

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK
Patent Owner.

Case IPR2018-00322
Patent 9,708,358

PATENT OWNER'S PRELIMINARY RESPONSE

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TABLE OF EXHIBITS

Exhibit No.	Description
2001	Declaration of Robert S. Schwartz in Support of Patent Owner's Motion for Admission Pro Hac Vice Under 37 C.F.R. §42.10
2002	U.S. Patent No. 7,790,869
2003	U.S. Patent No. 7,713,698
2004	U.S. Patent No. 8,088,575
2005	Exhibit number not used.
2006	Excerpts from the Prosecution History of U.S. Patent No. 9,725,480 not included in Ex-1038
2007	IPR2013-00517, Ex. 2011, Declaration of Floyd Romesberg, Ph.D. (May 5, 2014)
2008	IPR2013-00517, Paper 32, Illumina's Patent Owner Response (May 5, 2014)
2009	Excerpts from the <i>Ex Parte</i> Reexamination History of U.S. Patent No. 5,808,045
2010	Assignment data in connection with U.S. Patent No. 5,808,045
2011	PCT Publication WO 98/33939 ("Anazawa") (English translation)
2012	Metzker, et al., "Elimination of Residual Natural Nucleotides from 3'-O-Modified-dNTP Syntheses by Enzymatic Mop-Up," <i>BioTechniques</i> , 25:814-817 (1998)
2013	PCT Publication WO 00/53805 ("Stemple")
2014	Metzker, et al., "Stop-Start DNA Synthesis in the Base Addition Sequencing Scheme (BASS)," <i>Genome Mapping & Sequencing</i> (1994)

2015	U.S. Patent No. 7,541,444
2016	U.S. Patent No. 7,771,973
2017	U.S. Patent Application Publication No. 2007/0166705
2018	Boons, et al., “A New Procedure for the Isomerisation of Substituted and Unsubstituted Allyl Ethers of Carbohydrates,” Chemical Communications, 141-142 (1996)
2019	Ochiai, et al., “Hypervalent (<i>tert</i> -Butylperoxy)iodanes Generate Iodine-Centered Radicals at Room Temperature in Solution: Oxidation and Deprotection of Benzyl and Allyl Ethers, and Evidence for Generation of α -Oxy Carbon Radicals,” J. Am. Chem. Soc., 118:7716-7730 (1996)
2020	Olivero & Dunach, “Nickel-catalysed Electrochemical Reductive Deprotection of Allyl Ethers,” J. Chem. Soc., Chem. Commun., 2497-2498 (1995)
2021	U.S. Patent No. 6,232,465
2022	Excerpts from the <i>Ex Parte</i> Reexamination History of U.S. Patent No. 6,232,465
2023	Solexa, Inc.’s Fed. R. Civ. P. 7.1 Statement (Feb. 19, 2010)
2024	Solexa, Inc.’s Schedule 13D-A Submission to the United States Securities and Exchange Commission (Feb. 2, 2007)
2025	Litosh, et al., “Improved Nucleotide Selectivity and Termination of 3’-OH Unblocked Reversible Terminators by Molecular Tuning of 2-Nitrobenzyl Alkylated HOMedU Triphosphates,” Nucleic Acids Research, 39:1-13 (2011)
2026	IPR2017-02172, Paper 6, Preliminary Response of Patent Owner Illumina Cambridge Ltd. (January 23, 2018)
2027	IPR2017-02174, Paper 6, Preliminary Response of Patent Owner Illumina Cambridge Ltd. (January 23, 2018)
2028	U.S. Patent No. 7,566,537

2029	No. 2015-1123 (CAFC), Brief of Patent Owner-Appellant Illumina Cambridge Ltd., D.I. 27 (March 10, 2015)
2030	IPR2013-00266, Paper 39, Patent Owner Illumina's Reply to Petitioner's Opposition to Illumina's Motion to Amend (March 21, 2014)
2031	Canard & Sarfati, "DNA Polymerase Fluorescent Substrates with Reversible 3'-Tags," <i>Gene</i> , 148:1-6 (1994)
2032	IPR2013-00517, Paper 84, Oral Hearing Transcript (February 2, 2015)
2033	IPR2013-00517, Paper 64, Illumina's Motion for Observations on the Cross-Examination Testimony of Bruce Branchaud, Ph.D. and Michael Metzker, Ph.D. (September 2, 2014)
2034	IPR2012-00007, Paper 5, Petition for <i>Inter Partes</i> Review of U.S. Pat. No. 7,790,869 (September 16, 2012)
2035	IPR2013-00517, Exhibit 1025, Deposition of Floyd Romesberg, Ph.D. (July 28, 2014)
2036	IPR2012-00007, Paper 38, Decision on Petition for <i>Inter Partes</i> Review (March 12, 2013)
2037	Assignment data in connection with U.S. Patent Application Publication No. 2007/0166705 and U.S. Patent No. 7,541,444
2038	Assignment data in connection with U.S. Patent No. 6,232,465
2039	PCT Publication WO 98/33939 (Japanese language version of Anazawa)
2040	Translation Affidavit for Anazawa
2041	Welch & Burgess, "Synthesis of Fluorescent, Photolabile 3'-O-Protected Nucleoside Triphosphates for the Base Addition Sequencing Scheme," <i>Nucleosides & Nucleotides</i> , 18:197-201 (1999)
2042	IPR2013-00517, Paper 68, Illumina's Opposition to IBS Motion To Exclude Evidence
2043	Excerpts from the Prosecution History of U.S. Patent No. 7,771,973

2044	Exhibit number not used.
2045	Excerpts from the Prosecution History of U.S. Patent No. 9,708,358 not included in Ex-1065
2046	Froehler, et al. "Oligodeoxynucleotides Containing C-5 Propyne Analogs of 2'-Deoxyuridine and 2'-Deoxycytidine," Tetrahedron Letters, 33:5307-5310 (1992)

A. Introduction

In 2000, Columbia Professor Dr. Jingyue Ju and Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki (“the Columbia inventors”) solved a decade-old problem that Petitioner, Illumina, and its expert admitted was a “major challenge” and a “formidable obstacle.” Ex-2007 ¶¶60; Ex-2008 at 4-5; Ex-2042 at 6. They invented nucleotide analogues that permitted Sequencing by Synthesis (SBS) to become a practical reality. Others described a wide variety of features for a deoxyribonucleotide analogue for use in SBS, but no one defined the combination of features necessary for success. The Columbia inventors conceived nucleotide analogues comprising, *inter alia*, (i) on the deoxyribose 3’-oxygen, a chemically cleavable, chemical capping group having a “small” diameter (i.e., less than 3.7Å), which does not contain a ketone and does not form an ester or a methoxy group with the 3’-oxygen and (ii) on the 5-position of a cytosine base, a chemically cleavable, chemical linker attached to a detectable fluorescent moiety.

Contrary to Illumina’s arguments, the ’358 patent claim (“the challenged claim”) differs from the claims found unpatentable in prior IPR proceedings. Specifically, the challenged claim is substantially narrower than, and patentably distinct from, those earlier claims. Before allowing the challenged claim, the Examiner considered the prior art and the Board’s earlier rulings and correctly

determined the challenged claim recites novel and non-obvious nucleotide analogues.

Illumina's Ground 1 challenge relies solely on Tsien. Tsien discusses, without differentiation, a vast number of capping groups that include groups that contradict key limitations of the challenged claim. For example, Tsien teaches the use of capping groups that were *not* small, and/or that *were esters*, both of which are structural features excluded from the challenged claim. Illumina argues that one embodiment of the challenged claim would have been obvious to a person of ordinary skill in the art ("POSA"), i.e., a nucleotide analogue with the 3-carbon allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$) group capping the 3'-oxygen of the sugar, because a POSA reading Tsien's disclosure of capping groups would have selected the 3-carbon allyl capping group. This challenge fails because Tsien does not disclose the 3-carbon allyl capping group and, even if Tsien did disclose this group, Illumina has not established that a POSA would have been motivated to select this group from Tsien's disclosure, which Illumina in 2011 admitted "encompasses broad classes of compounds, perhaps hundreds or more potential blocking groups." Ex-2009 at 15. Illumina also ignores publications in the field subsequent to Tsien, which demonstrate there was no reason to select the 3-carbon allyl capping group. Indeed, in 2000 the *only* experimental results concerning a nucleotide analogue with this allyl capping group taught it was a poor choice for DNA sequencing and

pointed to other 3'-OH capping groups. Illumina offers no reason why a POSA would have diverged so drastically from the conventional understanding in 2000.

Importantly, Illumina previously argued the *opposite* position to the Patent Office. During a reexamination of its own U.S. Patent No. 6,232,465 claiming a nucleotide analogue with an allyl capping group, Illumina in 2007 admitted that “Tsien does not teach or suggest” a nucleotide analogue with the 3-carbon allyl group, and a POSA in 2000 “would not have been motivated to prepare” that nucleotide analogue “with a reasonable expectation that [it] could be used for DNA synthesis.” Ex-2022 at 14, 16. These admissions further demonstrate that Illumina cannot meet its burden of establishing that a POSA reading Tsien would have selected a 3-carbon allyl capping group for use in Tsien’s methods. Furthermore, Illumina’s failure to disclose its inconsistent positions in its Petition is a violation of its duty of candor to the Board.

Illumina’s Ground 2 challenge fails because none of Illumina’s references disclose or suggest a “chemically cleavable, chemical linker” on the nucleotide analogue’s base for attaching a fluorescent label. Illumina asserts Dower discloses this feature, but the Board previously rejected that argument, unambiguously finding Dower *does not* disclose such a linker. It is axiomatic that a claim cannot be rendered obvious by a combination of references none of which discloses or suggests a feature of the claim.

Finally, Illumina's Petition is long on allegations that the Federal Circuit and Board made determinations in prior IPRs that should be adopted here, but short on evidence establishing the prior art teaches what Columbia claims in the '358 patent. Illumina's reliance on alleged findings in prior IPRs concerning different claims is a smokescreen seeking to hide the lack of support for its challenges. For the reasons discussed herein, Illumina has not met its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 1 or Ground 2.

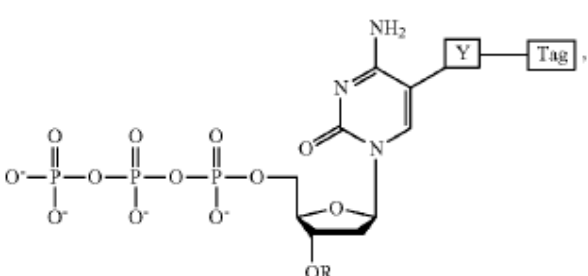
B. The Challenged Claim Is Patentably Distinct From Claims The Board Previously Considered

Prior to 2012, Columbia obtained several patents for what it believed to be the broad scope of its invention, including U.S. Patent Nos. 7,790,869; 7,713,698; and 8,088,575. Exs-2002, 2003, 2004. In September and October 2012, in the infancy of AIA trials, Illumina filed Petitions for *Inter Partes* Review challenging certain claims of these patents ("the Columbia Patent IPRs"). During those proceedings, in which the challenged claims were found unpatentable, the Board made findings regarding the prior art, including Tsien, Prober, and Dower. Exs-1005, 1006, 1007.

