's witness (Dr. Sutherland) explained that this prevention is due to the 3'-azide group being "directly linked to the 3'-carbon atom" such that any "[r]eduction of the azide would not result in the regeneration of a 3'-OH group, but the creation of a 3'-NH₂ group." Ex-1101 ¶92, n.3; Ex-1058 at 297.

Tsien discloses that its "sequencing scheme requires the blocking group to be removed to yield a viable 3'-OH site for continued chain synthesis." Ex-1003 at 23:28-31. Thus, there would not have been an expectation that incorporation of 3'-azido nucleotides would permit a polymerase to reinitiate DNA synthesis after incorporation, as required by Tsien's methods.

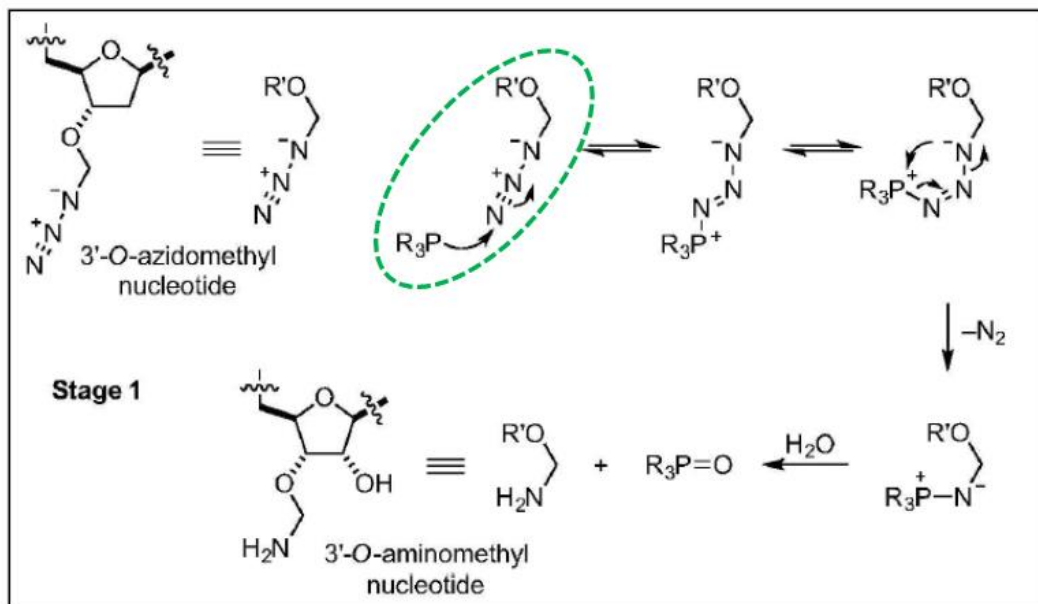
BGI asserts an expectation of compatibility with polymerases because azides were generally considered "to be unreactive towards biological systems (i.e., bi-orthogonal)." Petition at 39. BGI's high-level assertion fails to address the

specific evidence from the scientific literature that azides were expected to react with nucleophiles within the localized environment of the polymerase active site. For example, Canard 1995 indicates that “the polymerase-bound 3’ end of DNA lies in the vicinity of a powerful nucleophilic group in the active site involved either in polymerization or in 3’-substituent removal, a finding in accordance with crystallographic data for several DNA polymerases.” Ex-1042 at 10863; Ex-1092 at 15. Canard 1995 warns a POSITA that azides on the 3’-end of nucleotides are likely to be attacked by the powerful nucleotide as follows:

Other substituents at the 3’ end of DNA at such a position and distance of the sugar ring may also receive a nucleophilic attack. Strikingly, the central nitrogen of the 3’-azido group of AZT bears a partial positive charge in a position similar to the carbonyl group of 3’-esterified nucleotides, and the 3’-azido group of AZT is metabolized into a 3’-amino group in vivo.

Id. Canard 1995 was published in the highly respected Proceedings of the National Academy of Sciences, and his warning was acknowledged and implemented by other researchers. Ex-1038 at 3:12-20.

BGI’s witness (Dr. Sutherland) concedes that the azidomethyl group is susceptible to nucleophilic attack and shows the mechanism for this attack as follows:



Ex-1101 at page 81 (annotated) (showing nucleophile “ R_3P ” attacking the azide moiety on a 3'-O-azidomethyl nucleotide).

