

Filed January 23, 2018

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

IPR2017-02174

Patent 7,566,537

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

Columbia Exhibit 2027

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

IPR2018-00322

TABLE OF CONTENTS

	Page No.
I. INTRODUCTION	1
II. ILLUMINA’S CLAIMED INVENTION INCLUDES A NOVEL AND NONOBVIOUS 3’-OH PROTECTING GROUP FOR DNA SEQUENCING.....	6
III. THE BOARD, FEDERAL CIRCUIT, AND DISTRICT COURT PREVIOUSLY UPHELD PATENTABILITY OF THE CHALLENGED CLAIMS	12
A. The Board previously upheld the same claims in IPR2013-00517	12
B. The Federal Circuit affirmed the Board’s Decision from IPR2013-00517	14
C. The Northern District of California upheld the same claims from the same patent	14
IV. BGI’S SECOND FOLLOW-ON PETITION SHOULD BE DENIED UNDER 35 U.S.C. § 314(A)	15
A. Factor 1: Whether the same petitioner previously filed a petition directed to the same claims of the same patent.....	19
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.....	21
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	22

TABLE OF CONTENTS
(cont'd)

Page No.

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.....	23
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	24
F.	Factor 6: The finite resources of the Board.....	25
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	25
V.	THE PERSON OF ORDINARY SKILL	26
VI.	NEW CLAIM CONSTRUCTION IS UNNECESSARY	27
VII.	THE LAW OF NONOBVIOUSNESS	27
VIII.	THERE WAS NO MOTIVATION TO COMBINE DOWER WITH ZAVGORODNY AND CHURCH	27
A.	Introduction to Dower, Zavgorodny, and Church.....	28
B.	BGI Primary Issue 1: A POSITA would not have expected a 3'-O-azidomethyl group to be efficiently and accurately incorporated by a polymerase	29
1.	There was no motivation to use an azidomethyl group in Dower's sequencing methods because there was no expectation of efficient and accurate polymerase incorporation	30

TABLE OF CONTENTS
(cont'd)

	Page No.
2. BGI has not shown there was a reasonable expectation of success in arriving at the claimed “incorporation”.....	39
C. BGI Primary Issue 2: A POSITA would not have expected azidomethyl removal conditions to be “mild” for Dower’s SBS method.....	40
1. Phosphine deblocking conditions produce amines	41
2. Pyridine was a known DNA denaturant	44
3. Young’s cleavage conditions were not mild.....	44
D. BGI Primary Issue 3: A POSITA would not have expected azidomethyl to be cleaved with appropriate efficiency for SBS	45
E. BGI fails to address Illumina’s evidence that the electrophilic 3’-O-azidomethyl group would not be compatible with nucleophiles within the polymerase active site.....	47
IX. AZIDOMETHYL WAS NOT A SIMPLE SUBSTITUTION INTO DOWER’S SBS METHOD.....	50
X. MOTIVATION IS LACKING FROM BGI’S PETITION THAT IS PRESENT IN ILLUMINA’S PETITIONS	52
XI. THE DEPENDENT CLAIMS ARE NONOBVIOUS	54
XII. THE CLAIMS ARE NOT OBVIOUS IN LIGHT OF SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS	55
A. BGI was aware of Illumina’s evidence of non-obviousness, but failed to address the evidence	55

TABLE OF CONTENTS
(cont'd)

	Page No.
B. BGI avoids addressing Illumina's previously-presented unexpected results by using an unsupported and incorrect legal theory	56
C. BGI avoids addressing Illumina's previously-presented evidence of long-felt, unmet need	57
D. BGI incorrectly argues that since there is no evidence of a competing commercial product, there can be no evidence of copying	59
XIII. CONCLUSION.....	60

TABLE OF AUTHORITIES

	Page No(s).
<i>Akamai Tech. Inc. v. Cable & Wireless Internet Servs. Inc.</i> , 344 F.3d 1186 (Fed. Cir. 2003)	59
<i>In re Chu</i> , 66 F.3d 292 (Fed. Cir. 1995)	57
<i>Demaco Corp. v. F. Von Langsdorff Licensing Ltd.</i> , 851 F.2d 1387 (Fed. Cir. 1988)	58
<i>In re Fritch</i> , 972 F.2d 1260 (Fed Cir. 1992)	54
<i>General Plastic Industrial Co. Ltd. v. Canon Kabushiki Kaisha</i> , IPR2016-01357, Paper 19 (P.T.A.B. 2017).....	<i>passim</i>
<i>Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc.</i> , 655 F.3d 1291 (Fed. Cir. 2011)	56
<i>Illumina, Inc. v. Qiagen N.V.</i> , 207 F.Supp.3d 1081 (N.D. Cal. 2016).....	2, 14, 16, 60
<i>Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	<i>passim</i>
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	27
<i>LG Elecs. Inc. v. Core Wireless Licensing S.A.R.L.</i> , IPR2016-00986, Paper 12 (P.T.A.B. 2016).....	17, 19, 25
<i>Merial Ltd. v. Virbac</i> , IPR2014-01279, Paper 13 (P.T.A.B. 2015).....	55
<i>NetApp Inc. v. Realtime Data LLC</i> , IPR2017-01195, Paper 9 (P.T.A.B. 2017).....	20

TABLE OF AUTHORITIES

(cont'd)

Page No(s).

<i>NetApp Inc. v. Realtime Data LLC</i> , IPR2017-01196, Paper 10 (P.T.A.B. 2017).....	21
<i>NetApp Inc. v. Realtime Data LLC</i> , IPR2017-01354, Paper 16 (P.T.A.B. 2017).....	21
<i>NVIDIA Corp. v. Samsung Elec. Co.</i> , IPR2016-00134, Paper 9 (P.T.A.B. 2016).....	17, 19
<i>Omron Oilfield & Marine, Inc. v. MD/Totco</i> , IPR2013-00265, Paper 11 (P.T.A.B. 2013).....	55, 57
<i>R.J. Reynolds Vapor Co. v. Fontem Holdings I B.V.</i> , IPR2017-01117, Paper 10 (P.T.A.B. 2017).....	24
<i>Samsung Electronics Co., Ltd. v. ELM 3DS Innovations, LLC</i> , IPR2017-01305, Paper 11 (P.T.A.B. 2017).....	21
<i>Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.</i> , 748 F.3d 1354 (Fed. Cir. 2014)	57
<i>Starbucks Corp. v. Ameranth, Inc.</i> , CBM2017-00053, Paper 7 (P.T.A.B. 2017)	19
<i>Stratoflex, Inc. v. Aeroquip Corp.</i> , 713 F.2d 1530 (Fed. Cir. 1983)	55, 60
<i>Unified Patents, Inc. v. Personal Web Technologies, LLC</i> , IPR2014-00702, Paper 13 (P.T.A.B. 2014).....	21
<i>Xactware Solutions, Inc. v. Eagle View Techs., Inc.</i> , IPR2017-00034, Paper 9 (P.T.A.B. 2017).....	19

TABLE OF AUTHORITIES
(*cont'd*)

Page No(s).

