

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.

IPR2018-00291 (Patent 9,718,852)
IPR2018-00318 (Patent 9,719,139)
IPR2018-00322 (Patent 9,708,358)
IPR2018-00385 (Patent 9,725,480)¹

PATENT OWNER'S SUR-REPLY

¹ An identical Paper is being entered into each listed proceeding.

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I. Introduction

The Board encouraged the parties to brief certain issues. In response, Columbia explained in detail why there was no motivation to select the $\text{-CH}_2\text{-CH=CH}_2$ group (“the allyl capping group”), as covered by the challenged claim, and no expectation it would work for the claimed invention, citing prior art, Drs. Menchen’s and Romesberg’s testimony, Illumina’s prior admissions, and other evidence.

Illumina’s Reply ignores Columbia’s evidence and belatedly presents new theories—*e.g.*, asserting the admittedly unworkable cleavage conditions cited in the Petition could be modified, and Metzker’s failed 3’-O-allyl nucleotide could work at higher concentrations. Even if considered, Illumina’s new theories fail. There is no evidence Illumina’s new speculative cleavage conditions are SBS-compatible, *i.e.*, mild, aqueous conditions resulting in rapid, quantitative cleavage of allyl ethers. Therefore, a POSA had no motivation to use them in Tsien’s (Ground 1) and Dower’s (Ground 2) SBS methods. Similarly, a POSA would not be motivated to rehabilitate Metzker’s failed 3’-O-allyl nucleotide, and Illumina provided no evidence that a nucleotide incapable of achieving efficient termination at Metzker’s 50,000-fold excess concentration could do so if an even greater excess were used. Illumina conceded elsewhere that using high concentrations

results in loss of fidelity, *i.e.*, accuracy of incorporation, negating its utility for SBS.

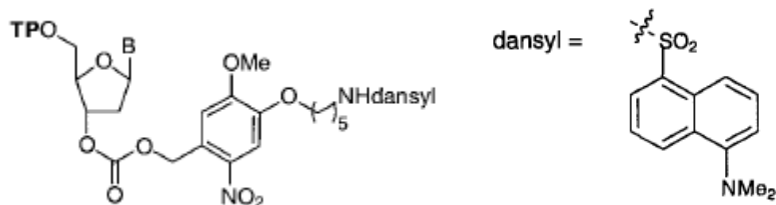
Facing these problems, Illumina spends much of its Reply declaring that if Columbia's inventions are non-obvious, then they are invalid for lack of "written description, enablement, and utility[.]" Illumina's irrelevant non-§103 arguments fail because they misstate the law, the prior art, and the patent's disclosures.

II. Illumina's Non-§103 Arguments Are Flawed And Irrelevant

Illumina tries to shift the focus away from its flawed §103 arguments by declaring that Columbia's patents have §§112 and 101 problems. Reply, 1-2.² However, these non-§103 issues are irrelevant in *inter partes* review proceedings under 35 U.S.C. § 311(b), and are based on a flawed premise that Columbia's patents contain "the same disclosure[s]" as Tsien. Reply, 1-2. To the contrary, prior to Columbia's invention, it was mistakenly *accepted as fact* that polymerases incorporated 3'-capping groups as large as 2-nitrobenzyl. Response, 46; Ex. 1016, 4259; Ex. 2131, 814-17; Ex. 2041, 198; Ex. 1019, 9:57-10:14; Ex. 2013, 13; Ex. 2014, 170. With that understanding, "a large number of companies and research groups" (Ex. 1119, ¶10) spent years unsuccessfully pursuing SBS-compatible

² Unless otherwise indicated, all Paper page citations are to IPR2018-00291.

nucleotides, unaware of the features required for success, and routinely testing nucleotides with **bulky** 3'-capping groups, *e.g.*:



Ex. 2041, 198. The Columbia inventors had the insight to appreciate the criticality of using small capping groups, *i.e.*, capping groups less than 3.7Å (Response, 9-10) in diameter.

During prosecution, Columbia explained this to the Examiner (Exs. 1009, 1062, 1065 at 22-24; Ex. 1068, 18-20), resulting in withdrawal of a §103 rejection over Tsien/Prober.³ Columbia's claimed invention combines that insight with other features identified by the inventors (*e.g.*, use no ketone, ester, or methoxy for the capping group), and identifies -CH₂-CH=CH₂ as a preferred capping group.⁴ This invention, which fundamentally changed the understanding of SBS, is disclosed in the patent-at-issue and allows the claims to be practiced without undue

³ Citations to Exs. 1009, 1062, 1065 and 1068 are only applicable to IPR2018-00291, -00318, -00322 and -00385, respectively.

⁴ The prior IPR patents involved broader claims. Response, 62-66.

experimentation. *E.g.*, Ex. 1001, Fig 1, 2:47-3:26, 3:31-3:41, 5:51-59, 8:24-27, 21:20-36, 22:14-22, claim 1; *see also* Exs. 1002-1004.

Contrary to Illumina's premise, Tsien does not contain the same disclosures. Tsien suggests using large 3'-capping groups (*e.g.*, 2-nitrobenzyl, 2,4-dinitrobenzene-sulphenyl), putting bulky labels on those groups, and using groups containing ketones, esters, and/or methoxy. Ex. 1013, 21. Unlike the patent-at-issue, a POSA reading Tsien would find no guidance that would lead to a useable nucleotide.

