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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.

IPR2018-00322
U.S. Patent 9,708,358

PETITIONER'S REPLY

TABLE OF CONTENTS

	Page No.
I. INTRODUCTION	1
II. CLAIM CONSTRUCTION	3
III. GROUND 1	3
A. Tsien discloses the 3'-O-allyl capping group.....	4
B. Several researchers disclosed the 3'-O-allyl capping group, including Dr. Menchen.....	6
C. There was motivation to use Tsien's 3'-O-allyl.....	7
1. Overview	7
2. Metzker demonstrated that the 3'-O-allyl capping group was incorporated by polymerase, and this would have encouraged a POSA.....	9
3. A POSA would have expected efficient incorporation.....	16
D. A POSA would have expected efficient cleavage	18
1. Tsien's disclosure of 3'-O-allyl cleavage	19
2. Columbia relies on Kamal	19
3. The prior art discloses SBS-compatible cleavage conditions	20
E. A POSA was motivated to select small capping groups.....	22
F. Reasonable expectation of success.....	22

TABLE OF CONTENTS
(Cont'd)

	Page No.
1. A POSA would expect thymine, cytosine, and guanine incorporation	22
2. A POSA would expect polymerase to recognize 3'- O-allyl-nucleotides.....	23
G. Judicial estoppel does not apply to Illumina	23
IV. GROUND 2	25
A. Ground 2 is distinct from Ground 1	25
B. Dower discloses a linker	25
V. ESTOPPEL APPLIES TO COLUMBIA	27
VI. CONCLUSION.....	29

TABLE OF AUTHORITIES

	Page No.
<i>Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.</i> , 713 F.3d 1369 (Fed. Cir. 2013)	5
<i>Gen. Elec. Co. v. Jewel Incandescent Lamp Co.</i> , 326 U.S. 242 (1945).....	8, 20
<i>In re Kubin</i> , 561 F.3d 1351 (Fed. Cir. 2009)	14
<i>MaxLinear, Inc. v. CF CRESPE LLC</i> , 880 F.3d 1373 (Fed. Cir. 2018)	28
<i>Merck & Co., Inc. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005)	2
<i>New Hampshire v. Maine</i> , 532 U.S. 742 (2001).....	24
<i>Ohio Willow Wood Co. v. Alps South, LLC</i> , 735 F.3d 1333 (Fed. Cir. 2013)	28
<i>PharmaStem Therapeutics, Inc. v. ViaCell, Inc.</i> , 491 F.3d 1342 (Fed. Cir. 2007)	8

OTHER AUTHORITIES

37 C.F.R. §42.73	28
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I. INTRODUCTION

The Tsien reference contains the same disclosure as Columbia's patent—both teach efficient polymerase incorporation and efficient cleavage of 3'-O-capped nucleotides. Columbia's declarant, Dr. Menchen, was asked to identify any disclosure in Columbia's patent that is not also in Tsien. The only difference he identified was: "Tsien doesn't describe allyl ethers." Ex. 1113, 329:2-14. This supposed difference is fictitious. Tsien expressly discloses "allyl ethers" as a capping group and its advantages (Ex. 1013, 24:29-25:3), which Dr. Menchen acknowledges. Ex. 1113, 324:6-326:20.

Not only does Tsien teach allyl ethers, but it is undisputed that 3'-O-allyl capped nucleotides are efficiently incorporated by polymerases and efficiently cleaved under appropriate conditions. Columbia's patent presumes this by claiming such nucleotides without any details explaining how to incorporate or cleave them. Yet Columbia's Patent Owner Response ("POR") spends pages criticizing Tsien, arguing that a person of ordinary skill in the art ("POSA") would not have expected 3'-O-allyl capped nucleotides to be efficiently incorporable based on the later-published Metzker reference. Dr. Menchen admitted, however, that he was motivated to include the 3'-O-allyl capping group in his own 1998 and 1999 patents precisely because of Metzker's disclosure. Ex. 1112, 189:5-13.

Columbia argues that a POSA would not have expected 3'-O-allyl nucleotides to be efficiently cleaved based on Tsien's "prophetic" disclosure. The Board and Federal Circuit rejected similar arguments in the prior IPRs because Columbia's patent is itself equally prophetic. The Federal Circuit, in affirming the Board's unpatentability determinations, stated "if novel and nonobvious chemistry was needed to practice the claimed inventions, Dr. Ju would have been obligated to disclose this chemistry in the patent." Ex. 1008, 31. Here, Columbia's criticisms of Tsien and the state of the art are so extreme that, if true, Columbia's patent would fail the written description, enablement, and utility requirements. Columbia fails to explain why it should receive exclusionary rights to the subject matter disclosed by Tsien without adding to Tsien's disclosure. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (reversing non-obviousness where "the claimed invention adds nothing beyond the teachings of [the prior art].").

Responding to the Dower-based challenge, Columbia only raises a nominal defense. It argues that this challenge fails for the same reasons as for Tsien. This fails to rebut the Board's detailed analysis and factual findings in its Institution Decision. Moreover, because Dower and Tsien are different references with different disclosures, it is superficial to argue that they can be distinguished on the same basis. Dower does not recite the same incorporation criteria as Tsien, nor the same quantitative cleavage criteria. Columbia's arguments against the Tsien-based

challenge are inapplicable to Dower. The Dower-based challenge remains unaddressed, except for the single argument that Dower's FMOC label allegedly lacks a cleavable linker. This argument has no merit. Dower's FMOC contains a cleavable $\text{--C(=O)-O-CH}_2\text{--}$ linker attaching the flourenyl moiety to the base.