OTHER AUTHORITIES

35 U.S.C. § 313	1
35 U.S.C. § 314	<i>passim</i>
35 U.S.C. § 316	18, 25
37 C.F.R. § 42.1	3, 25
37 C.F.R. § 42.107	1
37 C.F.R. § 42.108	19

Pursuant to 35 U.S.C. § 313, 37 C.F.R. § 42.107, and the October 23, 2017 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”). *See* Paper 1 (“BGI’s second follow-on petition”).

I. INTRODUCTION

This is BGI’s second attempt to challenge the ’537 Patent, and it 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 very same claims of the ’537 Patent have been battle tested in the crucible of district court and PTAB litigation. *Seven* judges have considered and rejected prior art attacks on the same claims from the same patent. 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. *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 prior art. *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 arguments it could. 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. 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).

BGI has been in the sequencing business for years, including, but not limited to, in the U.S. through its subsidiary CGI. BGI waited until after the Federal

Circuit affirmed patentability of Illumina's claims before filing two follow-on petitions attacking the same claims for a second and third time. BGI failed to file its own petition during the pendency of the prior IPR, and it did not 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 attacks 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 petitions attempt to pick up where Qiagen left off with a second and third bite at the apple. BGI's use of the previous proceedings as a roadmap to retool and rehash the previous arguments 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).

BGI's first follow-on petition in IPR2017-02172 is based on the same primary reference (Tsien) and secondary references (Zavgorodny and Greene & Wuts) over which the Board upheld the same claims in IPR2013-00517. This present petition is BGI's second follow-on petition, and it uses Dower as a primary reference along with Zavgorodny and Church as secondary references. All of these references were cited on the face of the '537 patent. Any reasonably diligent search by BGI would have uncovered these references at least by the issue date of the '537 patent, and certainly by the time the first petition against the '537 patent

was filed in IPR2013-00517. BGI makes no argument and presents no evidence showing there was any barrier to it presenting arguments based on these references during the pendency of IPR2013-00517.

The Board has put petitioners on notice that follow-on petitions will be heavily scrutinized under 35 U.S.C. § 314(a) even if there are no district court decisions or Federal Circuit decisions upholding the invalidity of the patent. 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 (and here, tertiary) petitions. In the face of 314(a), BGI does not even attempt to justify its belated secondary and tertiary petitions on the same claims from the same patent, and these petitions 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 petitions seek to abuse the IPR process by retreading and retooling where Qiagen lost.

This petition fails to establish a prima facie case of obviousness based on Dower in view of Zavgorodny and Church. Dower discloses SBS methods that use nucleotides having 3'-OH protecting groups. BGI concedes that a person of ordinary skill in the art ("POSITA") would have focused on three primary issues when selecting a reversible 3'-OH protecting group from the literature for use in Dower's SBS methods:

- (1) the ability of a polymerase to incorporate the nucleotide having the 3'-OH protecting group,
- (2) the selection of deblocking conditions that would remove the 3'-OH protecting group without harming the DNA, and
- (3) the incorporation and deblocking steps must result in a yield that is reasonable for the desired application.

This petition, however, fails to establish that an azidomethyl protecting group would have been known to satisfy these three primary requirements. This petition therefore fails to establish that a POSITA would have been motivated to use an azidomethyl group as Dower's 3'-blocking group.

Not only does this petition (which is BGI's second 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 trial, Illumina raised significant evidence of secondary considerations on 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 second 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 "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

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.

compete with the Illumina HiSeq² in terms of cost and throughout, 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 '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 present petition alleges that Claims 1-6 and 8 of the '537 patent would have been obvious to a POSITA based on a combination of Dower, Zavgorodny

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.

and Church. Dower was filed in 1990 and disclosed SBS methods using 3'-OH protected nucleotides. 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-1503 at 21:20-31);

(2) Dower (Affymax) contemplated at least "acetyl, tBOC, NBOC, and NVOC" 3'-OH protecting groups (Ex-1504 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-1541 at 4263);

(4) Canard investigated at least 3'-O-anthranyloyl and 3'-O-anthranyl derivatives (Ex-1542 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-1555 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-1538 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 the 3'-O-allyl group identified by Tsien was a reversible protecting group that could be incorporated effectively by polymerases. Ex-1503 at 24:29; Ex-1541 at 4263; Ex-1538 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-1501 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.

BGI's follow-on petitions assert unpatentability of the same '537 patent claims the Board and Federal Circuit previously upheld in IPR213-00517. The Board previously found that there was no motivation to use an azidomethyl protecting group because it would not have been expected to be deblocked under conditions suitable for use in the prior art sequencing methods. BGI's follow-on petitions use the previous Board and Federal Circuit decisions as a roadmap to stage arguments seeking to re-litigate whether an azidomethyl protecting group would have been expected to be deblocked under conditions suitable for use in sequencing methods. All other considerations aside, BGI's hindsight-driven petitions are an inappropriate and an unacceptable use of the IPR process. *See General Plastic Industrial Co. Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 17-18 (P.T.A.B. 2017) (Precedential) ("The 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.”). BGI should not be permitted yet another attack on the same claims from the same patent.

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

A. The Board previously upheld the same claims 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-1590 at 2, 49.

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-1590 at 38. BGI’s follow-on petition relies on the same SBS motivation asserted by Qiagen. Petition at 34 (“It would have been obvious to further combine Dower’s SBS method with Church’s disulfide linker with Zavgorodny’s azidomethyl protecting group.”); *id.* at 32, 52, 16, 25-26.

³ Qiagen acquired IBS in June of 2012. Ex-1592 at 1.