The challenged claim was prosecuted subsequent to those proceedings and is narrower and more precisely defines Columbia's invention. During prosecution,

Columbia made the Examiner fully aware of the Board’s earlier findings. Ex-2045 at 136, 144, 152. The Examiner reviewed those findings and prior art references submitted by Columbia, including those cited by Illumina in its Petition (Ex-2045 at 65 (Tsien (WO 1991/06678)), 99 (Metzker), 101 (Prober), 117 (Dower)), and allowed the challenged claim. At no time did Columbia “mislead the Examiner into issuing an unpatentable claim.” Petition at 52.

Asserting the challenged claim is the “same” as claims the Board previously considered, Illumina presents a comparison of *a portion* of the challenged claim and claim 21 of the ’869 patent. Petition at 18. A complete comparison reveals *numerous* features of the challenged claim not present in ’869 patent claim 21.

Claim 1 of ’358 patent	Claim 21 of ’869 patent
<p>1. A <u>cytosine</u>¹ deoxyribonucleotide analogue having the structure:</p>  <p>wherein R (a) represents a <u>small</u>,² <u>chemically cleavable</u>, chemical group</p>	<p>21. The nucleotide of claim 12 wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine.</p> <p>12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a</p>

¹ Features singly underlined are narrower than features in ’869 patent claim 21.

Claim 1 of '358 patent	Claim 21 of '869 patent
<p>capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue, (b) <u>does not interfere with recognition of the analogue as a substrate by a DNA polymerase</u>, (c) <u>is stable during a DNA polymerase reaction</u>, and (d) <u>does not contain a ketone group</u>;</p> <p><u>wherein OR is not a methoxy group or an ester group</u>;</p> <p><u>wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction</u>;</p> <p>wherein tag represents a detectable <u>fluorescent moiety</u>;</p> <p>wherein Y represents a <u>chemically cleavable, chemical linker</u> which (a) <u>does not interfere with recognition of the</u></p>	<p>deoxyribose comprising a cleavable chemical group capping the 3' OH group, wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.</p>

² Features doubly underlined are not present in '869 patent claim 21.

Claim 1 of '358 patent	Claim 21 of '869 patent
<p><u>analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction;</u></p> <p>and wherein the cytosine deoxyribonucleotide analogue:</p> <p>i) <u>is recognized as a substrate by a DNA polymerase,</u></p> <p>ii) <u>is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,</u></p> <p>iii) <u>produces a 3'-OH group on the deoxyribose upon cleavage of R,</u></p> <p>iv) <u>no longer includes a tag on the base upon cleavage of Y, and</u></p> <p>v) <u>is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue.</u></p>	

In addition, in the challenged claim, the cleavable linker is attached to the 5-position of the base, whereas the cleavable linker in claim 21 of the '869 patent can be attached to any position of the base. The complete comparison of these claims demonstrates the challenged claim is not the same as claim 21 of the '869 patent, nor is it the same as any of the other claims held unpatentable in the earlier Columbia Patent IPRs. Indeed, despite its assertions, Illumina failed to provide to the Board copies of the claims previously held unpatentable (Ex-2002 (claims 12, 13, 15-17, 20-26, 28, 29, 31, 33); Ex-2003 (claims 1-7, 11, 12, 14, 15, 17); Ex-2004 (claims 1-3, 6)) while conceding that the added claim features in the challenged claim are “carve-outs that Columbia added to avoid prior art.” Petition at 42. Illumina’s Petition also undermines its argument that there is nothing new about the challenged claim. Illumina’s Grounds are based solely on obviousness, while several of the Board’s previous findings were based on anticipation (*see* Ex-1005 at 7; Ex-1006 at 7-8; Ex-1007 at 7-8). Illumina thus implicitly acknowledges the challenged claim differs from Columbia’s earlier claims. Furthermore, the one claim embodiment that Illumina argues was obvious (the 3’-*O*-allyl nucleotide analogue) was not at issue in the earlier IPRs. As explained in Section H, the challenged claim is patentably distinct from those earlier claims.

C. Level Of Ordinary Skill In The Art

Columbia agrees with Illumina’s criteria for defining a POSA.

D. Claim Construction

Illumina asserts claim term construction is unnecessary. Columbia disagrees. To properly evaluate the differences between the challenged claim and the cited art, the following claim terms should be construed consistently with the Examiner's understanding of these terms:³

1. "Small"

In the context of the claimed feature R (the capping group on the 3'-oxygen of the sugar of the nucleotide analogue), "small" refers to the ability of the capping group to fit into the active site of the DNA polymerase whose three-dimensional structure is shown in Figure 1 of the '358 patent. More specifically, "small" means the group has a diameter less than 3.7Å. This construction is based on the '358 patent specification (Ex-1002 at 2:63-3:54, 5:52-59, Fig. 1, 7:51-8:28). As explained during prosecution of the patent, "[a]s of October 6, 2000, the POSA reading the specification would have understood that 'small' referred to the ability to fit into the active site of the polymerase defined by reference to the three-dimensional structure shown in FIG. 1" (Ex-1065 at 16), and capping group R must have "a diameter less than 3.7Å so that it would fit into the active site of the

³ A second Examiner concurred during prosecution of related U.S. Patent No. 9,725,480 (IPR2018-00385). Ex-2006 at 6.

polymerase” (*id.* at 17, 27-29). The Examiner adopted this meaning in the Notice of Allowability. Ex-1065 at 4, 11 (“The declaration of Jingyue Ju . . . is sufficient to explain what is meant by ‘small.’”).

2. “Chemical linker”

In the context of claimed feature Y, “chemical linker” means a chemical moiety attached by covalent bonds at one end to a specified position on the base of a nucleotide analogue and at the other end to a tag (detectable fluorescent moiety). It does not mean merely a covalent bond between the base and the label as disclosed in Dower. The specification supports this construction (Ex-1002 at 10:64-66, 14:8-10, the structures shown at columns 13-20, and Figs. 7, 8, 10, and 15A), which was expressly addressed during prosecution. Ex-1065 at 18-19, 30 (“Y is defined as a chemically cleavable, chemical linker and as shown in the structure shown in the pending claim, Y is attached by covalent bonds at one end to the base of a nucleotide analogue at a specific position and at the other end to a detectable fluorescent moiety.”).

Columbia also directed the Examiner to Tsien and Stemple for examples of chemical linkers. Ex-1065 at 19, 30. The linkers in those references are chemical moieties. *See* Ex-1013 at 28:26-29:2 (disclosing, e.g., silyl ethers, allyl ethers, and 2,4-dinitrophenylsulfenyls, and noting that “[t]ypical tethers are from about 2 to

about 20, and preferably from about 3 to about 10 atoms in length”). The Examiner found Columbia’s definitions “persuasive.” Ex-1065 at 4, 11.

E. State of the Art

Instead of proving its case, Illumina spends an inordinate amount of time alleging, incorrectly, admissions made by Columbia about the prior art. But there is no dispute that when Columbia filed its patent application in October 2000 there had been more than a decade of unsuccessful efforts to define a nucleotide analogue that could take SBS from a desired goal to a practical reality. Even Illumina and its expert acknowledge this was a “major challenge” and a “formidable obstacle.” Ex-2007 ¶60; Ex-2008 at 4-5; Ex-2042 at 6.⁴

The challenged claim defines nucleotide analogues having the features necessary for successfully performing SBS. These features include (i) a capping

⁴ Ex-2008 and Ex-2042 are Illumina Cambridge Ltd.’s documents from IPR2013-00517. In its Petition in IPR2018-00322, as well as in IPR2017-02172, Illumina refers to itself as both Illumina Inc. and Illumina Cambridge Ltd. *See* Petition at 78 (noting that Illumina is Patent Owner in IPR2017-02172), 40 (noting that IPR2013-00517 involved “Illumina’s nucleotide claims”); Ex-2026 at 58-61 (Illumina Cambridge Ltd. representing that it is the Petitioner in the present Petition (IPR2018-00322)).

group small enough (less than 3.7Å in diameter) to fit into the active site of a polymerase, but not containing a ketone and not forming a methoxy or an ester group with the 3'-oxygen of the sugar; and (ii) a chemically cleavable, chemical linker attached at one end to the 5-position of a cytosine base and at the other end to a detectable fluorescent moiety. As explained below, these insights were not obvious given the state of the art in October 2000.

By 1991, Tsien (Ex-1013) and Dower (Ex-1015) set forth prophetic methods for conducting SBS, both of which Illumina admits “encompass[] broad classes of compounds[.]” Ex-2009 at 15, 17.⁵ Tsien discloses a wide variety of preferred embodiments for the 3'-OH “blocking group,” including:

- i. “[E]ster blocking groups such as lower (1-4 carbon) alkanolic acid and substituted lower alkanolic acid esters, for example formyl, acetyl, isopropanoyl, alpha fluoro- and alpha chloroacetyl esters and the like;”

⁵ Ex-2009 contains submissions by Illumina to the Patent Office during reexamination of its U.S. Patent No. 5,808,045. *See* Ex-2009 at 3 (showing Illumina as patent assignee); *see also* Ex-2010 at 1. The Tsien reference discussed is the same Tsien at issue here. The Dower reference discussed is a PCT application substantially identical to the Dower at issue here.

- ii. “[E]ther blocking groups such as alkyl ethers;”
- iii. “[P]hosphate blocking groups;”
- iv. “[C]arbonate blocking groups such as 2-nitrobenzyl;” and
- v. “2,4-dinitrobenzene-sulfenyl and tetrahydrothiofuranyl ether blocking groups.”

Ex-1013 at 21. In Illumina’s words from 2011, when it was trying to overcome the references in a reexamination proceeding (*see supra* note 5), Tsien and Dower “constitute[] *speculation* about the existence of” useful nucleotide analogues. Ex-2009 at 15, 17 (emphasis added). In further characterizing Tsien as speculative, Illumina explained “[n]ot surprisingly, Tsien’s PCT publication never ultimately issued into a patent in apparent recognition of the general inoperability of the disclosure at that time.” Ex-2009 at 15.

In 1994, Metzker reported experimental results on 3’-OH capped nucleotide analogues in a DNA sequencing setting. As detailed in Section F(2)(b), Metzker examined the allyl capping group and abandoned it after reporting that it was a poor choice for DNA sequencing.⁶ Metzker instead concluded that one of the only

⁶ Throughout its Petition, Illumina refers to the “3’-O-allyl capping group.” This terminology is inaccurate and conflates a capping group and a capped sugar. The allyl group referred to in the ’358 patent is a specific 3-carbon allyl group

“interesting” capping groups for SBS was the 2-nitrobenzyl capping group (Ex-1016 at 4265), and a nucleotide analogue with this capping group was incorporated by several polymerases in his experiments (Ex-1016 at 4263, 4266), and was selected for further SBS experimentation because it was capable of a “complete cycle of termination, deprotection, and reinitiation of DNA synthesis.” Ex-1016 at 4259, 4265-67. This capping group is larger than 3.7Å. Ex-1065 at 23, 29. Metzker concluded the 2-nitrobenzyl capping group “*sets the stage in the development of [SBS]*,” and consistent with that conclusion, noted that his laboratory intended to continue developing nucleotide analogues with a 2-nitrobenzyl capping group. Ex-1016 at 4267 (emphasis added), *see also* 4259 (abstract).