Illumina's non-§103 arguments concerning the Columbia patent's cleavage disclosures similarly fail. Reply, 2. The pertinent issue in these proceedings is whether Illumina's *four Petition-cited references* (Tsien, Kamal, Boss, Qian) teach DNA-compatible conditions. As explained herein, Illumina and Dr. Romesberg concede *they do not*. Whether a POSA reading the patent-at-issue and prior art could formulate SBS-compatible conditions without undue experimentation is not at issue. Illumina's criticism of Columbia's patents is hypocritical. During an IPR, Illumina argued its claims were non-obvious because the Petitioner ("IBS") failed to identify SBS-compatible conditions in the prior art. Ex. 2008, 7 (Illumina claiming it discovered azidomethyl "*was surprisingly cleaved*" under SBS-compatible conditions, and that "[t]hese properties were not

known at the time the '537 Patent was filed").⁵ Yet, Illumina concedes its patent covering 3'-O-azidomethyl nucleotides (Ex. 2028, U.S. 7,566,537) provides no cleavage conditions. Ex. 2032, 49:25-50:17. Illumina cannot have it both ways.

III. Claim Construction

As explained in Columbia's Response, the Board should construe the terms "small" and "chemical linker." Response, 9-10.

IV. Illumina's Grounds Fail Because There Was No Motivation To Use The Allyl Capping Group For SBS

Illumina's Grounds rise or fall with its argument that the prior art would lead a POSA to select the allyl capping group for use in SBS. As explained below and in Columbia's Response, Illumina failed to meet its burden.

A. Real-World Evidence Shows No Motivation

Prior to 2000, many research groups pursued SBS-compatible nucleotides. Ex. 1119, ¶11. Despite this effort, *none* reported interest in the allyl capping group for SBS after Metzker 1994. Response, 23.

Illumina's Reply argues that other groups (Hiatt, Dr. Menchen) suggested using the allyl capping group, but those references *do not concern* SBS.⁶ Reply, 6-7. Hiatt teaches nucleic acid *synthesis* (Ex. 1106, Abstract), which does not relate

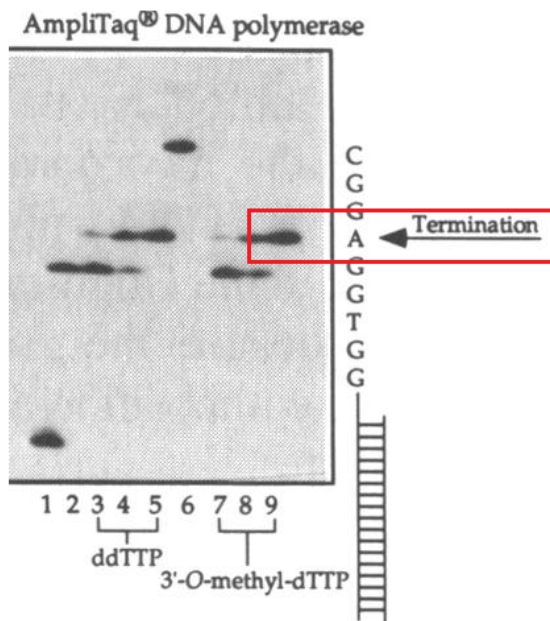
⁵ Emphases added throughout.

⁶ Illumina also cites to two Solexa patents, as discussed in Section IX, below.

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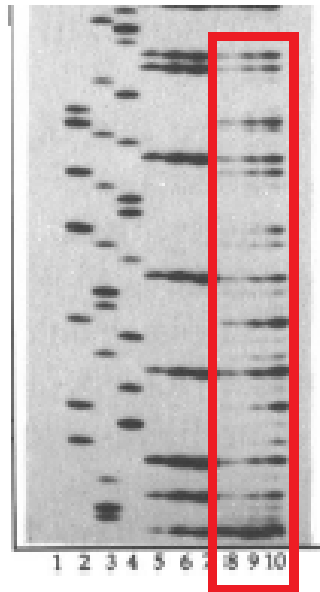
to *DNA sequencing*. Ex. 2140, 73:24-25 (Hiatt uses template-*independent* polymerase), 76:4-11 (SBS (Tsien, Dower) uses template-*directed* polymerase).

Dr. Menchen's patents relate to Sanger sequencing ("Sanger"), not SBS, which does not have SBS's stringent requirements. Ex. 1112, 81:18-20, 154:22-155:4; *see* Exs. 1091, 1092. Dr. Romesberg concedes that Sanger and SBS have fundamentally different termination efficiency requirements. Ex. 2140, 146:3-147:9, 148:11-149:17. While both methods synthesize many DNA strands, for SBS, the synthesis of *all* strands terminates upon the first encounter of a complementary template-base, as shown:



Ex. 1016, 4265 (box added). Achieving this result *requires* 3'-O-capped nucleotides capable of near-100% termination. Ex. 2140, 149:13-17; Ex. 1013, 16:21-30 (disparaging 98% termination for SBS).

In stark contrast, as Dr. Romesberg concedes (Ex. 2140, 146:3-147:24), Sanger *requires* 3'-O-capped nucleotides (or ddNTPs) with *low* termination rates (e.g., 0.8%), so that only *a fraction* of the strands terminate each time a complementary template-base is encountered, and the remaining strands continue to extend, creating a “ladder” (Ex. 2140, 148:11-149:17), as shown:



Ex. 1016, 4265 (box added). Given these fundamental differences, a suggestion regarding a capping group's utility for Sanger (irreversible capping group with low termination requirement) says nothing about its usefulness for SBS (reversible capping group with near-100% termination requirement). Thus, Illumina's citations to Sanger art (including Dr. Menchen's patents) lack relevance.

Contrary to Illumina's claim, Dr. Menchen did not include “allyloxy” (a genus (Ex. 1112, 45:3-46:6)) in his patents “precisely because of Metzker's

disclosure.” Reply, 1; Ex. 1112, 164:9-16 (“I don’t remember correlating the Metzker article with what we wrote here [regarding allyloxy.]”). Illumina’s citations do not show otherwise. Asked about identifying “allyl groups” and “suitable modifiers,” Dr. Menchen said only that Metzker referenced $-\text{CH}_2-\text{CH}=\text{CH}_2$ (“propenyl”) when discussing allyl in his 1994 paper. Ex. 1112, 189:5-13. Dr. Menchen’s response pertains to allyl *nomenclature* (“He calls it allyl in the [1994] paper,” *Id.*), not suitability, and he consistently testified that Metzker teaches the allyl capping group lacks suitability for SBS. *E.g.*, Ex. 1112, 289:11-290:10.