On May 5, 2014, Illumina filed 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 the prior art SBS methods of Tsien and Ju with the azidomethyl group disclosed by Zavgorodny. Ex-1592 at 12-42. Illumina supported its arguments by analyzing the prior art, 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-1594 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 concluded “Petitioner has not shown that a preponderance of the evidence supports a conclusion that an ordinary artisan would have considered it obvious to use Zavgorodny’s azidomethyl protecting group in the processes described in Tsien.” *Id.* at 18.

BGI’s petition argues that the Board did not consider the Reply arguments submitted during the previous IPR. Petition at 2, 6-7. BGI is incorrect. The Board considered the Reply arguments and found they were not persuasive. Ex-1594 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

On April 8, 2015, 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, on May 9, 2016, **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.

C. The Northern District of California upheld the same claims from the same patent

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. *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 the prior art. *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

⁴ Emphasis supplied unless otherwise noted.

enjoining it from infringing the '537 Patent, further underlining the proven validity of the patent.

**IV. BGI'S SECOND FOLLOW-ON PETITION SHOULD BE DENIED
UNDER 35 U.S.C. § 314(A)**

Qiagen filed the first petition challenging Claims 1-6 and 8 of the '537 patent. After a full trial and Federal Circuit affirmance, BGI filed two additional petitions challenging the same claims: a first follow-on petition in IPR2017-02172 and this second follow-on petition. BGI provides no reason to justify instituting a third petition challenging the same claims from the same patent.

BGI and 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 petitions 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 additional petition to retool and refine the previous petitioner's arguments. BGI's follow-on petitions are exactly the kind of excess and abuse of IPRs that Congress empowered the Board to combat when it enacted Section 314(a) of the AIA. This section provides 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 notifying petitioners that follow-on petitions will be scrutinized under 35 U.S.C. § 314(a), 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)); and
- *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)).

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 petitions under § 314(a). It is not surprising that BGI declines to address this section because the Board's decisions on § 314(a) demonstrate that BGI's follow-on petition should be denied.

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 Industrial Co. Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 15-16 (P.T.A.B. 2017) (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 Corp. v. Samsung Elec. Co.*, IPR2016-00134, Paper 9 at 6-7, (P.T.A.B. 2016); *LG Elecs. Inc. v. Core Wireless Licensing S.A.R.L.*, IPR2016-00986, Paper 12 at 6-7 (P.T.A.B. 2016); *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 the 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).

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. *See* Ex-1545 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 petitions. BGI appears to have spent years studying the previous proceedings to

develop strategies attempting to address deficiencies it perceived in the Board and Federal Circuit decisions.

The Board has denied several other follow-on petitions filed by different petitioners. *See, e.g., NetApp Inc. v. Realtime Data LLC*, IPR2017-01354, Paper 16 at 10 (P.T.A.B. 2017); *NetApp Inc. v. Realtime Data LLC*, IPR2017-01196, Paper 10 at 10 (P.T.A.B. 2017); *Samsung Electronics Co., Ltd. v. ELM 3DS Innovations, LLC*, IPR2017-01305, Paper 11 at 19 (P.T.A.B. 2017); *Unified Patents, Inc. v. Personal Web Technologies, LLC*, IPR2014-00702, Paper 13 at 7-8 (P.T.A.B. 2014) (Informative). 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 another 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 Dower, Zavgorodny, Church, and Prober. Petition at 8-9. BGI knew or should have known of each of these references. Dower, Zavgorodny, and Church are cited on the face of the '537 patent, which issued on July 28, 2009. Ex-1501 at 1-3. Prober is cited by the '537 patent. Ex-1501 at 5:30-31. Any

reasonably diligent search by BGI would have uncovered the asserted references at least by the issue date of the '537 patent, and certainly by the time the first petition against the '537 patent 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 convince the Board to reach the opposite outcome as the previous IPR trial and appeal. *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 claims from the same patent.

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 was essentially filed as a 14,000 word rebuttal to the analysis and reasoning applied by the Board and Federal Circuit in the previous proceedings. 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 this 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 Owners' 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 I 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 failure to even attempt to justify its delay underscores the fact that this belated

third petition against the same claims from the same patent 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 from the same patent for a third time. 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 from the same patent 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.

V. THE PERSON OF ORDINARY SKILL

Illumina submits that the POSITA at the time of the invention would have been a member of a team of scientists addressing SBS product development. Such a person would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience. Thus, a person of ordinary skill includes a person having a doctoral degree in a field related to chemistry, and at least five years of laboratory experience directed toward the research and development of DNA sequencing technologies.

This is the same definition submitted by Illumina in the prior IPR2013-00517. Ex-1592 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.1. Thus, there is no reason to deviate from Illumina’s definition.

VI. NEW CLAIM CONSTRUCTION IS UNNECESSARY

The Board previously construed Claim 1. Ex-1594 at 6-7. No additional claim construction is required at this stage.

VII. 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 teaching 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.

VIII. THERE WAS NO MOTIVATION TO COMBINE DOWER WITH ZAVGORODNY AND CHURCH

BGI’s second follow-on petition argues that Claims 1-6 and 8 would have been obvious over the SBS method disclosed by Dower in combination with the azidomethyl disclosure of Zavgorodny and the disulfide linker disclosure of Church. Petition at 32-34.

A. Introduction to Dower, Zavgorodny, and Church

Dower discloses SBS methods that use nucleotides having a 3'-OH protecting group. Dower does not disclose a removable 3'-OH azido protecting group.

Zavgorodny is a synthetic organic chemistry paper. Zavgorodny discloses over 180 compounds that are described as “useful specifically blocked synthons.” Ex-1508 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 Dower's sequencing method. Zavgorodny does not disclose DNA sequencing methods.

Church discloses a variety of different sequencing methods, one of which uses a nucleotide having a label linked to the base via a disulfide linker. None of Church's sequencing methods use nucleotides having a 3'-OH protecting group.

In this case, BGI admits there were three primary issues a POSITA would have focused on when selecting a 3'-OH protecting group from the literature for use in SBS methods:

A POSITA would have focused on three primary issues when selecting a reversible 3'-OH protecting group to use with his SBS methods: (1) the ability of a polymerase to incorporate the modified

nucleotide with the protecting group, (2) the selection of deblocking conditions that do not harm the DNA, and (3) the incorporation and deblocking steps that result in a yield that is reasonable for the desired application.