Following Metzker’s teachings, other researchers sought to advance SBS technology using the 2-nitrobenzyl capping group. In 1997, Anazawa filed a PCT Application disclosing sequencing DNA using dNTPs with capping groups on the 3’-oxygen of the sugar that contain 2-nitrobenzyl groups. Ex-2011 at 5, Figs. 27-

(-CH₂CH=CH₂), which is an example of an R group attached to the 3’-oxygen of the sugar in the challenged claim. In this Patent Owner Preliminary Response, Columbia refers to this group as “the allyl capping group” except when quoting Illumina’s Petition.

34. In 1998, Metzker reported results of further experiments involving nucleotides with a 2-nitrobenzyl capping group. Ex-2012 at 814-17. In 1999, Welch described studies using nucleotides with a 2-nitrobenzyl capping group and stated “[e]arlier work from these labs proved that 3’-O-(2’’-nitrobenzyl)adenosine triphosphate [] could be incorporated by a DNA polymerase.” Ex-2041 at 198 (citing Metzker 1994). And in March 2000, Stemple filed a PCT Application disclosing DNA sequencing nucleotides with a 2-nitrobenzyl capping group as a preferred embodiment and referenced Metzker’s 3’-O-(2-nitrobenzyl)-dATP nucleotide analogue. *See* Ex-1019 at 9:57-10:14; Ex-2013 at 13.

As of the October 2000 priority date of the ’358 patent, the literature taught that a nucleotide analogue with the 2-nitrobenzyl capping group was capable of a complete cycle of SBS (i.e., termination, deprotecting, and reinitiation). *See* Ex-1016 at 4259, 4265; Ex-2014 at 170 (1994 Abstract by Metzker reporting he used the 2-nitrobenzyl capping group for *five* cycles of SBS). When Columbia filed the application leading to the ’358 patent, there was no basis to conclude that capping groups smaller than the 2-nitrobenzyl (which has a diameter of 5.0Å; Ex-1065 at 23, 29) were needed for SBS.

Despite the conventional understanding at the time, the insights of the Columbia inventors led them to appreciate the criticality of using a capping group with a diameter less than 3.7Å. Their conception called into question the

contemporaneous understanding that larger capping groups like 2-nitrobenzyl could be useful for SBS. Much later, in 2007, Metzker confirmed the Columbia inventors' insight when he reported that his 1994 publication contained a critical error: the compound reported as the 3'-*O*-(2-nitrobenzyl) nucleotide analogue was missing the 3'-OH capping group. Ex-1017 at 6339-40. When the actual 3'-*O*-(2-nitrobenzyl) nucleotide analogue was made and tested by Metzker, the nucleotide analogue was not incorporated by a polymerase, just as the Columbia inventors predicted. Ex-1017 at 6339-40.

**F. Illumina's Ground 1 Challenge
For Obviousness Over Tsien Is Flawed**

Illumina's Ground 1 challenge fails for the following reasons, each of which is sufficient to deny institution:

1. Illumina has not established that Tsien discloses a capping group with the structural features required by the challenged claim: a "small" capping group R not containing a ketone and not forming a methoxy or an ester group with the 3'-oxygen of the sugar of the nucleotide analogue. A claim cannot be rendered obvious by a combination of references, none of which discloses or suggests a feature of the claim;

2. Illumina has not established that a POSA would have had a reason to combine disclosures in Tsien to arrive at a base-labeled nucleotide analogue with

the allyl capping group and all the other features recited in the challenged claim;
and

3. Illumina has not established that a POSA would have had a reasonable expectation of success in achieving the claimed nucleotide analogue.

Each of these reasons demonstrates that a base-labeled nucleotide analogue with the allyl capping group would not have been obvious to a POSA in 2000. This conclusion is underscored by Illumina's own patents in which Illumina claims to have invented the same nucleotide analogue *in 2002*:

Viewed from another aspect, the invention provides a 3'-*O-allyl nucleotide* or nucleoside which nucleotide or nucleoside comprises a detectable label linked to the base of the nucleoside or nucleotide, preferably by a cleavable linker.

Ex-2015 at 4:25-29 (emphasis added), 1:6-18 (claiming priority to 2002); *see also* Ex-2016 at claim 1 (claiming method of using the 3'-*O-allyl* nucleotide analogue), 1:6-20 (claiming priority to 2002); Ex-2017 at claim 12 (claiming the 3'-*O-allyl* nucleotide analogue).⁷ Illumina violated its duty of candor under 37 C.F.R.

⁷ Exs-2015, 2016, and 2017 were originally assigned to Illumina Cambridge Ltd. under its old name Solexa Limited and are now assigned to Illumina Cambridge Ltd. Ex-2037 at 1-2 (assignments for Ex-2015 and Ex-2017 and name change);

§42.11(a) and its discovery obligations under 37 C.F.R. §42.51(b)(1)(iii)⁸ by failing to disclose in its Petition, or to provide discovery concerning, its previous inconsistent position that in 2002 it invented the same nucleotide analogue it now claims was obvious in 2000. *See Sprint Spectrum L.P. v. General Access Solutions, Ltd.*, IPR2017-01885, Paper 8, 9 (March 9, 2018) (noting that duty of candor includes disclosing to the Board “information that is inconsistent with a position advanced by the petitioner during the proceeding”).

Ex-2043 at 20 (assignments for Ex-2016), 15 (name change); Ex-2015 at cover (assignment); Ex-2016 at cover (assignment); Ex-2007 ¶67 (name change).

Illumina refers to itself as both Illumina Inc. and Illumina Cambridge Ltd. (*see supra* note 4).

⁸ Illumina’s discovery obligations began with the filing of its Petition. 37 C.F.R. §42.51(b)(1)(iii) (noting discovery obligations “during the proceeding”); 37 C.F.R. §42.2 (“Proceeding means a trial or preliminary proceeding . . . [p]reliminary proceeding begins with the filing of a petition[.]”).

1. **Illumina Has Not Established That Tsien Discloses A “Small” Capping Group Not Containing A Ketone And Not Forming An Ester Or A Methoxy Group With The 3’-Oxygen Of The Nucleotide Analogue**

Illumina’s Ground 1 challenge requires that Tsien discloses the 3-carbon allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$) capping group. Unless Tsien discloses this capping group, Illumina has failed to even assert that Tsien discloses a capping group with the structural features the challenged claim requires: a “small” capping group not containing a ketone and not forming a methoxy or an ester group with the 3’-oxygen of the sugar of the nucleotide analogue. A claim cannot be rendered obvious by a combination of references none of which discloses or suggests a feature of the claim. *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (“[O]bviousness requires a suggestion of all limitations in a claim.”); *Medtronic, Inc., v. Barry*, IPR2014-01210, Paper 10, 21 (Feb. 10, 2015) (“To establish obviousness of a claimed invention, all the claim limitations must be taught or suggested in the prior art.”). Therefore, Illumina’s Ground 1 challenge fails unless Tsien discloses the allyl capping group. Illumina has failed to make this showing.

Illumina relies on a single sentence in Tsien to conclude that Tsien discloses the allyl capping group: “Allyl ethers are cleaved by treatment with Hg(II) in acetone/water (Gigg and Warren, 1968).” Petition at 22 (citing Ex-1013 at 24:29-

30). Illumina presented no evidence that “allyl ethers” in Tsien means anything other than its ordinary meaning, a broad genus including both unsubstituted and substituted allyl ethers. *See, e.g.*, Ex-1046 at 1906 (compounds XLIX (the allyl group being “CH₂-C(Me)=CH₂”) and LII (the allyl group being “CH₂-CH=CH-CH₃”)) and at 1907 (“We have shown that γ -substituted allyl ethers are eliminated”); Ex-2018 at 141 (Table 1); Ex-2019 at 7719 (Table 3); Ex-2020 at 2497 (Table 1). Illumina’s expert Dr. Romesberg concedes Tsien’s “allyl ethers” refers to a genus: “With respect to 3’-O-allyl **groups**, Tsien cites to Gigg [which] provides exemplary methods for preparing compounds with allyl **ethers**[.]” Ex-1067 ¶98 (emphasis added).

Moreover, Illumina has admitted that Tsien does not teach or suggest a nucleotide analogue with the allyl capping group. Specifically, Illumina owns U.S. Patent No. 6,232,465 (Ex-2038 at 1) which claims a nucleotide analogue with the allyl capping group. Ex-2021 at Reexamination Certificate, claim 1. During a reexamination of the ’465 patent and related U.S. Patent No. 5,763,594 (the “Hiatt reexaminations”), to overcome a rejection based on Tsien, Illumina in 2007 cited the same portion of Tsien it relies on in its Petition and admitted Tsien **does not** disclose a nucleotide analogue with the allyl capping group:

In the . . . section entitled “Deblocking Methods”, *Tsien* references a 1968 publication that allegedly teaches that

treatment with Hg(II) in acetone/water will cleave an allyl ether. See, *Tsien*, Page 24, lines 29-30. The mere description of general deblocking methods in this section does not describe a [nucleotide analogue] having an allyl removable blocking moiety, much less one having an allyl removable blocking moiety which is linked specifically at the 3' carbon[.]

Ex-2022 at 10-11.⁹ Illumina concluded that:

⁹ Illumina's wholly-owned subsidiary Solexa Inc. made the representations in the Hiatt reexaminations after it was acquired by Illumina on January 26, 2007. Ex-2024 at 3; Ex-2038 at 1-2 (assignment data). Illumina on February 8, 2010 merged Solexa "with and into itself," and Solexa is now part of Illumina. Ex-2023. Moreover, Illumina has attributed Solexa's statements during the Hiatt reexaminations to itself. Specifically, in a reexamination of another one of its patents, Illumina stated that ***Illumina***—not Solexa—successfully argued in the Hiatt reexaminations that a POSA would not have expected a nucleotide analogue with the allyl capping group to be useful. Ex-2009 at 82-83 (Illumina summarizing arguments that it ("Patent Owner") made in the '594 patent reexamination (Reexamination 90/008,149)).

Tsien does not teach or suggest [a nucleotide analogue] having an allyl removable blocking moiety protecting the 3' position linked to the 3' carbon via an ether linkage.

Id. at 14. And:

Tsien does not describe using an allyl ether at the 3' position [of a nucleotide analogue].

Id. at 12. And:

Tsien did not envision the compounds which are the subject matter of Claims 1 and 3 as amended [i.e., nucleotide analogues with the allyl capping group].

Id. at 10, 4 (amended claims). Illumina's failure to disclose in its Petition and by discovery that it previously took these inconsistent positions is a violation of its duty of candor and its discovery obligations. 37 C.F.R. §42.11(a); 37 C.F.R. §42.51(b)(1)(iii).

Illumina has not explained how a POSA reading *Tsien*'s reference to the genus "allyl ethers" would have understood the genus to equal the 3-carbon ($-\text{CH}_2\text{CH}=\text{CH}_2$) allyl species, which Illumina previously admitted is not disclosed.