B. Tsien Provides No Motivation

Ground 1 relies on Tsien “disclos[ing] that the allyl group is advantageous because it is ‘cleaved selectively using chemical procedures other than base hydrolysis ... [which has] some advantages over groups cleavable by base hydrolysis[.]’” Petition, 21. But Illumina now admits that Gigg teaches “allyl ether *is* cleavable by base hydrolysis” (Reply, 19), and its belated theory that Tsien additionally teaches non-base hydrolysis cleavage is belied by the fact that Tsien only cites Gigg for allyl ether cleavage conditions. Therefore, Ground 1 fails.

C. Metzker 1994 Provides No Motivation

Contrary to its Reply, Illumina failed to show that Metzker 1994 provides a motivation to select the allyl capping group for SBS.

1. Illumina's position is at odds with Metzker

Illumina does not dispute that Metzker abandoned the allyl capping group. Illumina instead alleges that the existence of “better alternatives” does not establish non-obviousness. That argument avoids the issue. Metzker abandoned the allyl capping group not because of better alternatives but because it was a “*poor substrate[]*” with “*limited activity*” that was “*not efficiently incorporated.*” Response, 22.

Illumina offers no convincing explanation for Metzker's statements. Rejecting its own expert's analysis (*see* Response, 24-25), Illumina belatedly theorizes that Metzker's Termination* taught one thing in 2000 (“highly efficient” (Reply, 10)) and the opposite in 2007 and 2011 (“poor substrate” and “not efficiently incorporated”) (Reply, 15-16). On this point, Illumina argues that SBS requirements changed after 2000 so that a substrate recognized as poorly incorporated after 2000 would be considered highly efficient before 2000. Reply, 15-16. This allegation fails: standards for SBS were always high, *e.g.*, Tsien in 1991 disparaged incorporation rates of **98%**. Ex. 1013, 16:21-30; Ex. 2013, 2-3 (“any inefficiencies of incorporation” “plague[]” SBS); Ex. 1113, 369:21-370:6.

The facts are clear. Metzker's 1994 experiments showed the 3'-O-allyl-dATP exhibited inefficient incorporation; his 1994 publication identified that finding as Termination* and he abandoned the allyl capping group (as did others in

the SBS field); later reaffirming what he previously reported, that the 3'-O-allyl-dATP was a poor substrate with limited activity that was inefficiently incorporated.

2. Termination* indicates inefficient incorporation

Illumina incorrectly alleges that Metzker's Termination* result provided motivation to select the allyl capping group for SBS. To the contrary, a POSA understood that Termination* indicated inefficient incorporation. Response, 18-21. Dr. Menchen agrees, Metzker himself agrees, and Dr. Romesberg has agreed. Ex. 2116, ¶31; Ex. 1017, 6348; Ex. 2025, 10; Ex. 2126, 128:20-21; Ex. 1119, ¶74 (arguing modifications to Termination* reaction "*could also result in* its being efficiently incorporated and able to sufficiently terminate DNA extension.").

Yet, Illumina now speculates, without support, that Termination* just indicates contamination. Reply, 9-10. But a POSA understood that Metzker's "trace" contamination had no meaningful effect on his conclusions. Response, 23-28. Nor is Columbia's position "contradicted" by Metzker 1998's teaching that contamination results in "decreased signal intensities." Reply, 10. Columbia's Response explained that, while contamination reduces "signal intensity," it does not prevent efficiency determinations. Response, 18 n.11, 26-27. The presence of an efficiency test band indicates incomplete termination due to inefficient incorporation, regardless of contamination. Response, 18-21, 23-28.

Illumina calls the efficiency test band “hypothetical,” with “no basis in reality.” Reply, 11. That criticism fails. First, Metzker 1994 and Metzker 1998 both show the band. Response, 20; Ex. 2131, Fig. 3. Second, Dr. Romesberg relies on that band himself, which he calls an “n-1 band,” to gauge incorporation rates. Ex. 1119, ¶87; Ex. 2140, 99:4-13. Third, Dr. Romesberg concedes that inefficient incorporation in Metzker’s experiments could appear as Dr. Menchen explained (except in two extreme exceptions). Ex. 2140, 127:1-128:24.

Unable to meaningfully dispute Dr. Menchen’s analysis, Illumina resorts to questioning his qualifications, despite evidence of his extensive expertise. Ex. 2116, ¶¶3-6 (30 years in DNA sequencing technology, including SBS; around 100 patents mostly related to the same); Ex. 2066. For decades, Dr. Menchen has been involved in designing labeled nucleotides as both irreversible and reversible polymerase terminators. Ex. 2066; Ex. 1112, 218:19-21, 37:12-39:14 (even discussing Metzker’s 1994 work with Metzker himself).

Illumina’s remaining arguments similarly fail. First, Metzker 1998 does not disprove the efficiency test band. Metzker 1998 shows the band at 5 μ M, and Dr. Romesberg agrees this result showed incomplete termination.⁷ Ex. 1119, ¶87. Second, Illumina argues that *Pfu*(exo-) can efficiently incorporate ddNTPs, and

⁷ Lane B for 25-50 μ M show “trace” artifact bands. Ex. 1113, 430:20-431:21.

therefore Metzker's report of incomplete termination with *Pfu*(exo-) cannot indicate inefficient incorporation. Reply, 10-11. But Illumina acknowledges that *Pfu*(exo-) requires high concentrations (450 μ M (Ex. 1119, ¶70; Ex. 1108, 2, 6)), which is why Metzker abandoned it. Ex. 1016, 4263. Third, Illumina alleges Dr. Menchen's explanation for Termination* actually describes "Inhibition." Reply, 13-14. But Metzker defines "Inhibition" as showing something else, *i.e.*, no incorporation, which results in no bands. Ex. 1016, 4263 ("[T]he test compound prevented the polymerase from incorporating the natural nucleotides.").