Petition at 20. In the first IPR, Illumina submitted extensive arguments and evidence demonstrating that a POSITA would not have been motivated to use an azidomethyl group in SBS methods because an azidomethyl group would not have been expected to meet the SBS requirements for a reversible 3'-OH nucleotide blocking group. Ex-1592 at 12-32. The Board and Federal Circuit agreed there was no such motivation. *Supra* Section III. In the next sections, Illumina explains that a POSITA would not have been motivated to select an azidomethyl group for use in Dower's SBS methods because an azidomethyl group would not have been expected to satisfy the three primary issues identified by BGI.

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

In Dower's SBS method, "a polymerase is used to extend a primer complementary to a target template." Ex-1504 at 14:48-50; *id.* at 15:3-5, 17:46-67, 18:28-30 ("there is a functional constraint that the polymerase be compatible with the monomer analogues selected"); 23:18-22; 26:6-9 ("The structures of the fluorescently labeled and reversible terminator base analogs are selected to be

compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension.”); Petition at 30, 38-39.

BGI argues a POSITA would have been “motivated to use an azidomethyl group with Dower’s SBS method and nucleotides due to the high likelihood that they would be incorporated by a DNA polymerase.” Petition at 47; *id.* at 39.

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-1592 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. Ex-1594 at 9. BGI has not demonstrated that a POSITA would have been motivated to use an azidomethyl group in Dower’s SBS method, nor that a POSITA would have had a reasonable expectation of success of incorporation.

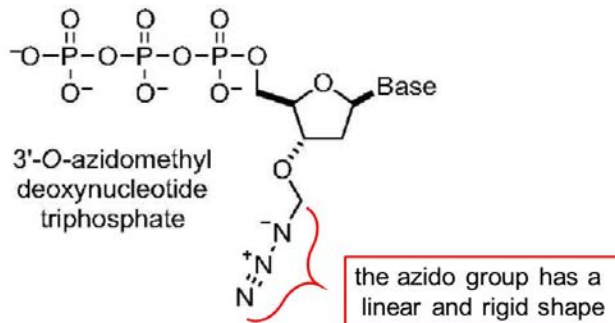
1. **There was no motivation to use an azidomethyl group in Dower’s sequencing methods because there was no expectation of efficient and accurate polymerase incorporation**

BGI argues that nucleotides bearing a 3’-O-azidomethyl group would have been expected to be incorporated because this group “is relatively small” compared to some groups that had been successfully incorporated and “would have expected

it to exhibit minimal steric interference.” Petition at 47 (citing Ex-1601 ¶¶104, 143-144).

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-1601 ¶143 (“DNA polymerase discriminates against nucleotide analogues based on size and shape”). An azidomethyl group has a linear shape. Petition at 42. The linear shape of an azidomethyl group is rigid along the three nitrogen atoms:



Ex-1601 ¶143 (page 99) (annotated); Ex-2024 ¶25. All three nitrogen atoms lie in essentially the same plane, as shown below:

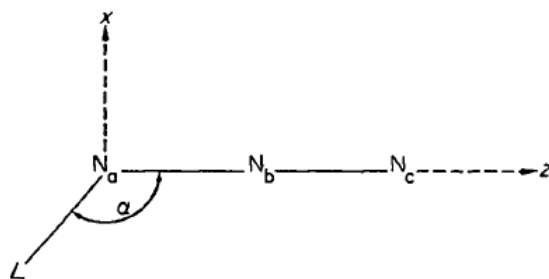


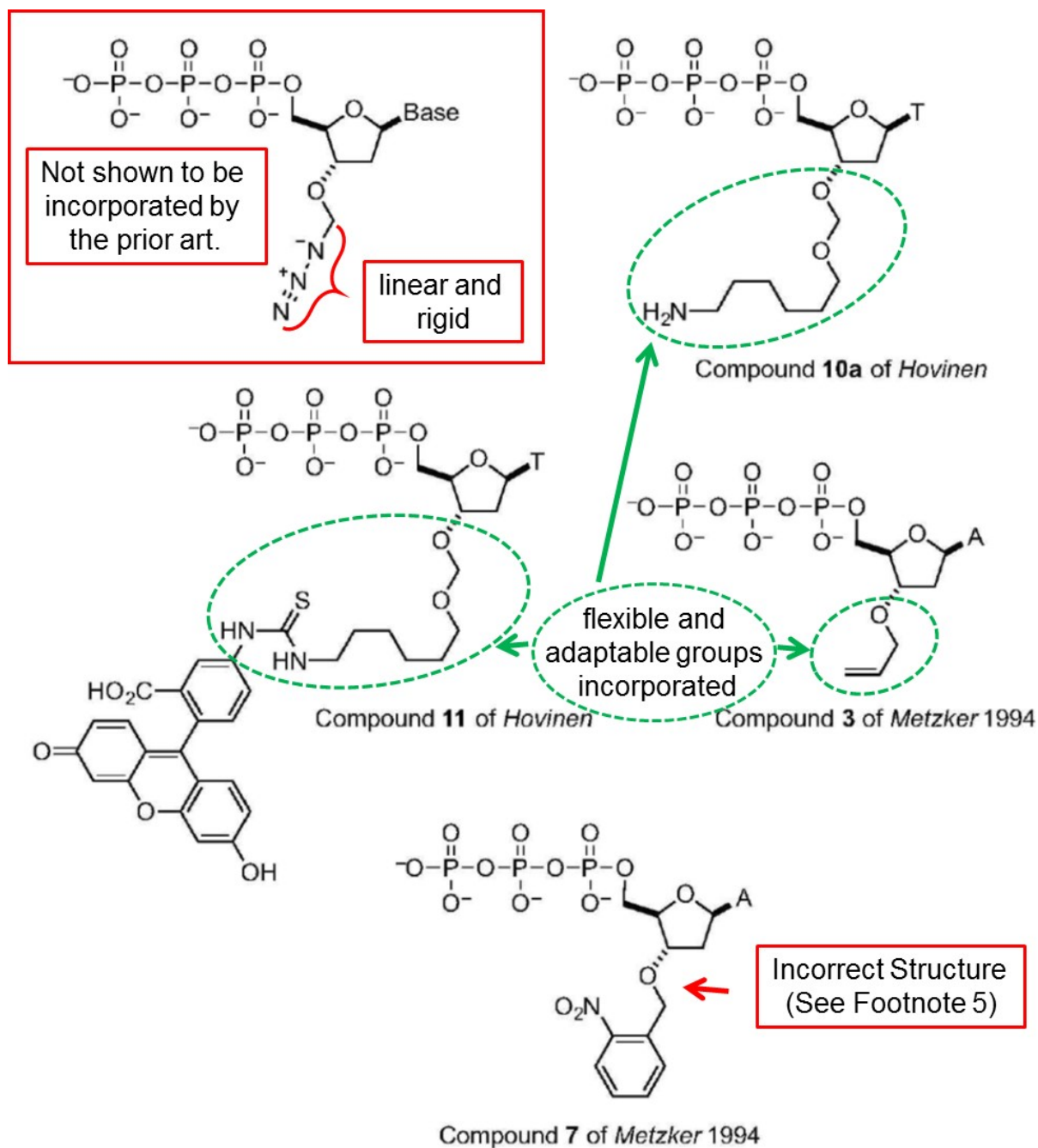
FIGURE 1. The geometry of covalent azides (L is the atom to which N_a is bound; all the nuclei lie in the xz plane).