Thus, Illumina has not met its burden of establishing that *Tsien* discloses or suggests a nucleotide analogue with a small (less than 3.7Å in diameter) capping group not containing a ketone and not forming a methoxy or an ester group with the 3'-oxygen of the sugar.

2. Illumina Has Not Established A Motivation To Select The Allyl Capping Group

As explained above, Tsien does not disclose the 3-carbon allyl capping group. But even if Tsien did disclose this group, Illumina has not established that a POSA would have been motivated to select the group from the multitude of groups disclosed in Tsien and use it in a base-labeled nucleotide for SBS. *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (a motivation to combine must exist whether the claim elements are in a single reference or several references).

As explained below, Illumina's motivation-to-combine analysis fails because (a) Tsien does not provide a motivation to select the allyl capping group, (b) a decade of developments in the field subsequent to Tsien's 1991 publication confirms that a POSA would not have been motivated to select the allyl capping group, (c) evaluation of Tsien's stated nucleotide analogue requirements for successful SBS, which the Board has found central to a motivation-to-combine analysis involving Tsien, would not have led to selecting the allyl capping group, and (d) there was no motivation to select a "small" 3'-OH capping group.

a. Tsien Does Not Provide Motivation To Select The Allyl Capping Group

Illumina asserts Tsien "would have motivated a POSA to select and use the 3'-O-allyl capping group on the nucleotide analogues disclosed by Tsien." Petition

at 35, 36 (“Tsien itself expressly encourages using the allyl group.”). Illumina is wrong.

The *only* motivation Illumina offers for selecting the allyl capping group from Tsien’s vast disclosure is that Tsien allegedly teaches this capping group is “*particularly advantageous*” over other capping groups. Petition at 26. There is no such teaching in Tsien. Illumina’s citation misleadingly omits that Tsien is discussing “some advantages”—namely “premature deblocking during incorporation is minimized”—that apply to “[a] *wide variety* of hydroxyl blocking groups [that] are cleaved selectively using chemical procedures other than base hydrolysis[,]” including but not limited to “[t]etrahydrothiofuranyl ethers[,]” “[a]llyl ethers[,]” and “2,4-[d]initrobenzenesulfonyl groups[.]” Ex-1013 at 24-25. Tsien also identifies properties of ester capping groups that offer the same advantage of “prevent[ing] significant premature deblocking[,]” (*id.* at 24) and identifies groups suitable for photochemical and enzymatic removal (*id.* at 25). Illumina has provided no rationale why a POSA would have focused on the “allyl ethers” genus. And even if a POSA would have focused on this genus, Illumina has provided no motivation for the POSA to select the undisclosed 3-carbon allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$) capping group that is the focus of its Petition from within that genus.

As preferred embodiments, Tsien discloses the broad genera “esters and ethers” (also “ester blocking groups” and “ether blocking groups”), “phosphate blocking groups,” and “carbonate blocking groups.” Ex-1013 at 21. In a reexamination of its own patent (*see supra* note 5), Illumina in 2011 conceded “Tsien encompasses broad classes of compounds, perhaps hundreds or more potential blocking groups.” Ex-2009 at 15.

Tsien discloses no preference or requirement regarding the size of the blocking group, and provides no other disclosures that would lead a POSA to use the allyl capping group. Illumina admitted this to the Patent Office in 2007 during reexamination of its own patents (*see supra* note 9). There, Illumina argued that a POSA reading Tsien would not be motivated to use the allyl capping group on a nucleotide analogue:

Tsien does not teach or suggest [a nucleotide analogue]
having an allyl removable blocking moiety protecting the
3' position linked to the 3' carbon via an ether linkage.

Ex-2022 at 14. And:

[T]he evidence shows that even 6 years after the time the presently claimed invention was made [i.e., September 2000], persons skilled in the art would not have been motivated to prepare the compounds of claims 1, 3 and 7 [nucleotide analogues with the allyl capping group], or

compositions containing them, with a reasonable expectation that they could be used for DNA synthesis.

Id. at 16. And:

Tsien does not suggest that an allyl blocking moiety would have been effective for purposes of nucleic acid synthesis due to an extant belief that it caused problems from the standpoints of hydrolysability and steric hindrance.

Id. at 24. Illumina's admissions that a POSA in September 2000 reading *Tsien* would ***not have been*** motivated to select the allyl capping group summarize the actual teachings of the prior art and are fatal to Illumina's contradictory assertions in its Petition. Illumina's failure to disclose these inconsistent positions in its Petition and by discovery is a further violation of its duty of candor and discovery obligations. 37 C.F.R. §42.11(a); 37 C.F.R. §42.51(b)(1)(iii).

Illumina has not met its burden of establishing a POSA would have understood *Tsien* to disclose, and been motivated to select, the allyl capping group. Accordingly, Illumina has not met its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 1.

b. The Art Subsequent To Tsien Shows The Field Was Not Interested In The Allyl Capping Group

Illumina has ignored the totality of the prior art as of October 2000. Specifically, Illumina's motivation-to-combine analysis (Petition at 34-37) does not account for *any* developments in the field during the nine years subsequent to Tsien's 1991 publication. Thus, Illumina's analysis is legally insufficient because the state of the art as a whole must be considered in determining obviousness. *E.g., In re Etter*, 756 F.2d 852, 859 (Fed. Cir. 1985).

Developments in the field between Tsien's 1991 publication and October 2000 demonstrate there was no motivation to select the allyl capping group for SBS. In 1994 Metzker tested a nucleotide analogue containing the allyl capping group and reported it was a poor choice for DNA sequencing. Specifically, Metzker tested whether a number of 3'-OH capped nucleotide analogues could be incorporated by polymerases and achieve termination of DNA synthesis. Metzker stated that 3'-*O*-allyl-dATP was incorporated by one of eight polymerases tested. Ex-1016 at 4263, 4265. But Metzker qualified his statement by indicating that the 3'-*O*-allyl-dATP's ability to achieve termination was not "specific" (Ex-1016 at 4263 (noting that only "[c]ompounds [1], [8], and [7] showed specific termination")) and termination activity was "incomplete at a final concentration of 250 μ M[.]" Ex-1016 at 4263 (Table 2). In other words, while some level of

incorporation was seen with one polymerase, *specific and complete* termination was not achieved, and Metzker abandoned the allyl capping group in further studies in the same and other papers. Ex-1016 at 4263-67; Ex-2012 at 814-17. Based on his experimental results, Metzker stated that of eight tested compounds, only three “proved to be interesting DNA synthesis terminators”: the 3’-*O*-(2-nitrobenzyl)-dATP, 3’-*O*-methyl-dATP, and 3’-*O*-methyl-dTTP. Ex-1016 at 4265. None of these are encompassed by the challenged claim. By extension, the five remaining compounds, including the 3’-*O*-allyl nucleotide analogue, were *not* interesting DNA synthesis terminators.

Metzker 1994 represents the only experimental evaluation of the allyl capping group for DNA sequencing available to a POSA in 2000. Later in 2007 Metzker confirmed that the conventional understanding of Metzker 1994 was that the 3’-*O*-allyl nucleotide analogue was a “poor substrate[]” that had “limited activity”:

3’-modified nucleotides . . . typically act as *poor substrates* for DNA polymerases. For example, screening 3’-*O*-allyl-dATP with eight different DNA polymerases [in Metzker 1994] revealed *limited activity* at high micromolar concentrations with only Vent(exo-) DNA polymerase.

Ex-1017 at 6348 (citing Metzker 1994) (emphasis added). And in 2011, Metzker similarly confirmed that Metzker 1994 taught that the 3'-O-allyl nucleotide analogue was "not efficiently incorporated." Ex-2025 at 10 (Metzker 1994 taught that the 3'-O-allyl nucleotide analogue was "*not efficiently incorporated*" (emphasis added)).

The '358 patent acknowledges Metzker was the first to evaluate the allyl capping group in a DNA sequencing context. Ex-1002 at 3:25-30, stating: "3'-O-allyl-dATP was . . . shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994)." Illumina cites this acknowledgment to support its conclusory rationale for obviousness. *E.g.*, Petition at 24-25. As explained above, Metzker did state that the 3'-O-allyl nucleotide analogue was incorporated, but Illumina ignores Metzker's qualification that the incorporation was non-specific and incomplete (Ex-1016 at 4263), i.e., the tested 3'-O-allyl-dATP was a poor substrate with limited activity (Ex-1017 at 6348) that was not efficiently incorporated (Ex-2025 at 10). Illumina also ignores that Metzker abandoned the allyl capping group and reported in the same paper further tests of the three "interesting" nucleotide analogues that do not include the allyl capping group (Ex-1016 at 4263-67). It was the Columbia inventors who appreciated that the allyl capping group could succeed for SBS, contrary to Metzker's 1994 results. Illumina's reliance on the '358 patent specification's

citation to Metzker 1994 is also misplaced because “[t]he inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

As explained above, Illumina has failed to demonstrate a POSA would have selected the allyl capping group despite Metzker’s contrary teachings. Therefore, Illumina has not met its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 1.

c. **A POSA Would Have Been Motivated To Select Only A 3’-OH Capping Group That Met Tsien’s SBS Requirements**

Tsien sets forth three requirements of a nucleotide analogue useful for SBS. Illumina has previously urged (and the Board agreed (Ex-1044 at 11-14)) that a POSA reading Tsien would select only a 3’-OH “blocking group” believed to meet these requirements. *See* Ex-2008 at 12-14, *see generally* 15-33; Ex-2026 at 5, *see generally* 35-56. These requirements are:

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

Ex-1013 at 20-21 (emphasis added). For example, in IPR2013-00517 Illumina argued a POSA would not be motivated to use an azidomethyl capping group because it did not satisfy Tsien's three requirements. Ex-2008 at 12-14; Ex-2007 ¶53 (a POSA would have expected that "Zavgorodny's removal conditions [for the azidomethyl capping group] would cleave with insufficient efficiency for Tsien[']s . . . DNA sequencing methods.").¹⁰ More recently, Illumina made the same argument in IPR2017-02172:

[The IPR Petition], however, fails to establish that an azidomethyl protecting group would have been known to meet any of [Tsien's three] criteria. A person of ordinary skill in the art . . . therefore would not have been motivated to use an azidomethyl group as Tsien's 3'-blocking group.

¹⁰ Illumina's U.S. Patent No. 7,566,537, with a priority date later than the '358 patent, covers methods of using an embodiment of the challenged claim: a 3'-O-azidomethyl (which has a diameter of 2.1Å) nucleotide analogue. Ex-2028 at 20:3-4 (claim 6). This patent was the subject of IPR2013-00517 and is currently the subject of IPR2017-02172. In those IPRs, Illumina maintains that a 3'-O-azidomethyl nucleotide analogue was not obvious over Tsien.