The exact same claim elements that Columbia argues are not present in Tsien were previously found to be in Tsien. Ex. 1005, 8-11; Petition, 24-25. Columbia fails to rebut convincingly the detailed obviousness analysis in the Institution Decision and Petition. The Board should cancel Columbia's claim, whether on the merits or by prohibiting re-litigation of identical issues.

II. CLAIM CONSTRUCTION

Columbia asserts that "small" and "chemical linker" require construction. POR, 9-11. The Board previously determined that these terms do not require construction. Institution Decision, 7. Columbia fails to identify any flaw in the Board's decision. The Board need not construe these terms to determine unpatentability. *Id.* (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g. Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

III. GROUND 1

Rather than presenting fully developed arguments, Columbia provides a scattershot of underdeveloped assertions. Illumina provides the following succinct Reply to those assertions.

A. Tsien discloses the 3'-O-allyl capping group

Columbia argues that Tsien does not disclose the 3'-O-allyl capping group. POR, 51-58. Indeed, this appears to be the only disputed difference between Tsien and Columbia's patent. Ex. 1113, 329:2-14. The Patent Office, however, has consistently found that Tsien discloses the 3'-O-allyl capping group. Ex. 1065, 98; Institution Decision, 23-24; Ex. 1095, 26, 9; Ex. 1096, 9-10. Columbia's previous expert, Dr. Trainor, admitted that Tsien discloses the small 3'-O-allyl capping group. Ex. 1098, 107:12-108:20. Columbia asks the Board to reach a different conclusion, contrary to the findings of the Patent Office and its own expert.

Columbia argues that Tsien's disclosure of "allyl ethers" does not refer to the $-\text{CH}_2-\text{CH}=\text{CH}_2$ group, but rather a genus of compounds. POR, 51-54. This contradicts the established definition of "allyl" set forth by the International Union of Pure and Applied Chemistry (IUPAC) that "allyl" is " $-\text{CH}_2-\text{CH}=\text{CH}_2$ " (Ex. 1099, 13, 305). "IUPAC is recognized throughout the world as the international authority on chemical nomenclature" (Ex. 1100, 505), and its definitions are intended for use in all "textbooks, journals and patents." Ex. 1099, xvii; Ex. 1119 ¶¶25-27. This definition is consistently recognized throughout industry handbooks and textbooks. Ex. 1101, 67; Ex. 1102, 2-71; Ex. 1103, 24; Ex. 1039, 503; Ex. 1104, 254; Ex. 1105, 209.

Columbia argues that Tsien's disclosure of the "allyl" capping group was an accident because Tsien meant to disclose "vinyl" groups. POR, 52-53. This argument has no merit. Tsien cites to Gigg (Ex. 1013, 24:29-30), and the title of Gigg unambiguously refers to "The Allyl Ether." Ex. 1046, 1903. Columbia's Exhibit 2018 recognizes Gigg as the pioneering work on the allyl ether as a hydroxyl protecting group. Ex. 2018, 141. Dr. Menchen admitted that Tsien's disclosure is directed to allyl ethers (Ex. 1113, 324:15-326:20), and that a POSA would understand from Tsien that allyl ethers are advantageous because "they wouldn't be cleaved by base hydrolysis when deblocking occurs." *Id.*, 326:5-20; Ex. 1119 ¶48. Thus, Tsien proposed the 3'-O-allyl capping group for its sequencing methods, and a POSA would have been motivated to use Tsien's 3'-O-allyl capping group based on Tsien's suggestion. *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1375-76 (Fed. Cir. 2013) (invalidating claims for obviousness where prior art illuminates a need or problem and "expressly propose the claimed solution").

Even if Tsien's "allyl ethers" describes a group of compounds, Dr. Menchen admitted that it would include the 3-carbon form. He testified that the allyl groups at 24:29-30 and 28:27-29 of Tsien covered identical compounds, including allyl groups having 3-10 atoms (the 3-carbon allyl having 8 atoms). Ex. 1113, 409:18-410:10. The 3-carbon allyl ether would have been immediately apparent to a POSA;

it is the simplest allylic ether, was the most commonly used allylic ether, and was the IUPAC definition of allyl. Ex. 2126, 214:14-215:24.

B. Several researchers disclosed the 3'-O-allyl capping group, including Dr. Menchen

Columbia argues that Metzker would have dissuaded a POSA from using Tsien's 3'-O-allyl capping group as evidenced by supposed lack of reports of 3'-O-allyl capping groups between Metzker's 1994 publication and Columbia's 2000 priority date. POR, 23. Columbia is wrong.

Beyond Tsien and Metzker, at least two other researchers disclosed the 3'-O-allyl capping group for DNA sequencing. In 1995, Hiatt repeatedly disclosed the 3'-O-allyl capping group for polymerase incorporation. Ex. 1106, 11:58, 12:39, 30:8.