The evidence indicates that a POSITA would have considered that nucleophiles within the polymerase active site might react with a 3'-O-azidomethyl group. This reaction would result in premature cleavage of the azidomethyl group *before* (not after) the deblocking step, which would cause inadvertent additions of other dNTPs by the polymerase. Ex-1003 at 12-22-29. Tsien's method relies on controlled deblocking conditions 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” and to “prevent inadvertent multiple additions” of nucleotides. *Id.*; *id.* at 24:16-17 (warning a POSITA to avoid “premature deblocking”). Thus, the susceptibility of the 3'-O-azidomethyl group to

nucleophilic attack within the polymerase active site would not have motivated a POSITA to use an azidomethyl group because it would not have been expected to meet Tsien's third requirement for reinitiation of DNA synthesis *after* deblocking.

Based on the foregoing, a POSITA would not have been motivated to use a 3'-O-azidomethyl group in Tsien's methods because Tsien provides no indication that a 3'-O-azidomethyl group would have been desirable and there was no basis to believe that a 3'-O-azidomethyl group would have met Tsien's 3'-protecting group requirements. Therefore, a POSITA would not have been motivated to use a 3'-O-azidoemthyl protecting group in Tsien's sequencing methods. The Board should deny BGI's follow-on petition for the same reason that it previously held it would not have been obvious to use an azidomethyl protecting group in the processes described in Tsien. Ex-1094 at 18; *IBS*, 821 F.3d at 1368.

XI. AZIDOMETHYL WAS NOT A SIMPLE SUBSTITUTION INTO TSIEN'S SBS METHOD

BGI argues "a POSITA would have recognized azidomethyl as a known element that could be simply substituted into Tsien's SBS method." Petition at 53. BGI's "simple substitution" theory ignores that at least 11 separate research teams tried to identify appropriate 3'-protecting groups for SBS. *Supra* Section II. If an azidomethyl group would have been a simple substitution, one or more of these research teams would have been expected to identify this group for use in SBS. But only Illumina identified the azidomethyl group. Also, a POSITA would not

have been motivated to substitute an azidomethyl group into Tsien's SBS methods because there was no basis to believe that an azidomethyl group would have met Tsien's 3'-protecting group requirements. *Supra* Section X.

Furthermore, BGI's simple substitution theory belies the testimony of its own witness (Dr. Sutherland). Dr. Sutherland asserts that a POSITA would follow a complicated process to select a protecting group for use in Tsien's methods from the myriad of protecting groups described in the literature. According to Dr. Sutherland, the process extends far beyond just selecting a protecting group—it also includes “numerous technical decisions, such as selecting a protecting group, optimizing deprotection conditions, selecting the proper polymerase, optimizing polymerization conditions, as well as selecting the proper label and linker.” Ex-1101 ¶¶60. Dr. Sutherland states that the optimization of each of these steps is further complicated by decisions concerning reaction conditions, reagent selection, temperature, pH, concentration and time. *Id.* Dr. Sutherland opines that Tsien's sequencing methods have many variables, and a POSITA would not expect that all of Tsien's criteria could be met. Ex-1101 ¶¶79 (“While it would be best to meet all of [Tsien's] criteria to the fullest extent possible, this is not always possible when optimizing a system with this many variables. Some trade-off is expected; increased reaction rate might come at the cost of harsh (as opposed to mild) reaction conditions.”). Dr. Sutherland further posits that an azidomethyl group

would not be expected to work in Tien's method if any of the Tsien's criteria would not be expected to be met because "[o]ne of ordinary skill would know that the entire sequencing method is only as strong as its weakest link: if further optimization of one part of the system will not result in improved read lengths or times because of deficiencies in other parts of the system, there will be no need for optimization of that part at that time." Ex-1101 ¶80. Thus, BGI's own witness undermines BGI's assertion that an azidomethyl group could be simply substituted into Tsien's methods.

XII. MOTIVATION IS LACKING FROM BGI'S PETITION THAT IS PRESENT IN ILLUMINA'S PETITIONS

In December 2017, Illumina submitted four IPR petitions challenging patents directed to nucleotide analogues owned by Columbia University in IPR2018-00291, IPR2018-00318, IPR2018-00322, and IPR2018-00385. BGI and Illumina's petitions both rely on Tsien as a primary obviousness reference. There are several important distinctions between Illumina's petitions and BGI's petition.