Ex-2026 at 5. The same motivation-to-combine framework advocated by Illumina before the Board in IPR2013-00517 and IPR2017-02172 should be applied in this proceeding. When Tsien's requirements are considered, Illumina cannot meet its burden of demonstrating a POSA would have been motivated to select the allyl capping group.

i. **A nucleotide analogue with the allyl capping group was not known to be incorporated "accurately and efficiently"**

Tsien's first requirement is "accurate[]" and "efficient[]" incorporation of a nucleotide analogue carrying the 3'-OH "blocking group." Ex-1013 at 20. Illumina does not allege, let alone provide evidence, that a 3'-*O*-allyl nucleotide analogue would have been expected to be "accurately and efficiently incorporate[d]" by polymerase. At most, Illumina asserts Metzker 1994 showed that a 3'-*O*-allyl nucleotide analogue was "incorporated." *E.g.*, Petition at 60. As explained in Section F(2)(b), that incorporation was insufficient to achieve specific and complete termination, indicating the 3'-*O*-allyl nucleotide analogue was a poor substrate with limited activity that was "***not efficiently incorporated***[]" Ex-2025 at 10 (emphasis added); *see also* Ex-1016 at 4263; Ex-1017 at 6348. Illumina has not met its burden of establishing that Metzker's 1994 results, or any other prior art, would have led a POSA to believe use of the allyl capping group would result

in the “accurate[.]” and “efficient[.]” incorporation of a nucleotide analogue required for Tsien’s method.

ii. **The allyl capping group was not known to be cleaved quantitatively and rapidly under mild conditions**

Tsien’s second requirement is *quantitative* and *rapid* cleavage under *mild conditions*. Ex-1013 at 20-21. Illumina does not assert that it was known that the allyl capping group could be cleaved rapidly. For this reason alone, Illumina has not established that there would have been any motivation to select the allyl capping group for use in Tsien’s SBS methods.

In fact, references relied upon by Illumina report that the allyl capping group is cleaved *slowly*. The reaction in Qian (Ex-1036 at 2185) required 2 hours, and the reaction in Boss (Ex-1035 at 558-59) required “a few hours.” Illumina’s expert, Dr. Romesberg, previously admitted a cleavage reaction requiring 2 hours was incompatible with Tsien’s methods. *E.g.*, Ex-2007 ¶47 (“This [cleavage] reaction . . . required 2 hours . . . [which] would have led one of ordinary skill to have expected [the cleavage conditions] to be incompatible with Tsien’s . . . requirements[.]”).

Illumina also failed to demonstrate that the allyl capping group could be cleaved *quantitatively* under *mild* conditions. Illumina cites Qian as evidence the allyl capping group could be cleaved quantitatively, but Qian’s conditions are *not*

mild, requiring the use of methanol (Ex-1036 at 2185) which Dr. Romesberg admitted was known to denature DNA. *E.g.*, Ex-2007 ¶47 (“This [cleavage] reaction was performed in methanol (which was known to denature DNA)[.]”), ¶55 (“Pyridine is not the only organic solvent that was known to be a denaturing agent in aqueous solution. In fact, most organic solvents (including tetrahydrofuran ‘THF’ and *methanol*) were known to denature DNA.” (Emphasis added.)). Thus, methanol would not meet Tsien’s required mild conditions. Similarly, Boss’ conditions are not mild, requiring use of heat (“60° to 80°C”) for extended periods of time (“a few hours”). Ex-1035 at 558-59. Illumina provides no evidence that 60° to 80°C for extended periods of time is compatible with DNA. Moreover, Qian’s and Boss’ cleavage reactions require use of PdCl₂ and Illumina provides no evidence PdCl₂ was known in 2000 to be compatible with DNA.

Illumina cites Kamal (Ex-1037) as evidence the allyl capping group could be cleaved under mild conditions, but Kamal’s conditions do not result in what Illumina terms quantitative cleavage, resulting instead in 93% cleavage. Ex-1037 at 372, Entry 8 (reporting 93% cleavage of allyl on sugar). Illumina previously asserted 93% cleavage is *not enough* to practice Tsien’s methods, and that anything less than quantitative cleavage is insufficient. *See* Ex-2029 at 45 (“One skilled in the art would not have been motivated to combine the prior art references for SBS unless there was a reasonable expectation that the combination would

provide a 3'-protecting group that cleaves with nearly 100% efficiency."), 28 ("[O]ver 97% . . . is required."); Ex-2030 at 1 ("[T]he [cleavage] efficiency needed to be >97%."); Ex-1045 at 6 (Federal Circuit finding that: "In order for the deblocking (i.e., the removal of the protecting group) to be quantitative, it must take place at 100% or near-100% efficiency.").

In addition, it is undisputed an allyl capping group forms an ether with the 3'-oxygen of the sugar (e.g., Petition at 50, 60), and Illumina has admitted that a POSA would *not* have selected an ether capping group for use in SBS because they are difficult to cleave under mild conditions. Specifically, in defending its own patent covering a base-labeled nucleotide with a 3'-oxygen azidomethyl ether (*see supra* note 10), Illumina admitted a POSA in 2002 would not select an ether capping group because a 1994 reference (Canard, Ex-2031) taught that ethers were difficult to cleave under conditions compatible with DNA sequencing:

[T]he prior art [as of 2002] teaches that it is difficult to cleave ethers under conditions compatible with DNA. Thus, the difficulty in cleaving ether bonds with DNA compatible conditions would have [led] a [POSA] to expect that Zavgorodny's 3'-*O*-azidomethyl ether would not cleave under conditions compatible with Tsien's DNA sequencing methods.

Ex-2008 at 23 (citations removed).

Illumina also admitted the prior art implicated “that the conditions needed to cleave an ether weren’t going to work in DNA synthesis.” Ex-2032 at 37:10-12; *see also* Ex-2033 at 3 (prior art taught it was hard to cleave ethers). Furthermore, according to Illumina’s own patent, conditions for successful cleavage of the allyl capping group under DNA compatible conditions had not been reported before 2002:

[T]here is to date [as of 2002], ***no concrete embodiment of the successful cleavage of a 3'-allyl group under DNA compatible conditions***, i.e. conditions under which the integrity of the DNA is not wholly or partially destroyed. In other words, it has not been possible hitherto to conduct DNA sequencing using 3'OH allyl-blocked nucleotides.

Ex-2015 at 2:60-65 (emphasis added).¹¹

Illumina’s current position that the allyl capping group was known to be cleavable under DNA-compatible conditions in 2000 (e.g., Petition at 69) is inconsistent with its prior admissions. Illumina’s failure to disclose these previous

¹¹ Columbia takes no position on the veracity of Illumina’s admissions. It is Illumina’s burden to demonstrate the challenged claim is obvious despite Illumina’s previous admissions.

inconsistent positions in its Petition and through discovery is another violation of Illumina's duty of candor and its discovery obligations (37 C.F.R. §42.11(a); 37 C.F.R. §42.51(b)(1)(iii)).

Illumina attempts to wash its hands from its prior inconsistent admissions by pointing to the '358 patent specification (e.g., Petition at 23) which cites Kamal for the proposition that the allyl capping group can be removed with high yield in mild conditions. Ex-1002 at 26:16-33. However, unlike Illumina which admitted a POSA in 2002 would believe that ether capping groups "*weren't going to work in DNA synthesis*," this passage in the '358 patent specification highlights the insight of the Columbia inventors that the allyl capping group would be useful for SBS.

iii. **It was not known that polymerase could reinitiate DNA synthesis after the allyl capping group was deblocked**

Tsien's third requirement is the ability of polymerase to reinitiate DNA synthesis subsequent to deblocking the 3'-OH capping group. Ex-1013 at 20-21. As Illumina admitted, Metzker 1994 (which contains the only experimental data available to a POSA in 2000) did not demonstrate "a complete cycle of termination, deprotection and *reinitiation* of DNA synthesis[.]" Ex-2015 at 2:26-30 (emphasis added). Illumina has not alleged, let alone established, that a POSA would have believed that a polymerase would *reinitiate* DNA synthesis subsequent to deblocking the allyl capping group.

iv. **Illumina’s argument that Tsien’s requirements are irrelevant should be rejected**

As explained above, Illumina has not established (or even asserted) that the allyl capping group would have been known to meet Tsien’s three requirements. Instead, Illumina contradicts its positions in IPR2013-00517 and IPR2017-02172—that Tsien’s three requirements must be met in selecting a 3’-OH capping group (Ex-2008 at 12-14; Ex-2026 at 5)—to now argue Tsien’s requirements are somehow irrelevant. Petition at 36-37.

Illumina attempts to justify its contradictory position by arguing “Tsien *itself* expressly encourages using the allyl group,” whereas an outside reference (Zavgorodny) allegedly encouraged use of the azidomethyl capping group in IPR2013-00517 and IPR2017-02172. *Id.* This argument fails as a matter of fact.

As discussed in Sections F(1) and F(2)(a), Tsien does not disclose let alone encourage using the allyl capping group. The only reference Illumina cites that discloses the allyl capping group is Metzker 1994, which is an outside reference just like Zavgorodny. And, as discussed above, Metzker taught that the allyl capping group was a poor choice for DNA sequencing.

Illumina urges that Tsien’s three requirements are irrelevant because a POSA would simply conclude that every “blocking modification” to the 3’-OH position disclosed in Tsien met Tsien’s three requirements. This is wrong. It is

undisputed that Tsien discloses blocking modifications that cannot be used for SBS. For example, in IPR2013-00517 Illumina explained that the 3'-N₃ group disclosed by Tsien was useless for SBS because it could not be removed to expose a 3'-OH group. *See, e.g.*, Ex-2008 at 12. Illumina concluded: "As a result, a person of ordinary skill in the art would not have been motivated to use the non-removable 3'-N₃ group of Tsien[.]" *Id.* Likewise, the Columbia inventors recognized a number of other capping groups in Tsien were incompatible with SBS including the methoxy group and ester groups. *See* Ex-1002 at claim 1. Because, as Illumina concedes, Tsien disclosed blocking modifications to the 3'-OH position that are useless for SBS, a POSA considering Tsien's prophetic disclosure would understand that any blocked nucleotide analogue would need to be evaluated to determine if it met Tsien's three requirements for practicing his SBS methods. Illumina has previously admitted as much:

Undue experimentation would be required to determine which of the multitude of potential blocking groups [in Tsien] would be expected to be removable blocking moieties that also protect the 3' position[.]

Ex-2009 at 15 (emphasis removed).

Illumina is also wrong as a matter of law. As the Federal Circuit recently explained, a motivation-to-combine must exist whether the elements of a claim are

in a single reference (as Illumina alleges here) or several references (as was allegedly the case in IPR2013-00517 and IPR2017-02172). *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017). Illumina cannot bypass the motivation-to-combine requirement by asserting the claim elements are found in a single reference.

For the reasons explained above, Tsien's three requirements for his SBS methods are not irrelevant, and Illumina has not established that a POSA reading Tsien would have selected the allyl capping group given those requirements.

d. Illumina's Contention That A Small 3'-OH Capping Group Would Have Been "Desirable" Is Unsupported

Illumina argues a POSA would have known that "small" capping groups, like the allyl capping group, "were desirable." *See* Petition at Heading VI(B)(1)(a). This is wrong for the following reasons.

i. The most promising capping group in 2000 was not small

As explained in Section E, prior to the present invention, no one recognized the criticality of using a small (less than 3.7Å in diameter) capping group for SBS. Illumina's contrary assertions are wrong.