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 can reduce its steric profile.” Petition at 47. 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.'').

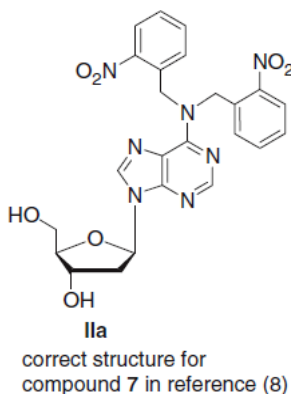
BGI relies on 3'-moieties that Hovinen and Metzker demonstrated were incorporable to assert that the allegedly "relatively small" azidomethyl group would also be expected to be incorporated. Petition at 47 (citing Ex-1601 ¶143). The linear and rigid shape of an azido group is very different from the 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-1601 ¶143⁵ (page 99) (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-1527 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.

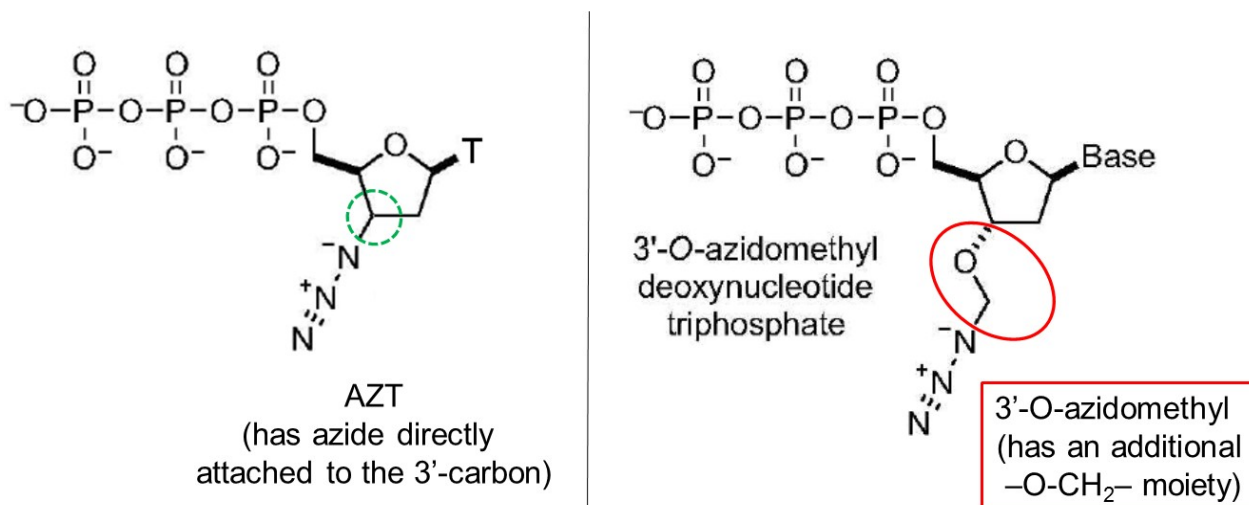
⁵ Ex-1601 ¶143 on page 99 shows an incorrect structure for Compound 7.

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 Dower’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 48 (citing Ex-1515 & Ex-1576); *id.* at 39; Ex-1515 at 21462 (discussing AZT incorporation); Ex-1576 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.

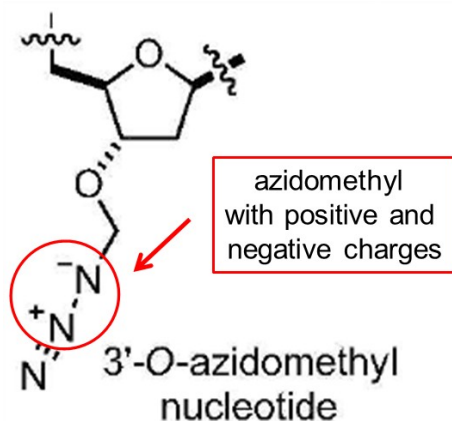
In 2001, Boyer studied the incorporation and positioning of AZT within the polymerase active site. Ex-2030 at 4832; Ex-2024 ¶29. Boyer determined that when the 3'-azido group of AZT is incorporated, it occupies the entire available space within the polymerase active site. Boyer reported, “when AZT is

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-1601 ¶104 (page 68); 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-1601 ¶104 (citing Ex-1526). 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 “relatively small” size. Petition at 47; *id.* at 39, 42. 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-1541 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 94 of Dr. Sutherland's declaration (the relevant portion of his declaration is reproduced below):



Ex-1601 ¶136 (page 94) (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 (Claim 1 "requires a single step of 'incorporating'"); Ex-1501 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’s petition fails to account for the negative influence on incorporability provided by the shape, steric bulk, and polarity of the azidomethyl group. BGI’s petition thus fails to establish an expectation of success for the claimed “incorporation.”

C. BGI Primary Issue 2: A POSITA would not have expected azidomethyl removal conditions to be “mild” for Dower’s SBS method

Dower discusses that the 3’-OH protecting group “should be removable under mild conditions.” Ex-1504 at 18:3-8; Petition at 20 (quoting Ex-1504 at 18:3-8).

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-1594 at 14; *see also 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.