A. BGI relies on disclosure of a 3'-protecting group *from outside of Tsien*, whereas Illumina's petitions rely on protecting group disclosures *within Tsien*

While both BGI and Illumina's petitions rely on Tsien as a primary obviousness reference, BGI's petition relies on disclosure of a 3'-O-azidomethyl protecting group from Greene & Wuts and Zavgorodny. Thus, BGI's petition relies on disclosure of a protecting group *from outside of Tsien*, and, in fact,

outside of the SBS literature. “When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references.” *IBS*, 821 F.3d at 1368. As discussed herein, there was no motivation to combine the azidomethyl group disclosed by Greene & Wuts and Zavgorodny with Tsien’s SBS method.

In critical contrast, Illumina’s petitions rely on Tsien’s disclosure of a 3’-O-allyl protecting group. Tsien discloses that the 3’-O-allyl group is advantageous and desirable for use in Tsien’s methods. Ex-1003 at 24:25-25:3. Illumina’s petitions assert that a POSITA would have been motivated to use Tsien’s 3’-O-allyl protecting group in Tsien’s methods because Tsien expressly discloses that the 3’-O-allyl group is advantageous and desirable for use in Tsien’s methods. Combining disclosures from within a single reference “does not require a leap of inventiveness.” *Boston Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). Thus, Illumina’s petitions present a markedly different situation from BGI’s petition. Illumina’s petitions rely on a protecting group disclosed *by Tsien itself* as advantageous and desirable for use in Tsien’s method, such that Illumina’s asserted motivation for selecting a 3’-protecting group is found within the four corners of Tsien.

B. Polymerase incorporation distinction

Another important distinction between BGI's petition and Illumina's petitions relates to polymerase incorporation. BGI alleges that a 3'-O-azidomethyl group would be incorporated by a polymerase, but BGI provides no evidence establishing a motivation to use a 3'-O-azidomethyl nucleotide as a polymerase substrate. *Supra* Section X.B. In contrast, Illumina's petitions rely on a 3'-O-allyl nucleotide, and there was motivation to use a 3'-O-allyl nucleotide because a 3'-O-allyl nucleotide had been demonstrated to be incorporated by a polymerase in the SBS literature. Ex-1041 at 4263; Ex-1038 at 3:7-9 ("3'-O-allyl-dATP was also shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994)."); *id.* at 3:20-23, 26:19-27.

C. Illumina's positions are consistent with previous Board and Federal Circuit decisions, whereas BGI's petition and Columbia's patents seek to undo those decisions

The above distinctions differentiate BGI's petition from Illumina's petitions, but there also is a common theme between all the petitions: the parties adverse to Illumina seek to undo prior rulings by the Board and Federal Circuit.

1. BGI's petition seeks to undo IPR2013-00517

As discussed throughout this response, BGI's petition seeks to undo the Board's holding in IPR2013-00517 and the Federal Circuit's affirmance thereof.

2. Columbia's patents seek to undo IPR2012-00006, IPR2012-00007, and IPR2013-00011

In three previous IPRs, the Board held unpatentable all claims challenged by Illumina from three Columbia patents. *Illumina v. Columbia*, IPR2012-00006, Paper 128 at 45; IPR2012-00007, Paper 140 at 49; IPR2013-00011, Paper 130 at 45 (P.T.A.B. 2014). The Federal Circuit unanimously affirmed unpatentability of Columbia's claims. *Columbia v. Illumina*, 620 Fed. Appx. 916, 934 (Fed. Cir. 2015).

Columbia improperly sought additional bites at the apple and violated the Board's patent owner estoppel rule by filing four continuation patent applications directed to the same subject matter held unpatentable by the Board. *See, e.g., Illumina v. Columbia*, IPR2018-00318, Paper 2 at 1-7. The four petitions filed by Illumina in December 2017 challenge the four patents that issued from Columbia's applications.

Illumina's preliminary response in this proceeding and Illumina's petitions against Columbia's four new patents ask the Board to follow the same analysis from the previous final written decisions in IPR2013-00517, IPR2012-00006, IPR2012-00007, and IPR2013-00011. In contrast, BGI and Columbia seek new rulings from the Board that contradict the previous final written decisions and Federal Circuit affirmances.