In 1998 and 1999, Columbia's own declarant (Dr. Menchen) repeatedly suggested the 3'-O-allyl capping group for polymerase-based DNA sequencing precisely because of Metzker. Ex. 1091, 5:56-61 (disclosing "3'-allyloxy"¹ nucleotides); *id.*, 12:54-59, 14:3-19, 27:35-28:6 (disclosing polymerase-based sequencing); Ex. 1092, 10:40-45, 50:58-62, 52:17-35, 4:25-30; *id.*, 11:22-24 (citing Metzker); Ex. 1112, 189:5-13. Dr. Menchen admitted that 3'-O-allyl nucleotides were part of the state of the art in 1998 (Ex. 1112, 98:14-99:1, 60:16-21) and

¹ "3'-allyloxy" is the 3'-O-allyl. Ex. 1119 ¶26; Ex. 1112, 49:25-50:6.

considered as good candidates for sequencing. *Id.*, 64:25-65:12, 69:15-21, 78:17-79:4, 154:22-155:9, 156:4-12, 62:3-6. Dr. Menchen attempts to explain away his own patents teaching 3'-O-allyl for sequencing as being limited to Sanger sequencing, which he asserts does not require efficient incorporation. This is nonsense because Sanger sequencing in fact requires efficient incorporation. Ex. 1119 ¶¶72, 98-103.

Solexa also described using the 3'-O-allyl group in its SBS patents. Ex. 1124, 22:34-23:24; Ex. 1125, 111:4-115:1. While these were filed after Columbia's, they were filed before Columbia's specification was published.

The disclosure of 3'-O-allyl nucleotides for DNA sequencing in numerous publications (e.g., Tsien, Metzker, Hiatt, Solexa, and Dr. Menchen's patents) shows that a POSA was motivated to use 3'-O-allyl nucleotides for polymerase-based DNA sequencing, even after Metzker published. Ex. 1005, 5-6.

C. There was motivation to use Tsien's 3'-O-allyl

1. Overview

Tsien identifies particular advantages of the 3'-O-allyl capping group, thus motivating a POSA to use this group in Tsien's methods. Petition, 34-37; Ex. 1013, 24:29-25:3. Columbia nonetheless disputes that a POSA would follow Tsien's instruction to use 3'-O-allyl. According to Columbia, a POSA would not have expected Tsien's 3'-O-allyl capping group to meet Tsien's criterion of efficient

polymerase incorporation. POR, 13. This argument is belied by Columbia's own patent. Columbia's patent has the same polymerase efficiency incorporation requirement as Tsien. Ex. 1002, 21:3-13; Ex. 1112, 168:6-24, 258:5-259:13. Columbia's patent fails to identify anything beyond its reference to Metzker to demonstrate that the 3'-O-allyl capping group is efficiently incorporated. Ex. 1112, 251:4-252:11. Columbia's patent admits that Metzker showed 3'-O-allyl-dATP was "incorporated by Vent (exo-) DNA polymerase in the growing strand of DNA." Ex. 1002, 3:28-30. "Admissions in the specification regarding the prior art are binding on the patentee." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007).

Columbia does not dispute that 3'-O-allyl nucleotides are, in fact, efficiently incorporated by a polymerase. POR, 2; Ex. 1066 ¶22a; Ex. 1112, 296:22-297:3, 147:11-25. Columbia's recognition from the prior art that 3'-O-allyl groups are capable of being efficiently incorporated is not an invention. Ex. 1005, 38 ("Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention.") (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)); *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945).

2. **Metzker demonstrated that the 3'-O-allyl capping group was incorporated by polymerase, and this would have encouraged a POSA**

Even though Columbia approvingly cited Metzker in its specification, it now argues that Metzker would have discouraged a POSA from pursuing the 3'-O-allyl capping group. POR, 21-31. Dr. Menchen admitted that Columbia's specification does not disclose how a 3'-O-allyl-dNTP would be efficiently incorporated by polymerase. Ex. 1112, 284:6-18. Columbia's specification relies on the same polymerases for incorporation as Metzker. Ex. 1002, 22:4-6; Ex. 1016, 4264. As explained by the Federal Circuit, "if novel and nonobvious chemistry was needed to practice the claimed inventions, Dr. Ju would have been obligated to disclose this chemistry in the patent." Ex. 1008, 31.

Columbia's argument that Metzker supposedly discourages a POSA depends on its exaggerated and unwarranted interpretation of an asterisk. Metzker reported that Vent(exo-) polymerase incorporated 250 μ M of 3'-O-allyl-dATP in Table 2 as "Termination*." Ex. 1016, 4263. Columbia spends pages trying to explain how Metzker's "Termination*" conclusion could have misled a POSA to believe that 3'-O-allyl nucleotides were inefficiently incorporated by Vent(exo-) polymerase. A POSA would not have reached such a conclusion.

The 3'-O-allyl-dATP used at 250 μ M in Metzker's assay included 1% contamination of natural dATP (i.e., 2.5 μ M). *Id.* This 2.5 μ M of natural dATP

competed with the 3'-O-allyl-dATP as a substrate. Ex. 1119 ¶65. Columbia acknowledges this contamination, yet argues it would not affect Metzker's results. POR, 26. Columbia's argument is contradicted by Dr. Metzker's 1998 publication explaining that dATP contamination of less than 0.5% "remains sufficiently high that the DNA polymerase selectively incorporates the preferred natural dNTP over the 3'-O-modified-dNTP analog." Ex. 2131, 814. This contamination "can significantly result in decreased signal intensities." Ex. 2131, 814; Ex. 1016, 4263.