3. Illumina's concentration theory fails

Recognizing the flaws in its Termination* arguments, Illumina belatedly and improperly argues a POSA would be motivated to salvage Metzker's failed 3'-O-allyl-dATP using high concentrations.

First, there was no motivation to focus on the unworkable 3'-O-allyl-dATP. A POSA seeking to practice Tsien's or Dower's SBS methods, upon reading Metzker, "would be discouraged from" selecting the allyl capping group for SBS, and "would be led in a direction divergent," *i.e.*, to the 2-nitrobenzyl. *Millennium Pharms., Inc. v. Sandoz*, 862 F.3d 1356, 1366-67 (Fed. Cir. 2017).

Second, there would be no motivation to raise concentrations. A POSA would know that "inefficient termination" "describes a property" of a nucleotide. Ex. 2140, 128:5-13. A nucleotide that cannot efficiently terminate synthesis is

“not a good substrate,” meaning “[i]t is not recognized well” by the polymerase. Ex. 2082, 66:17-67:9; Ex. 2126, 74:5-75:9. Attempting to “force” incorporation with high concentrations does not remedy this deficiency; it reaffirms that the nucleotide may not be a “very efficient chain terminator[.]” Ex. 2031, 3; Ex. 2081, ¶17. Dr. Romesberg admits that a POSA “would want an analog ... of sufficient efficiency ... that is ... sufficient enough to be used *at the lowest possible concentration.*” Ex. 2140, 160:20-161:5.

Moreover, as conceded by Dr. Romesberg, a POSA understood that increasing concentration results in increased misincorporation rates in SBS. Ex. 2081, 15 (“Polymerases lose the ability to accurately replicate a DNA strand at high nucleotide concentrations”); Ex. 2140, 173:2-6 (“mutation rates increase with a function of increasing concentration”), 178:19-24. As such, a POSA “would have been dissuaded from using” nucleotides requiring high concentrations for SBS. Ex. 2081, ¶17. Dr. Romesberg conceded that a POSA would recognize that SBS *requires* “moderate to low concentrations” (Ex. 2081, ¶17), with “200 micromolar” being “certainly not in the low range” and “probably in the moderate range” (Ex. 2126, 100-102), *i.e.*, it falls near the border of moderate to high. That conforms with data previously cited by Dr. Romesberg showing a 40-fold increase in mutation rates (due to misincorporation) at 202 μ M. Ex. 2140, 166:25-169:13. Metzker’s 3’-O-allyl-dATP inefficiently incorporated at an *even higher*

concentration, **250 μ M**. Ex. 1016, Table 2; Ex. 1017, 6348 (characterizing 1994 3'-O-allyl-dATP experiments as “high micromolar concentrations”). A POSA practicing SBS understood the need to use nucleotide concentrations “that did not cause loss in fidelity” (Ex. 2140, 178:19-24, 176:20-22), and would not be motivated to increase concentrations above Metzker’s already high 250 μ M for SBS.

Notably, Illumina’s belated suggestion that a POSA would increase concentrations to “1 mM,” “5 mM,” and “10 mM” contradicts its prior position that “1 mM” was *too high* to be useful for SBS. *Compare* Reply, 17, 22, and Ex. 1119, ¶¶75, 91, 97 (suggesting increases up to “10 mM”) *with* Ex. 2081, ¶17 (dissuading “1 mM” for SBS), Ex. 2082, 74:16-19 (“1 millimolar concentration will result in significant misincorporation[.]”).

Illumina builds its increasing-concentration theory on a mischaracterization, claiming that Metzker “instruct[s]” and “teach[es] to increase the concentration of 3'-O-modified-dNTP to enhance incorporation efficiency.” Reply, 16-17 (citing “Ex. 1016, 4266 (‘problems could be resolved by increasing the concentration’)”). Metzker has no such teaching. The “problem” Metzker referenced is “reduced enzyme fidelity” with 3'-O-methyl-thymine, not inefficient incorporation. Ex. 1016, 4266. Fidelity means *accuracy* of incorporation (Ex. 2082, 26:6-27:9; Ex. 1012, ¶91), a different concept than *efficiency* of incorporation. And Metzker’s

“resol[ution]” to this different problem is to “increase the concentration of *dATP*[.]” *i.e.*, the *natural* adenine, not the 3’-O-modified nucleotide. Ex. 1016, 4266. Metzker does not teach what Illumina asserts.

Moreover, 250 μ M was the maximum concentration in Metzker’s screening assays, and Metzker abandoned compounds incapable of demonstrating Termination at that concentration. Ex. 1016, Table 2, 4263-67. Metzker also used 250 μ M for his SBS (“BASS”) experiment. Ex. 1016, 4266 (Figure 5B, text). Higher concentrations were only used for assays (M13mp19) and compounds (3’-O-methyl-dNTPs) related to Sanger. Ex. 1016, Abstract (3’-O-methyl-dNTP testing done for Sanger), 4266 (M13mp19 is Sanger). As explained above, Sanger and SBS are fundamentally different, and the concentrations for Sanger says nothing about SBS, which Dr. Romesberg conceded requires “moderate to low concentrations[.]”

Nor does Tsien’s statement regarding “substantial excesses (over stoichiometry) of the dNTP’s” suggest raising concentrations above 250 μ M. Reply, 16. Metzker’s 3’-O-allyl experiments used dNTPs at **50,000-fold** concentration excess. Ex. 2140, 94:10-15. Illumina provided no evidence that a 50,000-fold excess is not “substantial,” or that increasing beyond a 50,000-fold excess would result in increased 3’-O-allyl-dATP incorporation. Nor did Dr. Menchen “admit[] that simply increasing the concentration” increases efficiency.