XIII. THE DEPENDENT CLAIMS ARE NONOBVIOUS

The method of Claim 1 would not have been obvious for at least the reasons discussed herein. Claims 2-6 and 8 depend from Claim 1 and are also nonobvious. *In re Fritch*, 972 F.2d 1260, 1266 (Fed Cir. 1992) (“dependent claims are nonobvious if the independent claims from which they depend are nonobvious”).

XIV. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

A. BGI failed to address Illumina’s evidence of non-obviousness

In the previous IPR trial, Illumina raised a number of objective indicia of non-obviousness, including long-felt but unmet need, unexpected results, and evidence of copying. Ex-1094 at 43-60. “[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record,” and “must always when present be considered en route to a determination of obviousness.” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Despite the central role of objective evidence of non-obviousness, BGI spent a scant five pages on the issue, the bulk of which advances incorrect legal theories while avoiding the actual evidence. BGI was required to substantively address these previously raised indicia as a threshold requirement for establishing reasonable likelihood of demonstrating obviousness under 35 U.S.C. § 314(a). *Omron Oilfield & Marine, Inc. v. MD/Totco*, IPR2013-00265, Paper 11 at 12-16 (P.T.A.B. 2013). It failed to do so, and thus the petition is facially deficient.

B. BGI advances an unsupported and incorrect legal theory regarding unexpected results

In the previous IPR, Illumina provided evidence that the claimed method performs unexpectedly better than what a POSITA might have gleaned from the combination of Tsien with Zavgorodny. Although the prior art taught that an azidomethyl group would have been cleaved at too low a yield and too slowly to be useful during sequencing, the inventors surprisingly found that azidomethyl was not only suitable but superior to the existing protecting group technologies. Ex-1092 at 54. Indeed, the Federal Circuit agreed there was no reason in the prior art suggesting Zavgorodny's azidomethyl protection would have been useful for sequencing. *IBS*, 821 F.3d at 1368.

Instead of addressing Illumina's evidence, BGI argues that the unexpectedly good results are "based on hindsight bias" because such results are not recited in the claims or the specification. Petition at 59-60. Hindsight bias by the patent owner is irrelevant to a secondary considerations analysis, and BGI's assertion that evidence of unexpected results must be explicitly recited in the specification or claims is wrong. The Federal Circuit has repeatedly explained: "it would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application." *Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F. 3d 1291, 1307 (Fed. Cir. 2011); *In*

re Chu, 66 F.3d 292, 299 (Fed. Cir. 1995) (“We have found no cases supporting the position that a patent applicant’s evidence and/or arguments traversing a § 103 rejection must be contained within the specification.”).

BGI cannot use a facially incorrect legal theory to avoid Illumina’s evidence of non-obviousness. Illumina’s evidence of unexpected results stands unaddressed and unrebutted. By failing to address these unexpected results, BGI fails to meet its burden to establish obviousness. *Omron*, IPR2013-00265, Paper 11 at 12-16.

C. BGI avoids addressing Illumina’s evidence of long-felt, unmet need

In the previous IPR, Illumina presented evidence that there was a long-felt need for protecting groups that could be efficiently and rapidly cleaved under conditions compatible with DNA sequencing. Ex-1092 at 44-49. Illumina established a clear relationship between the claimed invention and advances in SBS technology, including evidence that the claimed azidomethyl group was used as a crucial and necessary component in the cited advanced sequencing methods.

Instead of addressing this evidence, BGI sidesteps the issue entirely by arguing that other factors also contributed to Illumina’s success. In BGI’s view, it is not enough for the claimed invention to be an undisputedly necessary part of the successful advancement of the SBS methodology; instead, BGI asserts that the claimed invention must be the only thing contributing to Illumina’s SBS success. Petition at 57-59.

This is wrong: all that is needed is “a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of non-obviousness.” *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). Even if other advances also contributed to the development of SBS technology, the development of an appropriate protecting group was a limiting step and a major challenge in advancing SBS. Ex-1092 at 44-46. Indeed, BGI’s own exhibit explains the importance of identifying appropriate sequencing chemistry: “If the sequencing chemistry is no good, it doesn’t matter how good the instrument is. You might as well be making cappuccino.” Ex-1045 at 105.