The fact that Metzker observes termination with 2.5 μ M of natural dATP competing with the 3'-O-allyl-dATP indicates that 3'-O-allyl-dATP is a highly efficient substrate for Vent(exo-) polymerase. Ex. 2126, 129:18-130:4. For example, the dATP contamination of 2.5 μ M is five times more than the 0.5 μ M of dATP used in Metzker's Vent(exo-) polymerase experiment with 3'-O-modified-dTTP. Ex. 1016, 4262; Ex. 1119 ¶74. Thus, Metzker's 3'-O-allyl-dATP effectively competes with a significant amount of natural dATP. Ex. 2126, 129:18-130:4; Ex. 1119 ¶¶65-66.

Metzker's Termination* "means the activity was incomplete at a final concentration of 250 μ M." Ex. 1016, 4263. Columbia argues that the asterisk in "Termination*" suggests that 3'-O-allyl-dATP is inefficiently incorporated. POR, 18-21. The data in Table 1 of Metzker undermines Columbia's position. The legend of Table 1 uses similar "incomplete" language for incorporation of ddNTPs by

Pfu(exo-) polymerase. Ex. 1016, 4262 (“I/T means ddNTP termination was incomplete”). It was known that *Pfu*(exo-) actually provides efficient incorporation of ddNTPs. Ex. 1109, 121. For example, *Pfu*(exo-) was sold in a commercial DNA Sanger sequencing kit for use with ddNTPs at a concentration of 450 μM. Ex. 1107, 14:4-10; Ex. 1108, 1-2; Ex. 1119 ¶¶70. Columbia’s patent admits that ddNTPs are used in sequencing due to the “excellent efficiency with which they are incorporated by DNA polymerase.” Ex. 1002, 21:51-56. Thus, Metzker’s description of a nucleotide having “incomplete” activity does not indicate that the nucleotide is inefficiently incorporated. Columbia also ignores that a POSA would view efficiency as routinely improvable, e.g. by increasing nucleotide concentration or reaction time. Ex. 1119 ¶¶67-69, 72-73, 75-77, 85-87, 97.

Columbia ignores this description in Metzker and made up a cartoon with a hypothetical “efficiency test band” to supposedly illustrate “Termination*”. POR, 18-21; Ex. 1112, 195:14-17, 200:16-19. Columbia’s cartoon has no basis in reality. Ex. 1112, 206:9-17. During cross-examination, Dr. Menchen admitted that he has never worked with a polymerase (*id.*, 193:13-18), has never worked with reversibly capped nucleotides (*id.*, 218:13-18), and does not have sufficient knowledge of polymerases to determine whether a polymerase would efficiently incorporate 3’-O-allyl capped nucleotides. *Id.*, 141:19-142:9, 143:10-18, 178:22-179:6. Dr. Menchen directly admitted “I’m not an expert on polymerases.” *Id.* 270:2-16. Dr. Menchen

further conceded that he has no system for differentiating complete termination versus incomplete termination based on his “efficiency test band” theory. Ex. 1113, 435:6-13. He also admitted that the only possible evidence for his cartoon was Figure 3 of Metzker’s 1998 publication. Ex. 2131, 816; Ex. 1112, 210:2-211:21. The “evidence” in Figure 3 occurs in just one lane, at the lowest concentration (5 μ M, Lane A) of 3’-O-methyl-dATP:

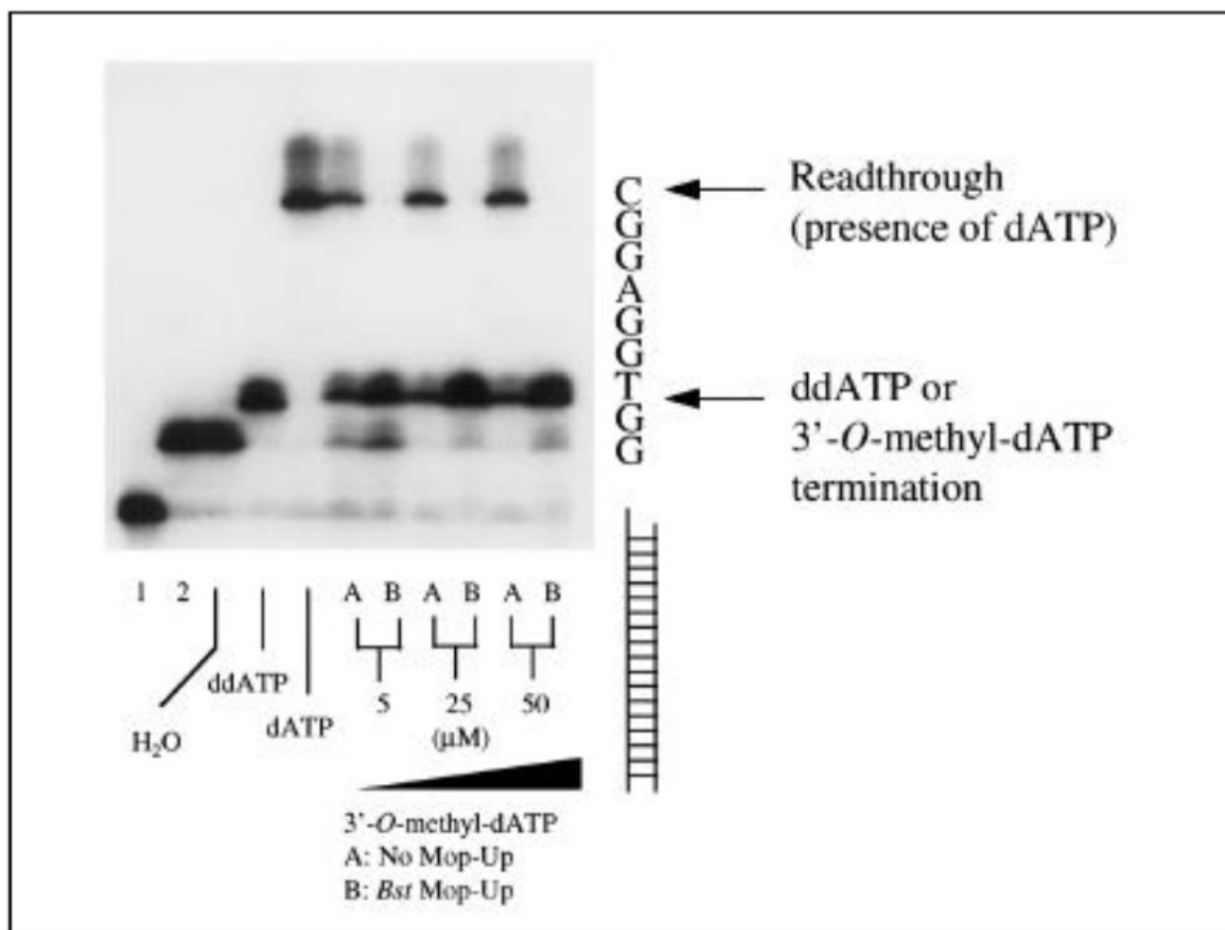


Figure 3. Complete termination of 3'-O-methyl-dATP by AMV-RT. As shown, various concentrations of 3'-O-methyl-dATP are assayed in the absence (lanes A) or after enzymatic mop-up (lanes B). All reactions contained ³²P-labeled universal primer-annealed to the oligo-template and AMV-RT in reaction buffer (lane 1). In addition, lane 2 contained dCTP and ddGTP. All other reactions contained dCTP, dTTP, ddGTP and compounds listed below each lane.

Ex. 2131, Fig. 3. The “efficiency test band” in Lane A (5 μ M) vanishes at the modestly higher concentrations of 25 and 50 μ M in the other A Lanes. *Id.*; Ex. 1113, 428:17-431:21. Thus, if anything, this figure demonstrates how to eliminate an “efficiency test band” by simply increasing the concentration of 3’-O-capped nucleotide.

Dr. Menchen admits that simply increasing the concentration of 3’-O-capped nucleotide was a known method for achieving efficient polymerase incorporation. Ex. 1112, 203:16-204:13; Ex. 1016, 4265 (Figure 4B, lanes 7-9); Ex. 1119 ¶91. A POSA reviewing Metzker would have reasonably expected increasing 3’-O-allyl nucleotide concentration (or increasing reaction time) would lead to even more efficient incorporation. Ex. 1119 ¶¶75-76.

Columbia argues that Metzker’s Termination* means that the 3’-O-allyl nucleotide “showed polymerase binding but slow incorporation.” POR, 26. According to Columbia, 3’-O-allyl-dATP binds and occupies the polymerase active site, but fails to be incorporated into the DNA. *Id.* Metzker refers to this type of behavior as “Inhibition.” Ex. 1016, 4263 (“Inhibition was revealed when the presence of the test compound prevented the polymerase from incorporating the natural nucleotides.”). Metzker, however, reports that 3’-O-allyl-dATP demonstrates “Termination*”, not “Inhibition.” *Id.*, Table 2. If 3’-O-capped nucleotides acted as an Inhibitor, then increasing nucleotide concentration would

result in increased inhibitor concentration, which in turn would result in an “efficiency test band” persisting at higher concentrations. Ex. 1119 ¶88. However, Figure 3 of Metzker’s 1998 publication shows that this is not the case. In Figure 3, the increased nucleotide concentrations resulted in efficient and complete termination. Ex. 2131, 816; Ex. 1113, 428:17-431:21. Thus, Columbia’s “slow incorporation” theory is incorrect.