Illumina claims Metzker 1994 provided "evidence confirming . . . that the 3'-O-capping group should be small." Petition at 60-61. But, the opposite is true. Metzker 1994 did not show that capping groups should be smaller than 3.7Å in

diameter. Instead, Metzker (and the art that followed) focused on the 2-nitrobenzyl capping group with a diameter of 5.0Å. *See* Section E, above.

Illumina has provided no evidence that a POSA in 2000 would have focused on small capping groups with a diameter less than 3.7Å. Rather than providing evidence from the prior art, Illumina alleges, incorrectly, that “Columbia conceded that by 2000 a POSA would have known whether a given blocking group was suitably small based on Pelletier’s crystal structure and available modeling software[.]” Petition at 12, 59-60. Illumina reaches this conclusion after selectively quoting the ’358 patent prosecution history. When read in context, including language omitted by Illumina, it is clear Columbia argued (to overcome an indefiniteness rejection) that a POSA reading the Columbia inventors’ specification would have been able to determine whether a capping group was suitably small. *E.g.*, Ex-1065 at 16 (“As of October 6, 2000, the POSA ***reading the specification*** would have understood that ‘small’ referred to the ability to fit into the active site of the polymerase defined by reference to the three-dimensional structure shown in FIG. 1 [of the specification].” (Emphasis added.)). It was and is Columbia’s position that the criticality of using a small (less than 3.7Å in diameter) capping group for SBS was not recognized prior to the Columbia inventors’ inventive insight.

Illumina has not established why, without Columbia's guidance in the '358 patent, a POSA would have had the insight to review Pelletier and appreciate the criticality of using capping groups smaller than 3.7Å in diameter. Pelletier was published in 1994 and related to HIV drug development, an entirely different field from SBS. Illumina has not pointed to any reference to Pelletier by other researchers developing nucleotide analogues for SBS. Quite the contrary, even long after Pelletier the field continued to pursue development of nucleotide analogues with capping groups that were not small, such as the 2-nitrobenzyl capping group, for SBS. *See* Section E.

ii. **The Board did not address whether a POSA would be motivated to select a small capping group in IPR2012-00007**

Illumina claims that “[a]ny argument that the size or ‘smallness’ of the 3’-O-capping group is inventive was fully and finally rejected by the Board” in IPR2012-00007. Petition at 2, 6, 24. Illumina's support for this assertion is that the Board previously found claim 31 of the '869 patent (which included the term “small”) unpatentable under 35 U.S.C. §102(b) for *anticipation* over Tsien. *See* Petition at 6, 24.

As an initial matter, the only embodiment of the challenged claim Illumina asserts was obvious as of 2000 is a base-labeled nucleotide with the allyl capping group. The Board did not consider this embodiment in finding Tsien anticipated

claim 31 of the '869 patent. In that proceeding, Illumina argued that the “small” limitation was satisfied by the following capping groups disclosed in Tsien: (i) “lower (1-4 carbon) alkanoic acid . . . esters, for example formyl, acetyl, isopropanol . . . esters”; and (ii) “-F, -NH₂, -OCH₃, -N₃, -OPO₃.” Ex-2034 at 26; *see also* Ex-1005 at 11. None of these groups fall within the scope of the challenged claim which expressly excludes ester groups and a methoxy group and groups that are not chemically cleavable when attached to the 3'-carbon.

Regardless, the Board in that proceeding did not determine whether a POSA would have had a *motivation* to select a “small” 3'-OH capping group, and did not address how a POSA would have had a *reasonable expectation* that including a “small” 3'-OH capping group would have achieved the claimed invention.

For the reasons explained above, Illumina has failed to meet its burden of establishing a POSA would have been motivated to select the allyl capping group.

3. Illumina Has Not Established A Reasonable Expectation of Success

In *Lupin Ltd. v. Pozen Inc.*, the Board held that the reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention, including functional limitations. IPR2015-01773, Paper 36, 26 (Feb. 28, 2017) (examining reasonable expectation of success of claim limitations, including functional limitations, *e.g.*, “we disagree

that the skilled artisan would have also reasonably expected successful *inhibition* of at least some naproxen until pH reaches 3.5.” (Emphasis added.)). Here, Illumina argues a POSA would have had a reasonable expectation of success with regard to each of the features in the challenged claim including “each of the recited functional limitations[.]” Petition at 39.

Illumina previously admitted that “the chemical arts are inherently unpredictable and, therefore, a reasonable expectation of success is harder to achieve.” Ex-2008 at 9 (presumptive priority date 2002). This was particularly true in 2000 for the discovery of nucleotide analogues useful for SBS, which Illumina admits was a “formidable obstacle” and a “major challenge.” Ex-2007 ¶60; Ex-2008 at 4-5; Ex-2042 at 6. In fact, Illumina’s expert Dr. Romesberg testified he was *amazed* that any nucleotide analogue with a 3’-OH capping group was useful for SBS. Ex-2035 at 67:7-8 (“Frankly, my intuition is I’m amazed any of them work . . .”).

Instead of addressing its own prior admissions, Illumina argues the Board decided in IPR2012-00007 that there was a reasonable expectation of achieving all of the ’358 patent’s claimed elements. Petition at 39. This is incorrect. The Board in IPR2012-00007 assessed only whether there was a reasonable expectation of incorporation (of the nucleotide analogue in those claims), which is only one of the

requirements of the nucleotide analogue recited in the challenged claim. Ex-1005 at 33.

In addition, Illumina's reasonable expectation of success evidence here relies on only one embodiment of the challenged claim—a base-labeled nucleotide analogue with an allyl capping group. The Board in IPR2012-00007 *never* considered the obviousness of this compound, and *never* considered whether there was a reasonable expectation that this compound would achieve the claimed features.

Against this backdrop, Illumina has not met its burden of showing a POSA would have had a reasonable expectation the 3'-*O*-allyl nucleotide analogue would meet the limitations of the challenged claim. First, Illumina has provided no evidence that a POSA would have had a reasonable expectation that the allyl capping group “does not interfere with recognition of the analogue as a substrate by a DNA polymerase,” as required by the challenged claim. As explained in Section F(2)(b), Metzker 1994 reported that the 3'-*O*-allyl nucleotide analogue was incapable of achieving specific and complete termination. Ex-1016 at 4263. In 2007 Metzker confirmed that the conventional understanding of Metzker 1994 was that the 3'-*O*-allyl nucleotide analogue was a “poor substrate[]” that had “limited activity” compared to the natural nucleotides. Ex-1017 at 6348. Said another way,

the allyl capping group interfered with recognition of the analogue as a polymerase substrate.

Second, the 3'-*O*-allyl nucleotide analogue tested in Metzker 1994 is less complex than the nucleotide analogues claimed in the '358 patent. Specifically, Metzker's 3'-*O*-allyl nucleotide analogue did not contain a chemically cleavable, chemical linker or detectable fluorescent tag (Ex-1016 at 4260), features required by the challenged claim (Ex-1002 at claim 1). Illumina has failed to explain how Metzker's results would provide a POSA with an expectation that a nucleotide analogue with the additional features of the challenged claim would have provided any, let alone all, of the claimed functional requirements (e.g., (i) to (v)).

Third, as explained in Section F(2)(c)(ii), Illumina admitted ether capping groups (which include 3'-*O*-allyl) were expected to be difficult to cleave under conditions compatible with SBS. Given these admissions, Illumina cannot establish a POSA would have had a reasonable expectation that the allyl capping group would be "chemically cleavable," as required by the challenged claim (Ex-1002 at claim 1).

To the extent that Illumina argues that a 3'-*O*-allyl capped nucleotide analogue with a label attached to the 5-position of the base by a cleavable linker somehow provides a greater expectation of success as compared to a 3'-*O*-allyl

capped nucleotide analogue without a base label, Illumina is wrong. Each of the above points applies regardless of whether the label is attached to the base.

Therefore, Illumina has failed to meet its burden of establishing a POSA would have had a reasonable expectation of success in achieving what is claimed in the challenged claim.

In summary, Illumina failed to meet its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 1.

4. The Lead Compound Analysis¹²

Illumina argues that if the lead compound analysis applies, a nucleotide analogue with the allyl capping group would be a lead compound. Petition at 43-45. In particular, Illumina alleges Metzker's use of a nucleotide analogue with the allyl capping group indicates it was a lead compound. *Id.* at 45. Illumina's allegation is inconsistent with the prior art.

As explained above, after testing the nucleotide analogue with the allyl capping group for incorporation by DNA polymerases, Metzker reported it was not useful for DNA sequencing, at a minimum because it was a non-specific and

¹² Illumina's Petition fails on the merits regardless of whether the Lead Compound Analysis applies. Therefore, the Board need not address the Lead Compound Analysis to deny institution of Illumina's Petition.

incomplete terminator that interfered with polymerase recognition. Ex-1016 at 4263; Ex-1017 at 6348; Ex-2025 at 10. Metzker rejected the 3'-O-allyl nucleotide analogue and instead selected other nucleotide analogues for further DNA sequencing studies. *See* Ex-1016 at 4263-67. The same is true regarding the acetyl capping group, which Illumina presents as an alternative lead compound. Petition at 46-47. Illumina previously admitted Metzker 1994 discouraged using the acetyl capping group. Ex-2008 at 17 (“Metzker, however, reports that nucleotides bearing removable 3'-O-protecting groups (including a 3'-O-acetyl ester group) would interfere with the recognition of several polymerases.”).

Thus, Illumina's lead compound analysis is factually incorrect and contradicts Illumina's prior admissions. For these reasons, Illumina has not met its burden for having an IPR instituted.

**5. The Board Should Also Deny Institution
On Ground 1 Based On 35 U.S.C. §325(d)**

The Board should also exercise its discretion under 35 U.S.C. §325(d) and deny institution on Ground 1 because Tsien was considered during prosecution of the '358 patent. Under 35 U.S.C. §325(d), the Board may “reject the petition or request because[] the same or substantially the same prior art or arguments previously were presented to the Office.”

During prosecution of the '358 patent, the Examiner rejected claim 1 as obvious over Stemple in view of Tsien and specifically addressed each reference including the reference to allyl ethers in Tsien. Ex-1065 at 96-98. Columbia overcame the rejection. Ex-1065 at 3-6. Since Columbia overcame an obviousness rejection which included the very reference relied on by Illumina, even after combining it with an additional reference (Stemple), Columbia necessarily established the non-obviousness of the challenged claim over Tsien.

The Board has exercised its discretion under 35 U.S.C. §325(d) and declined to institute trial where the Petitioner relies on the same references previously presented and considered during prosecution. *Neil Ziegman, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 13, 18-20 (Sept. 6, 2017); *see also Skechers USA, Inc. v. Adidas AG*, IPR2017-00320, Paper 7, 8-9 (May 30, 2017); *Edwards Lifesciences Corp. v. Boston Scientific Scimed, Inc.*, IPR2017-00072, Paper 8, 9-11 (Apr. 21, 2017); *Kayak Software Corp. v. Int'l Bus. Machines Corp.*, CBM2016-00075, Paper 16, 7-12 (Dec. 15, 2016) (Designated Informative March 21, 2018); *Becton, Dickinson & Co. v. B. Braun Melsungen Ag*, IPR2017-01586, Paper 8, 16-28 (Dec. 15, 2017) (Designated Informative March 21, 2018).