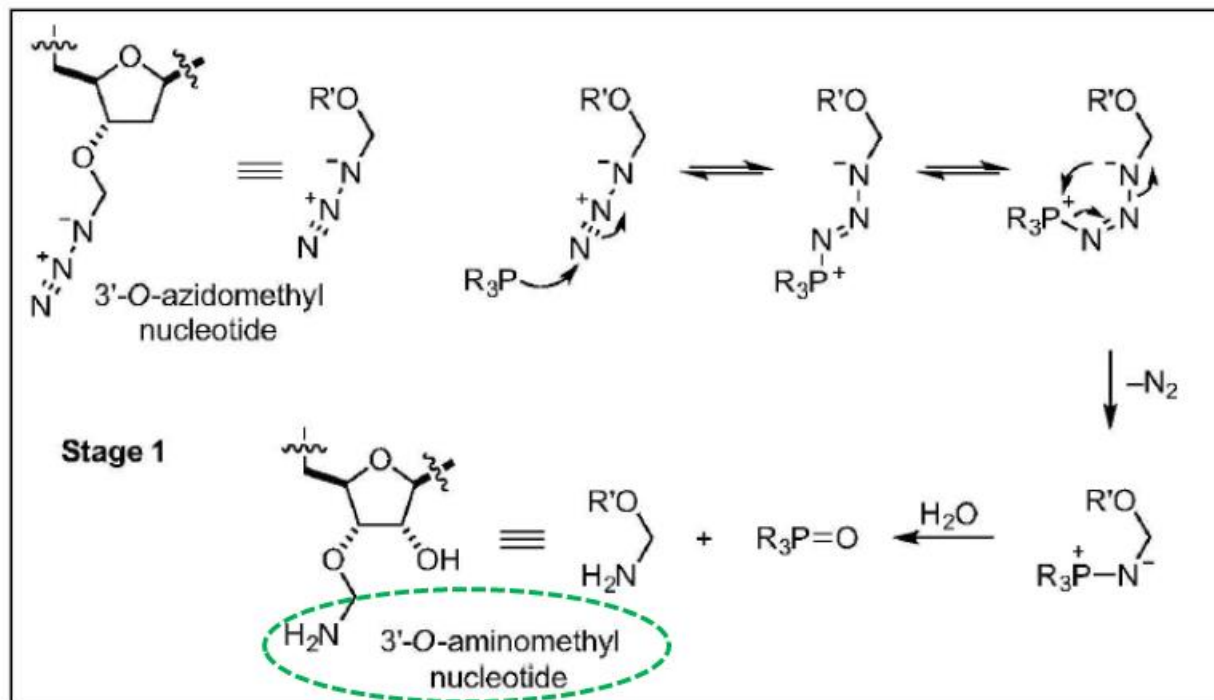
BGI argues that a POSITA would have expected azidomethyl cleavage conditions to be mild. *Id.* at 43-45. BGI admits that “mild conditions are those that would not degrade the DNA template moiety.” Petition at 20-21. But BGI fails to carry its burden of showing a POSITA would have been motivated to use 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 Dower’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 Dower’s method. Petition at 43-44. BGI further expands the allegedly “mild” conditions to “other phosphines” and “water-soluble phosphines.” *Id.* at 44. Dr. Sutherland, however, admits that the reaction of a phosphine with an azidomethyl group produces an amine. Ex-1601 ¶171 (“reduction of the azide to the amine is the rate-

determining step in the overall removal of an azidomethyl ether from an alcohol”).

Dr. Sutherland shows the amine formed by the phosphine reaction with an azidomethyl group on page 94 of his declaration, which is reproduced below with annotation:



Id. at page 94. Dr. Sutherland’s figure shows that the reaction of phosphine with a 3’-O-azidomethyl nucleotide produces a 3-O-aminomethyl nucleotide.

Evidence available at the time of Illumina’s invention indicated that this amine formation would not have been expected to be mild for Dower’s SBS method because nucleotides having amino groups were taught as undergoing an intramolecular reaction that spontaneously attacks and 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, which would 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-1546 at 85:10-13. BGI admits that degradation of DNA would not be mild. Petition at 20-21 (“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 Dower’s SBS method.

In the previous IPR, Illumina raised Stanton’s disclosures regarding the DNA degradation from phosphine deblocking conditions. Ex-2031 ¶5. BGI, however, failed to address this evidence of DNA degradation in its petition. *It therefore stands un rebutted that phosphine deblocking of an azidomethyl group was expected to cleave the backbone phosphate ester linkages in DNA, which would not have motivated a POSITA to use an azidomethyl group because it would not have been expected to meet Dower’s “mild” deblocking criteria.* A POSITA would have been discouraged from using an azidomethyl group due to this evidence of cleavage of the DNA backbone.

2. Pyridine was a known DNA denaturant

In the previous IPR, Illumina raised evidence and arguments that Zavgorodny's pyridine-based reaction conditions would denature DNA and would therefore not be mild for SBS. Ex-1592 at 19-23, 32-33; Ex-1598 ¶¶54-55; Ex-1533 at 57-58 (stating pyridine is an "especially effective" DNA denaturant). BGI acknowledges that Illumina raised evidence and arguments about Zavgorodny's pyridine-based reaction conditions denaturing DNA. Petition at 6. BGI, however, failed to address this evidence of DNA denaturation in its petition. It therefore stands un rebutted that Zavgorodny's deblocking conditions were expected to denature DNA, which would not have motivated a POSITA to use an azidomethyl group because it would not have been expected to meet Dower's "mild" deblocking criteria. 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 mild azidomethyl cleavage. Petition at 43. Young discloses two methods for removing an azidomethyl group: (1) $\text{SnCl}_2/\text{PhSH}/\text{Et}_3\text{N}$ (Ex-1551 at 67-68), and (2) concentrated trifluoroacetic acid ("TFA"). *Id.* at 65. Young's cleavage conditions would not have been expected to be mild in Dower's SBS

methods because Young's cleavage conditions were expected to degrade DNA. Ex-1598 ¶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 Dower's methods because no evidence establishes that azidomethyl deblocking conditions would have met Dower's "mild" criteria.

D. BGI Primary Issue 3: A POSITA would not have expected azidomethyl to be cleaved with appropriate efficiency for SBS

BGI's primary issue 3 for selecting a 3'-OH protecting group for SBS includes "deblocking steps that result in a yield that is reasonable for the desired application." Petition at 20. BGI relies on Young and Loubinoux to assert that a 3'-O-azidomethyl would have been expected to satisfy this requirement. *Id.* at 48-52.