Reply, 13. He testified the opposite, “I don’t think you can assume that,” explaining that increasing concentration only increases incorporation “[s]ometimes if it’s not saturated,” and that “it is well known in the literature” that doing so results in “bad things” happening such as “misincorporation[s.]” Ex. 1112, 205:6-17, 206:23-209:13.

Third, Dr. Romesberg argues a POSA was “motivated to screen related polymerases” for improved termination activity (Ex. 1119, ¶ 81), but he admits that the POSA “would not have known” whether other polymerases would incorporate 3’-O-allyl-dATP (*e.g.*, Ex. 2140, 130:8-22, 134:5-14). While referring to several modified polymerases, he conceded that his evidence does not show those polymerases being tested with *any* 3’-O-capped nucleotides. Ex. 2140, 128:25-130:24, 134:1-136:23, 152:8-25. Even if a POSA were motivated to conduct additional screening tests, that says nothing about whether there was a motivation to use the 3’-O-allyl-dATP in Tsien’s and Dower’s methods.

At bottom, the fact that nobody tried to rehabilitate Metzker’s 3’-O-allyl-dATP for six years (1994-2000) despite great interest in SBS shows that Illumina “resort[s] to hindsight[.]” *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013).

**D. Illumina Failed To Demonstrate
SBS-Compatible Cleavage Conditions**

Columbia explained that Illumina's Petition-cited references (Tsien, Kamal, Qian, Boss) do not teach SBS-compatible conditions. Response, 31-44. Illumina *does not* claim otherwise in its Reply. Illumina's silence defeats the Petition.

Illumina spends little time addressing whether Tsien, Kamal, Qian, and Boss provide SBS-compatible conditions, and the points it makes are easily dismissed. For example, Illumina says "Tsien provides an appropriate level of disclosure for allyl ether cleavage" (Reply, 19) but both experts agree that Tsien's only conditions ("Hg(II) in acetone/water") are incompatible with SBS. Response, 32-33. Illumina notes that Boss "discloses using p-toluenesulfonic acid" (Reply, 20) but Dr. Romesberg conceded this is a strong acid (Ex. 2140, 182:3-13), and its only documented use resulted in 84% cleavage (Ex. 1035, Table 1), which Dr. Romesberg conceded was SBS-incompatible. Ex. 2126, 86:19-87:7. Illumina says, "Columbia relies on Kamal" in its patent (Reply, 19), but the patent does not rely on Kamal for disclosure of SBS-compatible conditions, and Illumina and Dr. Romesberg agree Kamal's conditions are SBS-incompatible. Response, 34-37. Regarding Qian, Illumina says Dr. Menchen "conceded" that Wacker requires copper (Reply, 21), but Dr. Menchen testified that the reaction would occur without copper until palladium depletion. Ex. 1112, 184:9-17.

Abandoning its Petition-cited conditions, Illumina now cites numerous new references to argue that Qian's non-aqueous conditions could be *modified* to be aqueous. Reply, 20-21. This new theory is improper, as *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) makes clear. There, the petitioner ("IBS") argued Zavgorodny taught cleavage conditions for a 3'-O-azidomethyl nucleotide, Illumina's Response showed those conditions were not SBS-compatible, and IBS's Reply newly argued that other conditions could be used to modify Zavgorodny. 821 F.3d at 1369-70. At the Oral Hearing, Illumina argued "they are limited to the conditions in the petition" (Ex. 2032, 46), and the Federal Circuit agreed. 821 F.3d at 1369-70.

Illumina's new argument also fails on the merits. First, Illumina's new references relate to allyl esters, carbonates, and carbamates, *not* allyl ethers, and Illumina's Reply provides no prior art evidence of the applicability of those conditions to allyl ethers. Ex. 2140, 184:10-185:6, 186:13-187:7, 188:16-189:10; Exs. 1094, 1114, 1115. Second, even if a POSA would try to use those non-ether cleavage conditions, Illumina has not suggested, let alone shown, that the POSA would believe they would be SBS-compatible (*i.e.*, all of aqueous, mild, rapid, quantitative). The evidence shows there would be no such expectation. Ex. 2116, ¶75 (no expectation modified Qian conditions would be SBS-compatible). Third, Illumina's claim that "it would have been a matter of routine experimentation to

conduct Qian's cleavage under aqueous conditions" (Reply, 20) presupposes incorrectly that a POSA would have been motivated to rehabilitate Metzker's 3'-O-allyl-dATP, which for the reasons explained herein and in Columbia's Response, they would not have.

E. Illumina's Reliance On Pelletier Is Hindsight-driven

Illumina argues a POSA would review Pelletier. Illumina is wrong, because Pelletier's polymerase "wouldn't be ever considered for SBS sequencing or any sequencing." Ex. 1112, 267:6-268:20. "[H]igh fidelity [is] necessary for accurate sequencing" (Ex. 1029, 11:4-10), and the "fidelity" of Pelletier's polymerase is "the most error prone eukaryotic polymerase studied to date." (Ex. 1021, 1892, 1902 n.22). Even if a POSA reviewed Pelletier, Illumina failed to explain how the POSA would arrive at the inventors' insight, particularly when it went against years of conventional wisdom (*i.e.*, that 2-nitrobenzyl was incorporated). In fact, when other SBS investigators looked at polymerase crystal structures, even as late as 1999, they concluded that SBS required creation of new polymerases. Ex. 1023, 951, 960. Thus, Illumina's hindsight argument fails.

V. Illumina's Grounds Fail Because Its References Do Not Disclose Claim Elements

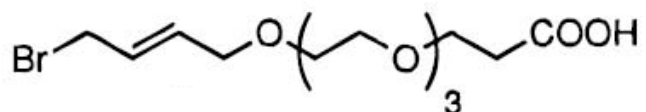
A. Tsien Does Not Describe The Claimed Allyl Capping Group

Ground 1 alleges Tsien describes the allyl capping group. At most, Tsien discloses a genus, allyl ethers, not the specific $-\text{CH}_2\text{-CH=CH}_2$ claimed.⁸ Illumina's Reply, however, waivers between trying to limit Tsien's disclosure to a species and implicitly acknowledging the genus problem.