Columbia asserts that Metzker discourages the use of 3’-O-allyl nucleotides because Metzker selected other 3’-capping groups for further evaluation. POR, 23. This does not evidence non-obviousness. In the previous IPRs, the Board explained that “[j]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” Ex. 1005, 28 (quoting *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)). The Federal Circuit agreed. Ex. 1008, 22. Rather than discourage a POSA, Metzker’s report of Termination* for 3’-O-allyl-nucleotides with Vent(exo-) polymerase would have “aroused a skilled artisan’s curiosity” for the 3’-O-allyl capping group. *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

Columbia alleges that “other researchers” cited Metzker as evidence of inefficient incorporation. POR, 27-28. None of the references cited by Columbia refer to inefficient incorporation of the 3’-O-allyl group, Columbia ignores that several other researchers cited to Metzker approvingly, including Dr. Menchen, and

SBS continued to be a popular approach notwithstanding Columbia's alleged drawbacks. Ex. 1092, 11:22-24; Ex. 1112, 157:10-19; Ex. 2100, 19:26-36; Ex. 1080, 16:26-33; Ex. 2013, 31; Ex. 1119 ¶¶9-10, 106-107. Dr. Menchen admitted that he was motivated to include the 3'-O-allyl capping group in his patent *because* of Metzker's disclosure. Ex. 1112, 189:5-13.

Columbia relies on materials published **after** its patent was filed to try to time-shift the knowledge of a POSA beyond what was known in 2000. POR, 2, 22, 24, 28. Columbia's post-filed exhibits were written based on the escalating expectations of a POSA in the mid-to-late 2000's, after the first human genome sequence was published in 2001 for \$3 billion. Ex. 1120, 1544; Ex. 1119 ¶¶7, 20. In 2004, the NIH launched a \$70 million grant program seeking to reduce this cost to just \$1000. Ex. 1120, 1544. To achieve such a dramatic cost reduction required improvements in polymerase-based sequencing efficiency.

Dr. Metzker's 2007 article (Ex. 1017) acknowledged the heightened efficiency standard required for the \$1000 genome. Ex. 1017, 6339 ("Next-generation technologies are being developed to advance sequencing to the \$100,000, and eventually the \$1000 genome."). His 2011 article (Ex. 2025) also acknowledged the heightened standards needed for "longer read-lengths" to meet the \$1000 genome. Ex. 2025, e39. The post-filing statements by Metzker about 3'-O-allyl-nucleotides were focused "on optimizing the cycle efficiency and time, which

determine read-length and throughput, respectively” to achieve the \$1000 genome. Ex. 1017, 6348. Similarly, Drs. Romesberg and Ju jointly submitted a grant in 2006. Ex. 2118, 27. The 2006 statements by Drs. Romesberg and Ju in the grant reflect the NIH’s call to dramatically reduce sequencing costs. Ex. 1119 ¶¶11, 18. Furthermore, post-filing statements about the 3’-O-allyl capping group provide a positive indicator of the allyl group’s status as a measuring stick for new sequencing methods. *Id.* ¶21.

3. A POSA would have expected efficient incorporation

Columbia alleges that a POSA would not have used Tsien’s 3’-O-allyl-dNTPs because Metzker discloses 250 μ M, while Tsien discloses concentrations of 1.5-30 μ M. POR, 30. Tsien’s concentration range is not so limited. Tsien explains that “especially with derivatized dNTP’s it may often be helpful to use substantial excesses (over stoichiometry) of the dNTP’s.” Ex. 1013, 20:17-22; Ex. 1119 ¶¶92-93.

Columbia asserts that “Termination*” reported by Metzker at 250 μ M for 3’-O-allyl-dATP indicates inefficient incorporation. POR, 21. Columbia ignores Metzker’s teaching to increase the concentration of 3’-O-modified-dNTP to enhance incorporation efficiency. Ex. 1016, 4266 (“problems could be resolved by increasing the concentration”). Metzker demonstrates that increasing the concentration of a 3’-O-modified-dNTP to 500 μ M with Vent(exo-) polymerase

results in efficient incorporation. *Id.*, Figure 4(B); Ex. 1119 ¶¶91; Ex. 1112, 204:8-13. Metzker discloses concentrations up to 5 mM do not adversely affect incorporation fidelity. Ex. 1016, Figure 4(A); Ex. 1112, 222:9-13. A POSA following Metzker's instruction to increase concentrations of 3'-O-allyl-nucleotides would reasonably have expected to achieve efficient incorporation. Ex. 1119 ¶¶75, 91.

Menchen's citation (in a footnote) to one article about possible adverse effects of high concentrations is overstated. Ex. 2116 ¶50, n.9. That article addresses concentrations of natural nucleotides, not 3'-O-capped nucleotides. Ex. 1119 ¶¶94-96.

Columbia relies on a 1992 article to generally assert that adding a label to a 3'-O-allyl-dNTP would reduce polymerase efficiency. POR, 30-31. Columbia's own exhibit instructs a POSA that increasing the concentration of Vent(exo-) polymerase "typically produces a proportionate increase in extension product." Ex. 2132, 6. Columbia ignores the prior art cited in the Petition that discloses attaching labels to the specific 7-position of 7-deazapurines and the 5-position of pyrimidines provided efficient incorporation by Vent(exo-) polymerase. Petition, 31; Ex. 1040, 3228, 3230; Ex. 1041, 4832-33; Ex. 1067 ¶77. By 1999, Vent(exo-) variants were available that were "more tolerant toward incorporation of nucleotides with substituted bases" and modified 3'-groups. Ex. 1122, 2552; Ex. 1113, 347:13-25.

Columbia's patent does not exemplify any chemically cleavable linker for adding a label to the base, and it asserted that selecting linkers for labels was within the skill in the sequencing art. Ex. 1065, 19; Ex. 1119 ¶¶17, 13-16. Thus, a POSA would have reasonably expected a polymerase to incorporate the labeled 3'-O-allyl-dNTPs discussed in the Petition.