Illumina's attempt to address the Examiner's consideration of the prior art fails. First, Illumina argues "Columbia never attempted to distinguish its claim over Tsien." Petition at 6. Illumina is wrong. During prosecution, addressing an

indefiniteness rejection, Columbia specifically noted that the claim's exclusion of methoxy and ester groups was “*contrary to the teachings of Tsien* that such groups could be used in sequencing by synthesis[.]” Ex-1065 at 18 (emphasis added). Columbia also spent five pages distinguishing its claim over Tsien during the prosecution of related U.S. Patent No. 9,725,480 and specifically explained that Tsien “does not disclose the species of blocking group” recited in the '480 patent claim (which claims the same capping groups as the '358 patent claim). Ex-1038 at 2-6. *See Becton v. Braun*, IPR2017-01586, Paper 8, 16-28 (Dec. 15, 2017) (considering prosecution history of related application in Section 325(d) analysis).

Second, Illumina contends it presents significant evidence not considered during prosecution of the '358 patent, and that Columbia “never addressed patentability over Tsien's disclosure of the 3'-*O*-allyl capping group.” Petition at 53. Illumina's contention relies on its repeated mischaracterization of Tsien as disclosing the 3-carbon allyl capping group. As explained in Section F(1), Tsien does not disclose this capping group. Illumina's assertion that it is presenting Tsien “in a new light” (Petition at 54) not considered by the Examiner is premised on this repeated mischaracterization of Tsien, along with its failure to discuss the Examiner's analysis of Tsien in allowing claim 1. Mischaracterizing a reference is not presenting the reference in a new light and the Board should exercise its discretion under 35 U.S.C. §325(d) and deny institution of Ground 1.

**G. Illumina’s Ground 2 Challenge For Obviousness
Over Dower In View Of Prober And Metzker Is Flawed**

Illumina’s Ground 2 challenge fails for many of the same reasons as its Ground 1 challenge, but also because none of its references (Dower, Prober, or Metzker) disclose a “chemically cleavable, chemical linker” as required by the challenged claim.

1. Missing Claim Features In Illumina’s Challenge

**a. Dower Does Not Disclose A
Chemically Cleavable, Chemical Linker**

Illumina asserts that “Dower discloses cleavably linking the label to the base.” Petition at 55; *see also* Petition at 71 (“Dower discloses a nucleotide analogue having a cleavably linked fluorescent label”). The challenged claim, however, does not simply require that the label be linked to the base in a manner that is cleavable, it requires the presence of “Y,” a “chemically cleavable, chemical linker” between the label and the base. The Board rejected the same argument by Illumina in IPR2012-00007. *See* Ex-2036 at 14-15. There, as here, Illumina cited portions of Dower that describe attaching a label *directly* to the nucleotide base (i.e., with no cleavable linker) and characterized those portions of Dower as disclosing a cleavable linker. *Id.* The Board disagreed:

The cited disclosures in Dower *do not expressly identify a “cleavable linker” as joining the “base” to the “detectable label.”* Removal of a detectable label from a

nucleotide is described, but such disclosure does not specify that removal occurs at cleavable linker which joins the label to the base. In the absence of such description, there is not a reasonable likelihood that Illumina would prevail in demonstrating unpatentability based on Dower, alone.

Id. at 15 (emphasis added). As the Board found, Dower does not disclose a label attached to a nucleotide base by a cleavable linker, let alone a chemically cleavable, chemical linker as required by the challenged claim.¹³ The portions of Dower cited in Illumina's Petition show the label directly attached to the base. *E.g.*, Petition at 57 (citing Ex-1015 at Fig. 9). Illumina has not established that Dower discloses the claimed feature Y, a "chemically cleavable, chemical linker" attaching the label to the base.

While Illumina relied solely on Dower for this feature, neither Prober (Ex-1014) nor Metzker (Ex-1016) remedy this deficiency. Prober discloses a chemical linker attached to the base but Prober's linker is not chemically cleavable under conditions compatible with DNA, and Illumina does not assert otherwise. And

¹³ The portions of Dower cited by Illumina in its Petition for this limitation (*see* Petition at 64-65) are the same, or substantively the same, as the portions of Dower the Board previously considered.

Metzker does not disclose any chemical linker attaching a label to the base, let alone a chemically cleavable, chemical linker, and Illumina does not assert otherwise.

Illumina's failure to provide any evidence that combining Dower with Prober and Metzker discloses or suggests feature Y of the challenged claim (a chemically cleavable, chemical linker attaching a label to the base) forecloses Illumina's ability to meet its burden of establishing that there is a reasonable likelihood the challenged claim is unpatentable.

b. Since None Of Dower, Prober, Or Metzker Disclose A “Chemically Cleavable, Chemical Linker” Y, They Cannot Disclose Features (a) Or (b) Of Feature Y

Since none of Dower, Prober, or Metzker disclose a chemically cleavable, chemical linker, these references cannot disclose features (a) or (b) of the “chemically cleavable, chemical linker” Y. More specifically, they cannot disclose that the chemically cleavable, chemical linker “does not interfere with . . . a DNA polymerase” or is “stable during a DNA polymerase reaction.”

Columbia's '358 patent does *not* admit “it was known that DNA polymerase recognizes nucleotides with linkers or other bulky groups at the 5-position of pyrimidines.” Petition at 65. The passage cited by Illumina (presumably 2:57-63,

not 2:57-63:3) *does not refer to linkers at all*, only to bulky groups such as energy transfer dyes. Ex-1002 at 2:57-63.

Therefore, as explained above, neither Dower, Prober, nor Metzker disclose features (a) or (b) of the “chemically cleavable, chemical linker” Y.

c. **None Of Dower, Prober, Or Metzker
Disclose The Functional Features Present In The
Claimed 5-Substituted Cytosine Nucleotide Analogue**

Illumina presents no evidence that Dower, Prober, or Metzker disclose a 5-substituted cytosine nucleotide analogue with all the required structural features of the challenged claim, let alone one that also has the claimed functional features, such as “not interfer[ing] with recognition of the analogue as a substrate by a DNA polymerase.”

For the reasons discussed above, Illumina has failed to meet its burden of establishing that the combination of Dower, Prober and Metzker discloses or suggests all of the features of the challenged claim.

2. **Illumina Has Not Established A Motivation
To Select The Allyl Capping Group And
A 5-Substituted Cytosine Nucleotide Analogue**

As with Ground 1, Illumina summarily asserts a POSA would have been motivated to combine Dower, Prober, and Metzker to arrive at a base-labeled nucleotide with the allyl capping group that has all the features of the challenged claim. As explained below, Illumina’s motivation-to-combine analysis fails

because (a) Metzker 1994 provides no motivation to select the allyl capping group, (b) the three SBS requirements that Illumina previously admitted are central to a motivation-to-combine analysis involving Dower would not lead to selection of the allyl capping group, (c) there was no motivation to select a small capping group (i.e., one with a diameter less than 3.7Å), and (d) Illumina failed to address its admission that a POSA would *not* select an ether capping group (e.g., the 3'-*O*-allyl group) because ethers would not work in DNA synthesis. In addition, Illumina did not demonstrate that a POSA would have been motivated to use Prober's 5-substituted cytosine in Dower's methods.

a. Metzker 1994 Provides No Motivation To Select The Allyl Capping Group

Illumina's assertion that "Metzker's results would have motivated a POSA to use Metzker's ether groups, such as the 3'-*O*-allyl ether" (Petition at 60) is wrong. As discussed in Section F(2)(b), the evidence supports the opposite conclusion. Metzker 1994 taught that the allyl capping group was a non-specific and incomplete terminator, even at very high concentrations, and concluded it was not an "interesting DNA synthesis terminator[]." Ex-1016 at 4263, 4265; *see also* Ex-1017 at 6348 (Metzker 2007 reporting that Metzker 1994 taught the allyl capping group was a "poor substrate[]" that had "limited activity"); Ex-2025 at 10 (Metzker 2011 reporting that Metzker 1994 taught the 3'-*O*-allyl nucleotide

analogue was “not efficiently incorporated”). Contrary to Illumina’s assertions, Metzker 1994 would have discouraged selecting the allyl capping group for DNA sequencing.

For this reason, Illumina has not established a POSA would have been motivated to select the allyl capping group in view of Metzker 1994’s teachings, and has not met its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 2.

b. A POSA Reading Dower Would Have Been Motivated To Select Only A 3’-OH Capping Group That Met Three SBS Requirements

In IPR2017-02174, Illumina admitted a POSA reading Dower would only select a capping group that met the following three requirements:

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

Ex-2027 at 5. In IPR2017-02174, Illumina argued the Petitioner failed to establish Illumina’s azidomethyl capping group would satisfy these three requirements, and

therefore, there was no motivation to combine Dower with a reference disclosing the azidomethyl capping group:

[The IPR 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.

Ex-2027 at 6 (emphasis added). The same motivation-to-combine framework should be applied in this proceeding.

In particular, Illumina has not suggested, let alone demonstrated, that the allyl capping group would satisfy the third requirement for selecting a capping group for use in Dower's SBS methods (the incorporation and deblocking steps result in a yield that is reasonable for the desired application). This is particularly true given that Illumina has not addressed the teachings of Metzker 1994, detailed in Section F(2)(b), that the allyl capping group was a poor choice for DNA sequencing.

c. **Illumina's Contention That A Small 3'-OH Capping Group Would Have Been "Desirable" Is Unsupported**

Illumina argues a POSA would have been motivated to select Metzker's allyl capping group because it was known that "small 3'-capping groups were

desirable.” See Petition at Heading VI(B)(1)(a). This is wrong for the following reasons:

i. **The most promising capping group in 2000 was not small**

As explained in Section F(2)(d)(i), Illumina has failed to provide any credible explanation for its position that a POSA in 2000 would have known the criticality of selecting a “small” capping group. Unable to find support in the prior art for selecting a “small” capping group, Illumina instead alleges Columbia conceded during prosecution a POSA would know that “small” capping groups were desirable. As explained in that Section, this allegation is based on mischaracterizing the ’358 patent prosecution history. It was and is Columbia’s position that the criticality of using a “small” (less than 3.7Å in diameter) capping group for SBS was not recognized prior to the Columbia inventors’ inventive insights.

ii. **The Board did not address whether a POSA would have been motivated to select a small capping group in IPR2012-00007**

As explained in Section F(2)(d)(ii), and contrary to Illumina’s assertions, the Board in IPR2012-00007 did not determine whether a POSA would have had a *motivation* to select a “small” 3’-OH capping group, and did not address whether a POSA would have had a *reasonable expectation* that a “small” 3’-OH capping group would achieve the claimed invention.

iii. **Dower does not teach that**
“small” capping groups are desirable

Illumina alleges Dower “disclosed the desirability of nucleotides having ‘small blocking groups’ on the 3’-OH.” Petition at 12, 58. Illumina is wrong. Nowhere in Dower does it require the use of small blocking groups for its SBS methods. Nevertheless, to support its contention Illumina relies on a single sentence in Dower: “Examples of . . . these compounds are deoxynucleotide triphosphates with small blocking groups such as acetyl, tBOC, NBOC and NVOC on the 3’OH.” Ex-1015 at 25:48-51.