Tsien refers to "allyl ethers" twice, once for deblocking capping groups and once as linkers (called "tethers"). Ex. 1013, 24, 28. Tsien cites Gigg for deblocking and Dr. Romesberg concedes that Gigg teaches a genus of allyl ethers. Ex. 2126, 212:18-214:13 ("[T]hroughout Gigg ... there are disclosures of allyl ethers that are both unsubstituted and substituted" and "allyl ethers other than a three carbon allyl ether[.]"). As linkers, Tsien's "allyl ethers" undisputedly refers to a genus of groups that can include allyl groups but does not describe the 3-carbon allyl capping group of the challenged claim. Ex. 2140, 41:22-42:14 (Tsien's allyl ethers is "a group of linkers," each of which "should have an allyl group in it"), 34:4-35:2, 39:16-40:24. Dr. Romesberg concedes that the structure

⁸ A POSA reading Gigg would question whether Tsien meant to refer to vinyl ethers. Response, 53-54.

below is an allyl ether linker, which contains an allyl group but not the 3-carbon allyl group ($-\text{CH}_2-\text{CH}=\text{CH}_2$) covered by the challenged claim:



Ex. 1078, ¶135; Ex. 2140, 39:16-39:25. Dr. Romesberg also concedes that scientists “common[ly]” use “allyl ethers” to refer to a genus (Ex. 2113 at 127:6-17, 130:1-25), a fact confirmed by the prior art. Response, 53.

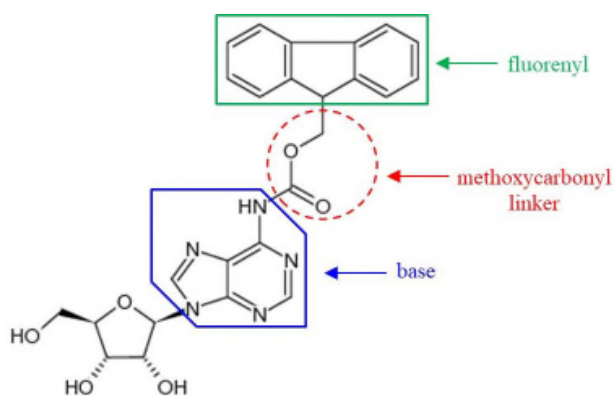
Ignoring Columbia’s evidence, Illumina belatedly cites new references where $-\text{CH}_2-\text{CH}=\text{CH}_2$ is called allyl. Reply, 4-6. This misses the point. Tsien only discloses a genus, and Illumina’s evidence merely shows that one undescribed species of the genus, $-\text{CH}_2-\text{CH}=\text{CH}_2$, can be referred to as allyl. Illumina also claims that the Patent Office “has consistently found that Tsien discloses the 3’-O-allyl capping group.” *Id.* But whether disclosure of “allyl ethers” is a genus or the specific $-\text{CH}_2-\text{CH}=\text{CH}_2$ species has not previously been before the Patent Office. *E.g.*, Ex. 1095, 26.

Ultimately, Illumina appears to concede that Tsien’s “allyl ethers” *is* a genus, characterizing “[t]he 3-carbon allyl ether” as “the simplest allylic ether” and “the most commonly used allylic ether[.]” Reply, 5-6. With that acknowledgement, Illumina attempts to salvage its Petition, newly theorizing that

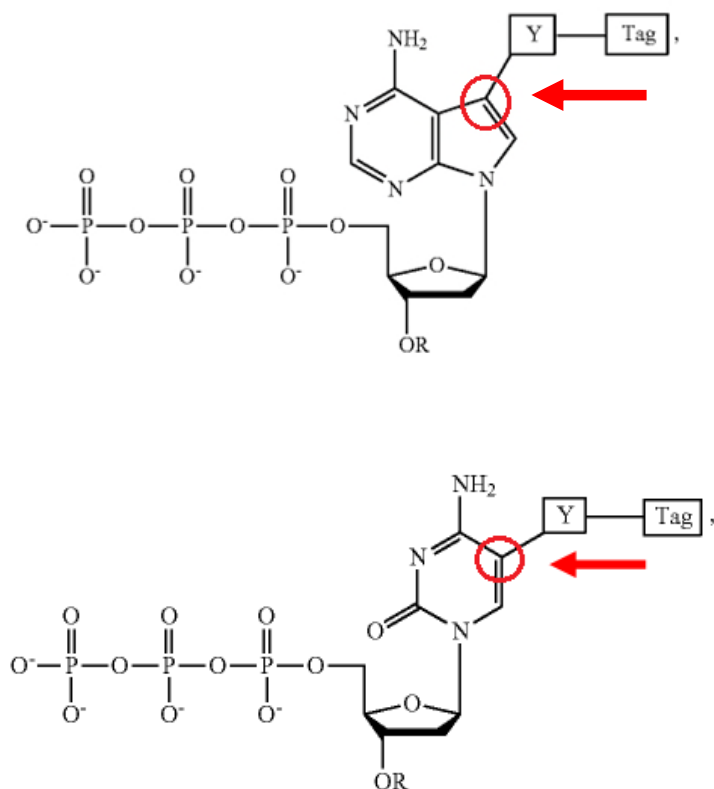
the “3-carbon allyl ether would have been immediately apparent to a POSA” reading Tsien’s “allyl ethers.” Reply, 5-6. Columbia disagrees. *See, e.g.*, Response, 54 (citing *Janssen*, 2012 WL 3990221, at *7 (rejecting argument that a genus discloses a species that “stood out” to a POSA)). Regardless, Illumina offered no motivation for selecting that particular capping group. And, Illumina’s new position improperly relies on “new theories or arguments necessary to make out petitioner’s case-in-chief[.]” Trial Practice Guide, August 2018, at 15; *Intelligent*, 821 F.3d at 1369-70.