D. A POSA would have expected efficient cleavage

Columbia argues that a POSA would not have expected Tsien's 3'-O-allyl group to be efficiently cleaved under SBS-compatible conditions. POR, 31-44. Columbia's patent requires cleavage in "high yield" under mild conditions that allow the growing strand of DNA to remain annealed to the DNA template. Ex. 1002, 21:1-19. The Board and Federal Circuit previously found that Columbia's fundamental "high yield" requirement is equivalent to Tsien's quantitative cleavage conditions. Ex. 1044, 20-21; Ex. 1045, 5-6. Dr. Menchen agrees. Ex. 1112, 138:4-9, 124:2-7. Columbia's specification discloses only two 3'-O-capping groups: allyl and MOM. Ex. 1002, 26:22-33; Ex. 1066 ¶16; Ex. 1112, 110:14-21. Columbia's specification, however, lacks any disclosure of cleavage conditions that would meet its requirements. Ex. 1112, 235:19-236:4, 239:5-11. Columbia cannot require more from the prior art than its own specification. Ex. 1008, 31.

1. Tsien's disclosure of 3'-O-allyl cleavage

Columbia argues Tsien does not teach appropriate cleavage conditions. POR, 32-34. Columbia's argument does not account for the state of the art in allyl ether cleavage. Tsien cites to the pioneering 1968 Gigg article, which discloses that allyl ether is cleavable by base hydrolysis. Ex. 1013, 24:29-30; Ex. 1046, 1905-06. Tsien further discloses that allyl capping groups are advantageous specifically because they are cleavable by methods "other than base hydrolysis." Ex. 1013, 24:29-25:3. Such non-basic methods were well known in the prior art. Petition, 22, 32-33. Indeed, Greene disclosed that "[t]he use of allyl ethers for the protection of alcohols is common in the literature on carbohydrates" and "the many mild methods for its cleavage in the presence of numerous other protective groups, and its general stability have made the allyl ether a mainstay of many orthogonal sets." Ex. 1101, 67. Tsien provides an appropriate level of disclosure for allyl ether cleavage.

2. Columbia relies on Kamal

Columbia argues that Kamal is incompatible with SBS cleavage conditions. POR, 34-37. The only allyl ether cleavage conditions provided in Columbia's specification are Kamal's. Ex. 1002, 26:22-33, 28:15-23. Columbia's contradictory stance on Kamal is untenable. Ex. 1008, 31.

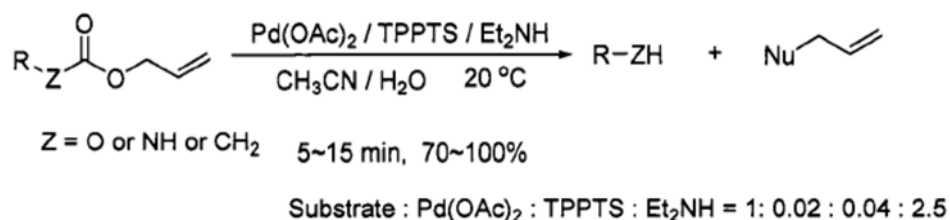
3. The prior art discloses SBS-compatible cleavage conditions

Columbia argues the prior art does not disclose appropriate allyl ether cleavage conditions. POR, 37-44. It is undisputed that 3'-O-allyl capping groups are, in fact, cleavable under SBS conditions. POR, 2; Ex. 1066 ¶22a; Ex. 1112, 296:22-297:3, 147:11-25. Columbia's specification does not provide any new allyl ether cleavage conditions. Columbia's mere recognition that the 3'-O-allyl capping group possesses the latent property of being cleavable under SBS conditions is not an invention, especially where Tsien made the same suggestion. Ex. 1005, 38; *Gen. Elec. Co.*, 326 U.S. at 249.

Columbia criticizes Boss for using perchloric acid (a strong acid). POR, 37-38. However, Boss discloses using p-toluenesulfonic acid (a milder, water-soluble acid). Ex. 1035, 558-59; Ex. 1119 ¶44.

Columbia criticizes Qian for conducting Pd-catalyzed allyl ether cleavage in methanol rather than water. POR, 40-43. It would have been a matter of routine experimentation to conduct Qian's cleavage under aqueous conditions. Ex. 2126, 158:20-159:2. Genet published several articles disclosing an efficient water-soluble Pd-catalyst that demonstrated cleavage of an allyl group from alcohols in 100% yield in 30 minutes or less. Ex. 1094, 499; Ex. 1114, 8784; Ex. 1115, 249. In 2006, Dr. Ju's laboratory admitted that such allyl ether cleavage conditions had been known for decades. Ex. 1116, 163-64 ("**In the past decades**, chemists have developed

efficient catalysts to cleave allyl groups from allyl ethers” for DNA sequencing including Genet’s “efficient water-soluble catalyst generated from palladium (II) acetate and TPPTS.”). His laboratory further admitted that Genet’s “reaction conditions were very mild, and most reactions were complete in less than 15 minutes at room temperature” as shown below:



Scheme 3-2. Genet’s method to cleave an allyl group from allyl esters, allyl carbonates or allyl carbamates using an aqueous palladium-phosphine system.⁸

Id., 164 (citing prior art Exhibits 1094, 1114, 1115). Dr. Ju admitted that “TPPTS has been widely used as a ligand for Pd-mediated deallylation under aqueous conditions” based on Genet’s work. Ex. 1093, 5934 (citing Ex. 1094). Dr. Menchen admitted that Genet’s method was within the ordinary skill in the art. Ex. 1113, 360:25-361:6; Ex. 1119 ¶29. Thus, by at least the mid-1990’s, the state of the art included appropriate allyl cleavage conditions.