BGI never addressed Illumina’s evidence of a long-felt need, and instead merely attempted to deflect the issue with a legally incorrect theory. Illumina’s evidence stands unrebutted. As such, BGI’s petition is insufficient and should be denied.

D. BGI incorrectly argues that since there is no evidence of a competing commercial product, there can be no evidence of copying

BGI dismisses Illumina’s evidence of copying as “erroneous” because “there was apparently no evidence that Dr. Ju’s group attempted to replicate any specific product of Illumina.” Petition at 59-61. But this is an overly formalistic understanding of what it means to copy an invention. Evidence that a competitor looked at a patent and copied the claimed invention for its own use must also be

probative evidence of non-obviousness, regardless of whether the patentee sold a commercial embodiment. *Cf. Akamai Tech, Inc.. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1196 (Fed. Cir. 2003) (copying an invention is especially good evidence of non-obviousness when the copyist tried and failed to design a similar device). If anything, this type of evidence of copying is even more compelling because it creates a direct link between the copying and the patented invention: it is still copying when the patent, and not a commercial product, is used as a blueprint. That is exactly the evidence previously proffered by Illumina: one of Illumina's competitors that had spent years attempting to optimize the use of a different protecting group for sequencing, switched to the claimed azidomethyl group after reading Illumina's patent disclosures. Ex-1092 at 55-59. Illumina's patent documents were explicitly cited for their disclosure of both the azidomethyl group and its cleavage during the sequencing process, and yielded superior results in the sequencing application. *Id.* The district court found one of Illumina's competitors, Qiagen, had copied Illumina's patented invention. *Illumina*, 207 F.Supp.3d at 1093-94 (finding Qiagen "pirated" Illumina's technology). The adoption of patented technology by a competitor who recognized the invention's benefits is clearly evidence of non-obviousness. *Stratoflex*, 713 F.2d at 1538. It is erroneous for BGI to dismiss this evidence simply because it

involved a competitor copying the invention from the patent itself, and not via a commercial product embodying the claimed invention.

XV. CONCLUSION

For the foregoing reasons, the Board should deny BGI's follow-on petition.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 23, 2018

By: /Kerry Taylor/
Kerry Taylor (Reg. No. 43,947)
Michael L. Fuller (Reg. No. 36,516)
Nathanael R. Luman (Reg. No. 63,160)
Attorneys for Patent Owner
Illumina Cambridge Ltd.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(b), the undersigned certifies that the foregoing **PRELIMINARY RESPONSE OF PATENT OWNER ILLUMINA CAMBRIDGE LTD.**, exclusive of the parts exempted as provided in 37 C.F.R. § 42.24(a), contains 13,821 words and therefore complies with the Board's word count limit.

This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and the spacing requirements of 37 C.F.R. § 42.6(a)(2)(iii) & (iv).

Dated: January 23, 2018

By: /Kerry Taylor/
Kerry Taylor (Reg. No. 43,947)
Michael L. Fuller (Reg. No. 36,516)
Nathanael R. Luman (Reg. No. 63,160)
Attorneys for Patent Owner
Illumina Cambridge Ltd.

CERTIFICATE OF SERVICE

I hereby certify that, pursuant to 37 C.F.R. § 42.6(e)(1) and agreement of the parties, a true and correct copy of **PRELIMINARY RESPONSE OF PATENT OWNER ILLUMINA CAMBRIDGE LTD.** is being served via email on January 23, 2018, to counsel for Complete Genomics, Inc., at the email addresses below:

Jennifer A. Sklenar

Jennifer.Sklenar@apks.com

Michael J. Malecek

Michael.Malecek@apks.com

Katie J.L. Scott

Katie.Scott@apks.com

ARNOLD & PORTER KAYE SCHOLER LLP
777 South Figueroa Street, 44th Floor
Los Angeles, CA 90017-5844

Dated: January 23, 2018

By: /Kerry Taylor/

Kerry Taylor (Reg. No. 43,947)

Michael L. Fuller (Reg. No. 36,516)

Nathanael R. Luman (Reg. No. 63,160)

Attorneys for Patent Owner

Illumina Cambridge Ltd.