BGI asserts that Young reported quantitative azidomethyl cleavage. Petition at 49-50. Young discloses two methods for reducing an azidomethyl group: (1) $\text{SnCl}_2/\text{PhSH}/\text{Et}_3\text{N}$ (Ex-1551 at 67-68), and (2) concentrated trifluoroacetic acid ("TFA"). Ex-1551 at 65. These methods would not have motivated a POSITA to use an azidomethyl protecting group in Dower's SBS methods because Young's cleavage methods would have been expected to degrade DNA. *Supra* Section VIII.C.3; Ex-1598 ¶47; Ex-2024 ¶34.

BGI argues that Loubinoux's reported pure product yields "would have suggested to a POSITA that the azidomethyl group could be deblocked in extremely high efficiency" when used in Dower's SBS method. Petition at 50. Loubinoux discloses several methods for reducing an azidomethyl group: (1) $\text{SnCl}_2/\text{MeOH}$ (Ex-1006 at 7), (2) LiAlH_4 (*id.* at 2), (3) H_2 with Pd/C (*id.* at 4), and (4) triphenylphosphine (*id.* at 3). None of these methods would have motivated a POSITA to use an azidomethyl protecting group in Dower's SBS methods because all of Loubinoux's cleavage methods would have been expected to degrade DNA. *Supra* Section VIII.C.3; Ex-1598 ¶¶44-47. BGI focuses on using a phosphine to cleave the azidomethyl group via the Staudinger reaction. However, Loubinoux found that triphenylphosphine gave worse results than other methods. Ex-1006 at 3 ("Generally, the method using hydrogen gives better results than that using triphenylphosphine."). This disclosure would have discouraged a POSITA from pursuing cleavage of an azidomethyl group in Dower's SBS methods because none of these methods would have been sufficiently mild to leave the DNA intact. Further, Loubinoux would have led the ordinary artisan to believe that phosphine-based cleavage was the least desirable of the disclosed cleavage methods.

BGI has not demonstrated that azidomethyl deblocking conditions would have been expected to be compatible with Dower's SBS methods. Therefore, BGI

has not demonstrated that a POSITA would have been motivated to use an azidomethyl group in Dower's SBS methods.

E. BGI fails to address Illumina's evidence that the electrophilic 3'-O-azidomethyl group would not be compatible with nucleophiles within the polymerase active site

Illumina previously explained and presented evidence that a POSITA would not have been motivated to use a 3'-O-azidomethyl group in SBS methods because the electrophilic azidomethyl group was expected to react with nucleophiles within the polymerase active site. Ex-1592 at 15-16, 31-33.

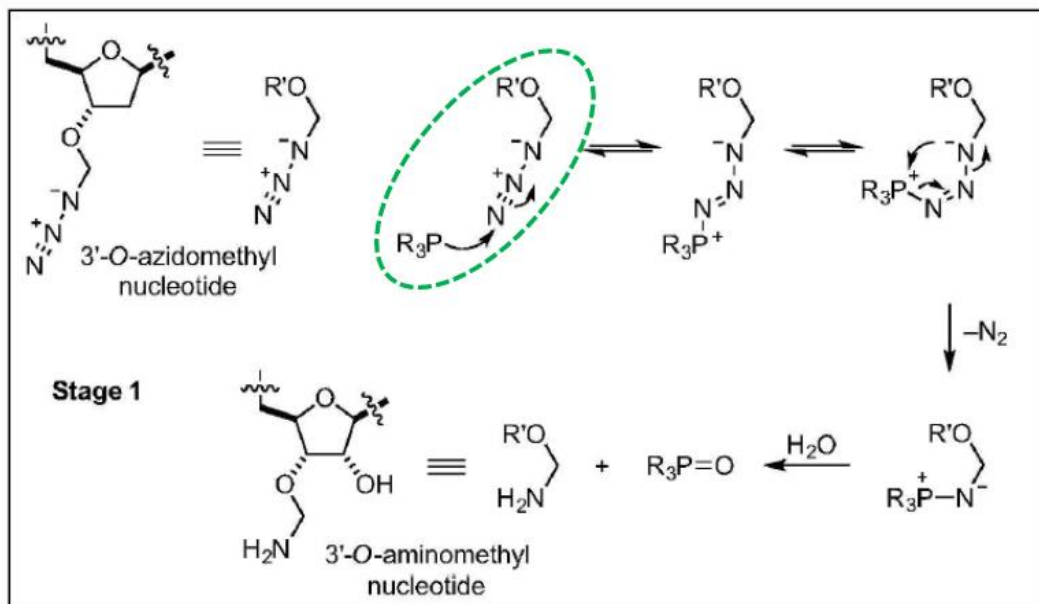
BGI does not directly respond to this evidence. Instead, BGI generally asserts that azides were expected to be compatible with polymerases because azides were considered to be "unreactive towards biological systems, such as polymerases." Petition at 42. BGI's high-level assertion fails to address the specific evidence from the scientific literature that azides were expected to react with nucleophiles within the localized environment of the polymerase active site. In the previous IPR, Illumina presented evidence from the literature that "electrophilic characteristics of Zavgorodny's azidomethyl group would likely react with strong nucleophiles within the polymerase active site." Ex-1592 at 15. For example, Canard 1995 was published in the highly respected and prestigious Proceedings of the National Academy of Sciences of the United States of America. 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-1542 at 10863. 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'-aminno group in vivo.

Id. This warning was acknowledged and implemented by other researchers. Ex-1538 at 3:12-20 (noting the “existence of strong nucleophiles in the polymerase”). BGI never addresses Illumina’s significant evidence of polymerase incompatibility with 3'-azido groups.

BGI’s witness (Dr. Sutherland) concedes that the azidomethyl group is susceptible to nucleophilic attack. Dr. Sutherland shows the mechanism for azidomethyl reduction begins with a nucleophilic attack on the azide as follows:



Ex-1601 at page 94 (annotated). Dr. Sutherland's mechanism shows nucleophile " R_3P " attacking the azide moiety on a 3'-O-azidomethyl nucleotide.

Dr. Sutherland admits "the protecting group must be stable enough to avoid premature deblocking." Ex-1601 ¶113. Dower discloses that the polymerase should be compatible with the nucleotide protecting group. Ex-1004 at 18:28-30 ("[T]here is a functional constraint that the polymerase be compatible with the monomer analogues selected"). 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, which would cause inadvertent additions of other dNTPs by the polymerase. Dower's method relies on controlled deblocking of the 3'-OH protecting group to bring about addition of the one, and only the one, labeled

dNTP at a time. *Id.* at 14:50-53 (“The primer is elongated one nucleotide at a time by use of a particular modified nucleotide analog to which a blocking agent is added and which prevents further elongation.”); *id.* at 7:23-30. Thus, the susceptibility of the 3'-O-azidomethyl group to premature deblocking via 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 be compatible with Dower's polymerase-based SBS methods.