B. Dower/Prober Do Not Describe A Cleavable Linker As Claimed

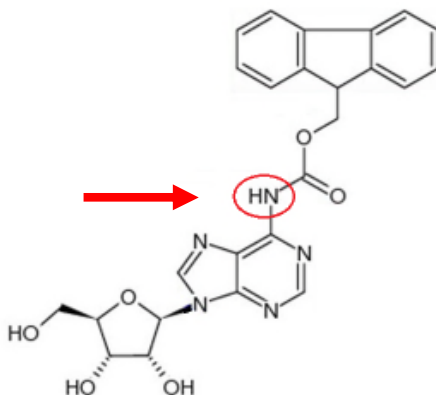
Illumina’s Ground 2 asserts that Dower/Prober describe the claimed cleavable linker. After Columbia’s Response showed that Illumina failed to meet its burden, Illumina’s Reply theorizes that Dower’s Fmoc inherently discloses a cleavable linker, as shown below:



Reply, 26. This argument does not satisfy the challenged claim limitations, which require attachment of the linker to a specific **carbon** (5-pyrimidine, 7-deazapurine), *e.g.*:



(Exs. 1001-1002, claim 1; *see also* Exs. 1003-1004, claim 1). Illumina concedes that Dower's FMOC, in contrast, is attached to the nitrogen of an exocyclic **amine**:



Reply, 26 (relabeled); Ex. 2140, 198:10-16. Dower’s Fmoc is not a cleavable linker (Y) attached to a *carbon*, and Dr. Romesberg admitted he is not aware of evidence showing Fmoc could be so attached. Ex. 2140, 201:8-23. Instead, Dr. Romesberg now says that Fmoc’s cleavable linker could be attached to the carbon in the challenged claim via “*an additional linker*[.]” Ex. 2140, 197:16-198:8. No such theory exists in Illumina’s Petition. And, Illumina’s double-linker is excluded from the claim, which requires one linker (Y), not two linkers (Y Y). Moreover, the claim mandates non-interference and stability properties, and there is no evidence Illumina’s double-linker satisfies those properties. Further, Dr. Romesberg provided only conclusory testimony that a POSA knew the chemistry to accomplish this double-linker attachment (Ex. 2140, 217:2-218:3). Thus, Ground 2 fails.

While irrelevant, Columbia’s patent does not “merely say[] that the linker can be chemically cleaved” without providing an example. Reply, 26. It discloses

the 2-nitrobenzyl linker, which was known to be both chemically- and photo-cleavable. Ex. 1001, 11:16-18, 14:21-22, Figure 7; Exs. 1009, 99-100 (Examiner explaining this fact during prosecution).

VI. No Expectation Of Success

A. No Expectation Of Incorporation With 3'-O-Allyl Thymine, Cytosine, Or Guanine

Illumina offers no meaningful rebuttal to Columbia's explanation that there was no expectation of incorporating a 3'-O-allyl *thymine*, *cytosine*, or *guanine*. Response, 48-50. In fact, 3'-O-allyl thymine is *not* incorporated by Vent(exo-) polymerase. Ex. 1116, 89. Illumina provides no explanation why a POSA would believe differently.

Illumina's rebuttal mischaracterizes Metzker as teaching that "increasing the concentration of the nucleotide" is a solution for "any unexpected differences in nucleobase incorporation." Reply, 22. Metzker contains no such teaching. After noting no polymerase incorporated both 3'-O-modified-dATP and 3'-O-modified-dTTP, Metzker suggests "testing more polymerases," not increasing 3'-O-modified-dNTP concentrations. Ex. 1016, 4266.

Illumina says Kutateladze "demonstrated incorporation of all four 3'-O-methyl-dNTPs at a concentration of 1 mM." Reply, 22. Kutateladze is irrelevant because it (i) used AMV-RT (Ex. 1016, 4266), which failed to incorporate 3'-O-allyl-dATP (*Id.*, Table 2); (ii) did not test thymine (using uracil instead) (*Id.*,

4266); and (iii) used 1 mM, which Dr. Romesberg conceded is too high, as detailed above.

Last, Illumina says “[s]creening for efficient polymerases was routine.” Reply, 23. Even if true, that says nothing about whether a POSA would expect success with the claimed compounds with other polymerases, particularly given Metzker’s negative results with 8 polymerases. Response, 48-51.

B. No Expectation Of Not Interfering With Polymerase Recognition

Illumina’s only argument why no polymerase interference would be expected posits that 3’-O-allyl-dNTPs were expected to be “efficiently incorporated[.]” This premise fails, as discussed above and in Columbia’s Response.

VII. Columbia Refuted Illumina’s Ground 2

Ground 2 does not “remain[] unaddressed.” Reply, 25, 2-3. Beyond the cleavable linker point, Columbia detailed *six* reasons why Ground 2 fails. Response, 60-61.

While “Dower and Tsien are different references” (Reply, 2), both concern SBS and a POSA understood them to have the same requirements. Ex. 2114, ¶¶14-16. Illumina’s new claim that Dower permits inefficient incorporation lacks support. As Illumina concedes, “Dower also discloses the label and 3’-blocking group ‘are selected to be compatible with *efficient incorporation*.’” Petition, 60-

61; Ex. 1015, 26:6-12. Dr. Romesberg agrees that “SBS requires *highly efficient* nucleotide incorporation” (Ex. 2126, 72:2-73:1, 76:3-77:10), and Dower’s methods are SBS. Illumina previously admitted that Dower has an efficient incorporation requirement. Ex. 2027, 29-30. The evidence contradicts Illumina’s claim that a POSA would select an inefficiently incorporated nucleotide for Dower’s methods, based on an alleged fix found therein. It is also a position its own expert was apparently unwilling to adopt and, as such, remains unsupported (and belated) attorney argument.