That Dower uses the term “small” to describe several capping groups does not support a conclusion that Dower teaches that “small” capping groups are “desirable.” Dower does not state that the four capping groups it characterizes as small are desirable because of their size and Illumina does not assert it is obvious to use any of them. Regardless, Dower’s use of “small” when referring to capping groups does not equate to “small” as defined by the ’358 patent (i.e., smaller than 3.7Å in diameter). For example, the NBOC (“2-*nitrobenzyl*oxycarbonyl”; Ex-1015 at 18:54 (emphasis added)) capping group contains “nitrobenzyl,” which as explained above, is not “small” (Ex-1065 at 23, 29).

In addition, as Illumina admitted in 2011 during a reexamination of its own patent, “Dower encompasses broad classes of compounds, perhaps hundreds or

more potential blocking groups.” Ex-2009 at 17. Illumina has not explained why a POSA would ignore the hundreds of capping groups disclosed in Dower, who never disclosed the allyl capping group, and instead use Metzker’s allyl capping group. Illumina also does not explain why a POSA would not have selected Dower’s acetyl capping group (Ex-1015 at 25:50), which is small but expressly excluded in the ’358 patent challenged claim.

**d. Illumina Admitted A POSA
Would Not Select An Ether Capping Group**

As explained in Section F(2)(c)(ii), Illumina has admitted a POSA would *not* have selected an ether capping group (such as the allyl capping group) for use in SBS because the prior art taught ethers were difficult to cleave under DNA compatible conditions. Illumina has not explained how it has met its burden of establishing a POSA would select the allyl capping group given its inconsistent admissions.

In addition, Illumina’s failure to disclose its previous inconsistent positions in its Petition and to provide required discovery is an additional violation of Illumina’s duty of candor and its discovery obligations (37 C.F.R. §42.11(a); 37 C.F.R. §42.51(b)(1)(iii)).

e. **Illumina Has Not Established That
A POSA Would Have Been Motivated
To Use Prober's 5-Substituted Cytosine
In Dower's Methods**

Illumina concedes that Dower does not disclose a 5-substituted cytosine, as required by the challenged claim, but asserts that a POSA reading Dower would have been motivated to use Prober's 5-substituted cytosine. Petition at 71-73. According to Illumina, this is because Dower repeatedly cites to Prober for its disclosure of labeled nucleotide analogues. Petition at 65, 71 (citing Ex-1015 at 23:16-26, 25:4-12, 25:44-47). However, the Board previously considered these disclosures in Dower and found that "Illumina did not identify a teaching in Dower where Dower describes using Prober [] to modify Dower's nucleotides[.]" Ex-1007 at 14.

Specifically, the Board found that Dower (a) at 23:18-24, refers to Prober only to describe the four distinct dyes used to label the ddNTPs (Ex-1007 at 14-15); (b) at 25:4-10, refers to Prober only for the conditions used to accomplish the polymerase reaction and not for using the analogues themselves (Ex-1007 at 15); and (c) at 25:41-64, does not teach using Prober's bases in a nucleotide with a reversible 3'-OH group (Ex-1007 at 15).¹⁴ Therefore, Dower does not repeatedly

¹⁴ Illumina also cites Dower at 20:39-42, which refers to Prober for the description of labels, similarly to 23:18-24; Illumina also cites 17:35-36 and 28:6-17 which

cite Prober for labeled nucleotide analogues, and Illumina has not explained how a POSA would have been motivated to use Prober's cytosine with an uncleavable acetylenic linker on its 5-position to make a nucleotide analogue for Dower's methods given the Board's previous findings.

Illumina seeks to disturb the Board's previous findings by arguing they are not binding because they related to a determination on the issue of incorporation by reference rather than obviousness. Petition at 71-72. Illumina's argument should be rejected and the Board's previous factual findings adopted. The Board's prior findings undermine Illumina's assertions that Dower cites to Prober for its disclosure of labeled nucleotide analogues (Petition at 65, 71-72) and are inconsistent with Illumina's assertions that a POSA would be motivated to use Prober's cytosine with an uncleavable linker on its 5-position to modify a nucleotide analogue for use in Dower's SBS methods.

Further, Illumina cites to Exs-1029 and 1031 as disclosing that linking labels to the 5-position of cytosine was advantageous. Petition at 72. However, the chemical linker in each of these references is uncleavable. *See* Ex-1029 at 27:52-

refer to Prober for the description of polymerase reaction conditions similarly to 25:4-10.

65 (using acetylenic linker); Ex-1031 at 3049 (reporting results from Froehler 1992 (Ex-2046), which used an acetylenic linker).

Thus, Illumina has failed to meet its burden of establishing a POSA would have been motivated to select the allyl capping group and a 5-substituted cytosine nucleotide analogue with a chemically cleavable, chemical linker for connecting a detectable fluorescent moiety.

**3. Illumina Has Not Established
A Reasonable Expectation of Success**

Illumina has not met its burden of showing a POSA would have had a reasonable expectation the 3'-*O*-allyl nucleotide analogue would meet the limitations of the challenged claim. As discussed in Section F(3), Illumina's failure is evidenced by: (1) Metzker's teaching that the allyl capping group "interfere[d] with recognition of the analogue as a substrate by a DNA polymerase," and (2) Illumina's admissions regarding a POSA's expectation that the allyl capping group would not be "chemically cleavable" because ether capping groups (e.g., the 3'-*O*-allyl) were expected to be difficult to cleave under conditions compatible with SBS.

As explained in Section F(3), to the extent that Illumina argues that a 3'-*O*-allyl capped nucleotide analogue with a label attached to the 5-position of the base by a cleavable linker somehow provides a greater expectation of success as

compared to a 3'-*O*-allyl capped nucleotide analogue without a base label, Illumina is wrong. Each of the above points applies regardless of whether the label is attached to the base.

Therefore, Illumina has failed to meet its burden of establishing a POSA would have had a reasonable expectation of success in achieving what is claimed in the challenged claim.

In summary, Illumina failed to meet its burden of establishing a reasonable likelihood the challenged claim is unpatentable under Ground 2.

H. Neither Patent Owner Estoppel Nor Judicial Estoppel Applies

Illumina asserts Columbia “clearly violate[d] the patent owner estoppel provisions of 37 C.F.R. §42.73(d)(3)(i)[,]” should be barred from participating in the present proceedings, and the challenged claim should be canceled. Petition at 2-3, 7. As an initial matter, Illumina cites no authority for its argument that Patent Owner Estoppel can be a basis for instituting an IPR.

In any event, Illumina’s assertion that Columbia violated the Patent Owner Estoppel provisions of 37 C.F.R. §42.73(d)(3)(i) is wrong. As explained in Section B, the challenged claim was specifically drafted to be narrower than the claims previously found unpatentable. Patent Owner Estoppel does not apply because it only concerns a party obtaining claims that are “not patentably distinct” from

canceled claims. 37 C.F.R. §42.73(d)(3)(i). Here, the challenged claim *is* patentably distinct from the claims at issue in the earlier Columbia Patent IPRs.

Illumina asserts that the Examiner rejected the challenged claim as not patentably distinct over claims 17 and 28 of the '869 patent, which were canceled in the earlier Columbia Patent IPRs. Petition at 4-5, 7. This assertion is also wrong. The Examiner's double patenting rejection referenced **17** different claims (Ex-1065 at 100), 15 of which were not canceled in the earlier IPRs. The Examiner's rejection was not based on *any individual claim*, let alone claim 17 or 28. For example, the Examiner's rejection stated that "[t]he '869 patent claims a deoxyribonucleotide triphosphate wherein the base is a pyrimidine, the 3'-OH capping group is MOM or allyl, containing a detectable fluorophore label attached through a cleavable linker (claims 1-10, 17-19)." *Id.* The limitations MOM and allyl are in claims 18 and 19, neither of which were found unpatentable in the earlier IPRs. *See* Ex-2002 at claims 18, 19.

In addition, contrary to Illumina's allegations, Columbia's filing of a terminal disclaimer during prosecution to overcome the Examiner's nonstatutory double patenting rejection was not improper, and does not give rise to estoppel under 37 C.F.R. §42.73(d)(3)(i). Illumina failed to cite any legal authority to support its position and failed to acknowledge (let alone distinguish) the Manual of Patent Examining Procedure provision that is directly on point:

The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is ***not an admission*** of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991). In *Quad Environmental Technologies*, the court indicated that the “filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and ***raises neither a presumption nor estoppel on the merits of the rejection.***”

M.P.E.P. §804.02 (emphasis added); *see also Tristar Products, Inc. v. Choon’s Design, LLC*, IPR2015-01883, Paper 6, 7-8, n.1 (March 9, 2016) (rejecting argument that filing a terminal disclaimer to overcome a nonstatutory double patenting rejection is somehow improper).¹⁵

Illumina also raises a Judicial Estoppel argument (Petition at 5-6), which makes no sense and, importantly, is premised on a mischaracterization of the prosecution history. Illumina claims that Columbia overcame a lack of written description rejection by asserting the challenged claim “is supported because it covers the ***same*** subject matter as the previously issued claims” cited in the

¹⁵ Columbia noted during prosecution that it was filing a terminal disclaimer “without conceding the correctness of these rejections[.]” Ex-1065 at 24.

Examiner’s obviousness-type double patenting rejection. *Id.* at 5 (emphasis added). Illumina then concludes that Columbia “embrac[ed] the Examiner’s patentably indistinct finding to establish written description” and judicial estoppel prevents Columbia from arguing that the claims are distinct. *Id.* But Columbia never said that the challenged claim covers the *same* subject matter as the canceled claims. In fact, Columbia made clear that the challenged claim is narrower than the canceled claims: “The invention was ready for patenting as evidenced by the grant of *broad*er claims in related patents[.]” Ex-1065 at 21 (emphasis added). Therefore, Illumina’s judicial estoppel allegation is based on a false premise and cannot be sustained.

I. Conclusion

For the foregoing reasons, the Board should deny Illumina’s Petition.¹⁶

¹⁶ The United States Supreme Court is currently considering the constitutionality of *inter partes* review in *Oil States Energy Servs., LLC v. Greene’s Energy Grp., LLC*, No. 16-712 (U.S. 2017). While Columbia believes this Petition should be denied for the reasons above, Columbia reserves the right to make arguments concerning the effect of *Oil States* on this proceeding once that case is decided.

CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE**, exclusive of the parts exempted as provided in 37 C.F.R. § 42.24(a), contains 13,868 words and therefore complies with the type-volume limitations of 37 C.F.R. § 42.24(b)(1).

Respectfully submitted,

Dated: April 9, 2018

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CERTIFICATE OF SERVICE

I hereby certify that a computer disk containing a true and correct copy of the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE** and **EXHIBITS 2002-2004, 2006-2043, 2045-2046** is being served on April 9, 2018, via Federal Express overnight mail to Counsel for Petitioner at:

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