Based on the foregoing, a POSITA would not have been motivated to use a 3'-O-azidomethyl group in Dower's SBS methods because Dower 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 the primary issues identified by BGI for selecting a 3'-protecting group for use in Dower's SBS method. Therefore, a POSITA would not have been motivated to use a 3'-O-azidoemthyl protecting group in Dower's SBS methods. The Board should thus deny BGI's follow-on petition for failing to establish a prima facie case of obviousness.

IX. AZIDOMETHYL WAS NOT A SIMPLE SUBSTITUTION INTO DOWER'S SBS METHOD

BGI argues that the azidomethyl group would have been a “simple substitution” into Dower's SBS method. Petition at 34. BGI's “simple substitution” theory ignores that at least 11 separate research teams tried to identify

appropriate 3'-protecting groups for SBS from the scientific literature. *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 for use in SBS. In addition, a POSITA would not have been motivated to substitute an azidomethyl group into Dower's SBS methods because there was no basis to believe that an azidomethyl group would have met the primary issues identified by BGI for selecting a 3'-protecting group from the literature. *Supra* Section VIII.

Furthermore, BGI's position that azidomethyl is a simple substitution into Dower's methods 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 Dower'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-1601 ¶81. 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. Ex-1601 ¶81 (“The optimization of each of these steps would have required

decisions to be made concerning reaction conditions, such as reagent selection, temperature, pH, concentration and time.”). Dr. Sutherland opines that Dower’s sequencing methods have many variables, and a POSITA would not expect that all of the SBS 3’-blocking group criteria could be met. Ex-2037 ¶79 (“While it would be best to meet all of these [3’-blocking group] 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 Dower’s method if any of the primary issues for selecting a 3’-protecting group were not 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-1601 ¶112. Thus, BGI’s own witness undermines and contradicts BGI’s assertion that an azidomethyl group could be simply substituted into Dower’s methods.

X. 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 The Trustees of Columbia

University (“Columbia”) in IPR2018-00291, IPR2018-00318, IPR2018-00322, and IPR2018-00385. BGI and Illumina’s petitions both rely on Dower as a primary obviousness reference. There are important distinctions between Illumina’s petitions and BGI’s petition.

One 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 VIII.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-1541 at 4263; *see also* Ex-1538 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).”); *see also id.* at 3:20-23 (discussing the known benefits of the 3’-O-allyl group); *id.* at 26:19-27.

Another distinction relates to mild deprotection conditions. A POSITA would not have been motivated to use a 3’-O-azidomethyl protecting group in Dower’s SBS methods because it was not expected to cleave under mild conditions compatible with DNA sequencing. *Supra* Section VIII.C. In contrast, the 3’-O-allyl protecting group cited in Illumina’s petition was known to cleave under mild

conditions compatible with DNA sequencing. Ex-1538 at 26:19-27 (“The chemical cleavage of the MOM and allyl groups is fairly mild and specific, so as not to degrade the DNA template moiety.”). Thus, a POSITA would have been motivated to use the 3'-O-allyl protecting group in Dower's methods, but would not have been motivated to use the 3'-O-azidomethyl group.

XI. THE DEPENDENT CLAIMS ARE NONOBVIOUS

Independent Claim 1 is directed to a method of labeling a nucleic acid molecule by incorporating a nucleotide or nucleoside molecule having a detectable label linked to the base via a cleavable linker and a protecting group comprising an azido group that can be modified or removed to expose a 3'-OH group. Ex-1501 at 19:49-60. Claim 1 would not have been obvious for at least the reasons discussed herein.

Claims 2-6 and 8 depend from Claim 1. A dependent claim is nonobvious if the independent claim from which it depends is 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”). Therefore, Claims 2-6 and 8 also are nonobvious over the asserted references.

**XII. THE CLAIMS ARE NOT OBVIOUS IN LIGHT OF SECONDARY
CONSIDERATIONS OF NONOBVIOUSNESS**

**A. BGI was aware of Illumina’s evidence of non-obviousness, but failed to
address the evidence**

In the previous IPR involving the ’537 patent, Illumina raised a number of objective indicia in support of the non-obviousness of its patent claims, including long-felt but unmet need, unexpected results, and evidence of copying. Ex-1594 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 raised by Illumina, 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 in its petition 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); *Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13 at 26-27 (P.T.A.B. 2015). It failed to do so, and thus the petition is facially deficient.

B. BGI avoids addressing Illumina’s previously-presented unexpected results by using an unsupported and incorrect legal theory

In the previous IPR, Illumina provided evidence that the claimed method performs unexpectedly better than what a POSITA might have gleaned from the prior art. In particular, 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 nevertheless surprisingly found that azidomethyl was not only suitable but superior to the existing protecting-group technologies. Ex-1592 at 54. Indeed, the Federal Circuit agreed that there was no reason in the prior art that suggested 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 evidence of unexpectedly good results in the prior review is “based on hindsight bias” because such results are not recited in the claims or the specification. Petition at 61. 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. As 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); *see also Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) (“[P]atentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest.”); *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 addressing the merits of the secondary considerations evidence. Thus, 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 a reasonable likelihood of demonstrating obviousness. *Omron*, IPR2013-00265, Paper 11 at 12-16.

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

In the previous IPR, Illumina also 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-1592 at 44-49. Illumina established a clear relationship between the claimed invention and advances in SBS technology, including evidence that the claimed azidomethyl protected nucleic acid was used as a crucial and necessary component in the cited advanced sequencing methods.

Instead of addressing the evidence that the claimed azidomethyl protected nucleic acid allowed the development of advanced SBS techniques, BGI sidesteps the issue entirely. BGI argues 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 59-60.

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 nucleic acid was a limiting step and a major challenge in advancing sequencing technology. Ex-1592 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-1545 at 105.

Illumina's azidomethyl technology was a necessary component of a successful SBS methodology, and each of the SBS techniques cited in the previous IPR use the claimed azidomethyl protected nucleic acids. Ex-1592 at 45-46. BGI

never addressed Illumina's evidence, 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 62. 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-1592 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, and must be addressed as part of the obviousness analysis. *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.

XIII. CONCLUSION

For the foregoing reasons, the Board should deny BGI's second 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 12,199 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.