Regarding cleavage, a POSA also understood that SBS methods (including Dower’s) require quantitative, rapid cleavage, as taught by Tsien. Ex. 2114, ¶¶15-16. Illumina provides no evidence to the contrary. Illumina also does not dispute that Dower requires mild, aqueous conditions. Reply, 25 (only disputing other criteria); *see* Ex. 1015, 15:52-56, 18:3-8, 25:18-19; Ex. 2027, 40-46. Illumina’s Petition-cited references fail to demonstrate mild, aqueous cleavage conditions (Response, 31-44), which alone renders those references incompatible with Dower. Ex. 2126, 51:8-22.

VIII. Illumina’s Prior Inconsistent Positions

Columbia’s Response identified over a dozen instances where Illumina’s positions contradict positions it took when defending its own patent claims covering 3’-O-capped nucleotides for SBS. For example, in 2002, Illumina

asserted that due to a lack of DNA-compatible cleavage conditions, “it has not been possible hitherto to conduct DNA sequencing using 3’OH allyl-blocked nucleotides.” Ex. 2015, 2:18-65. It now asserts the opposite.

Illumina does not dispute it took these positions. At most, it says the priority date for one proceeding (out of many) was 1994. Reply, 24. But Illumina argued there was no motivation to make 3’-O-allyl nucleotides “even 6 years after” 1994, *i.e.*, in 2000. Response, 58-59. Also in its Reply, Illumina says its prior position, that Tsien does not disclose 3’-O-allyl nucleotides, proved unsuccessful. Reply, 24. But the Examiner found that Tsien does not “explicitly teach a [nucleotide] with a 3’-allyl protective group” (Ex. 2065, 101), and Illumina now argues otherwise.

As the Board indicated, Illumina’s inconsistent positions may “have bearing on [Illumina’s] credibility[.]” IPR2018-00797, Paper 20 (Institution Decision) at 27-28 (PTAB Sept. 18, 2018).

IX. Illumina Mischaracterizes Evidence

Illumina repeatedly mischaracterizes evidence. For example, Illumina contends that “Dr. Menchen admitted that 3’-O-allyl nucleotides were ... considered as good candidates for sequencing.” Reply, 6-7. He did not. Illumina’s support for this supposed “admission” includes the following:

Q. And how did you know that that was a good candidate to include it in your patent as something?

A. We didn't know it was a good candidate.

Ex. 1112, 64:16-20. Dr. Menchen consistently testified to that effect. *See id.*, 64:16-68:4 (*e.g.*, “[W]e had no reason to believe that [it] would be [a good candidate,]” “I don’t remember learning that [it would be a good candidate]”).

Illumina also claims two patents show that Solexa independently discovered that the allyl capping group was useful for SBS. Reply, 7 (alleging Solexa patents were “filed before Columbia’s specification was published”). The Solexa patents show the opposite, crediting Columbia’s “WO02/29003” as “describ[ing] a sequencing method which may include the use of an allyl protecting group[.]” Ex. 1125, 3-4; Ex. 1124, 3-4. These patents validate Columbia’s point—after Metzker 1994, nobody pursued the allyl capping group for SBS until Columbia’s invention, after which others (like Solexa) copied.

Such misstatements permeate Illumina’s Reply, as discussed above to the extent possible within Columbia’s Sur-reply word limit.

X. Illumina Improperly Incorporates Material

Illumina circumvented its word limit by improperly incorporating large portions of Dr. Romesberg’s 51-page Declaration into its 5,599-word Reply. *E.g.*:

The aqueous Pd-mediated allyl cleavage ... are not Wacker process methods. *Ex. 1119 ¶¶30-43.*

Sanger sequencing in fact requires efficient incorporation. *Ex. 1119 ¶¶72, 98-103.*

[S]creening for efficient polymerases was routine ... *Ex. 1119 ¶¶78-81[.]*

Reply, 21-22, 7, 23. These non-limiting examples incorporate thousands of words, including new exhibits and arguments, putting the Reply almost 3,000 words over Illumina's 5,600 word limit. The incorporated material should not be considered. 37 C.F.R. § 42.6(a)(3); Trial Practice Guide Update, August 2018, at 4, 6 (citing *Cisco*).

XI. Estoppel Does Not Apply To Columbia

The Board found the Petition's estoppel arguments deficient and questioned the applicability of 37 C.F.R. § 42.73(d)(3)(i). Decision, 35-36. Illumina's attempted do-over is improper.

Illumina's assertion that the Board "reject[ed] a claim specifically reciting the 3-carbon allyl protecting group over Tsien" is misleading. Reply, 27. The '869 patent has a dependent claim to a 3'-O-allyl nucleotide (claim 19), which

Illumina *did not challenge* in the prior IPRs. Illumina cites a Paper that denied amendments to a *different claim* (claim 15). The Board never considered the obviousness of Columbia's 3'-O-allyl nucleotide.

Nor do the current proceedings involve "identical issues." Reply, 3, 27-28. The claim here was specifically drafted to be narrower than the prior challenged claims (Response, 62-66), and Columbia has been vigilant not to reargue issues previously decided. The issues here are new, a fact highlighted by Illumina's inability to identify with particularity any issue as one being re-litigated.

XII. Conclusion

The Board should deny Illumina's Petition.

Respectfully submitted,

Dated: February 5, 2019

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing **PATENT OWNER'S SUR-REPLY**, exclusive of the parts exempted as provided in 37 C.F.R. § 42.24(c), contains 5,508 words and therefore complies with the type-volume limitations of 37 C.F.R. § 42.24(c).

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PATENT OWNER'S SUR-REPLY** and **EXHIBITS 2131, 2132, and 2140** are being served on February 5, 2019, via email to Counsel for Petitioner at the email addresses below:

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