Columbia argues that allyl cleavage would follow the Wacker process. POR, 42. Dr. Menchen conceded that the Wacker process requires copper and oxygen. Ex. 1112, 184:18-185:7; Ex. 2115, 102-03. The aqueous Pd-mediated allyl cleavage described by Boss, Qian, and Genet do not use copper, and thus are not Wacker process methods. Ex. 1119 ¶¶30-43.

E. A POSA was motivated to select small capping groups

Dr. Ju was not the first to recognize the small space in polymerases for the nucleotide's 3'-position. Ex. 1119 ¶¶51-53. Columbia argues that a POSA would not have reviewed the polymerase crystal structure in Pelletier because this article relates to HIV drug development rather than SBS. POR, 46-47. Columbia's attempt to pigeonhole Pelletier is disingenuous. Tsien pointed to viral drug development articles for guidance on selecting polymerases (Ex. 1013, 21:17-19; Ex. 1126; Ex. 1119 ¶58), and other groups studied the structure of polymerases for improving DNA sequencing methods in the 1990s. Ex. 1023, 955; Ex. 1119 ¶¶54-60.

F. Reasonable expectation of success

1. A POSA would expect thymine, cytosine, and guanine incorporation

Columbia argues that there was no expectation a 3'-O-allyl thymine, cytosine, or guanine nucleotide would be incorporated based on Metzker. POR, 48-50. Metzker provided potential solutions for any unexpected differences in nucleobase incorporation, including increasing the concentration of the nucleotide. Ex. 1016, 4266. Kutateladze demonstrated incorporation of all four 3'-O-methyl-dNTPs at a concentration of 1 mM. *Id.*; Ex. 1118, 206-208. It was known that Vent(exo-) polymerase incorporates nucleotides having labels attached at the 7-position of 7-deazapurines and 5-position of pyrimidines. Petition, 31; Ex. 1040, 3228, 3230; Ex.

1041, 4832-33; Ex. 1067 ¶¶77. Columbia's specification does not disclose any unique polymerases that efficiently incorporate all four 3'-O-allyl-dNTPs. Ex. 1112, 284:6-18. If some unusual polymerase were required to incorporate 3'-O-allyl-dTTP/dCTP/dGTP, then Columbia's specification was obligated to disclose that polymerase. Ex. 1008, 31. As previously found, screening for efficient polymerases was routine. Ex. 1005, 34; Ex. 1119 ¶¶78-81; Ex. 1015, 17:12-67.

2. A POSA would expect polymerase to recognize 3'-O-allyl-nucleotides

Columbia argues that a POSA would expect the 3'-O-allyl cap to interfere with polymerase recognition. POR, 50-51. As discussed above and in the Petition, 3'-O-allyl-dNTPs were expected to be efficiently incorporated by Vent(exo-) polymerase. There is no dispute that 3'-O-allyl does not actually interfere with polymerase recognition. POR, 2; Ex. 1066 ¶22a; Ex. 1112, 296:22-297:3, 147:11-25. Columbia's recognition that the 3'-O-allyl capping group possesses the property of not interfering with polymerase recognition is not an invention. Ex. 1005, 38.

G. Judicial estoppel does not apply to Illumina

Columbia argues that Illumina is judicially estopped from relying on Tsien's 3'-O-allyl capping groups because statements made in the '465 reexamination allegedly persuaded the Examiner that Tsien does not disclose the allyl capping group. POR, 57-59. Columbia misrepresents the reexamination record. The Examiner found that Tsien **does** disclose the 3'-O-allyl capping group, and rejected

contrary arguments. Ex. 2065, 101 (rejecting patent owner's arguments; finding "the person of skill in the art would immediately envision the 3'-OH protected by an allyl group"); *id.* (finding a 3'-OH allyl capping group is "implicitly disclosed in Tsien et al."). The Examiner eventually issued the reexamination certificate for other reasons. *Id.*, 126. Judicial estoppel therefore does not apply to Illumina. *New Hampshire v. Maine*, 532 U.S. 742, 750-51 (2001) (judicial estoppel inapplicable where a party failed "in persuading a court to accept that party's earlier position"). Illumina's petition in this proceeding is consistent with the Patent Office's repeated determination that Tsien discloses 3'-O-allyl nucleotides.

Furthermore, Columbia fails to acknowledge that the non-obviousness arguments submitted during reexamination were from the perspective of a POSA in September of 1994 (Ex. 2065, 129), which was before relevant intervening art confirmed Tsien's disclosure, such as Metzker's evidence of polymerase incorporation (Exs. 1097, 1016), and Qian's and Kamal's evidence of cleavage (Exs. 1036-1037). If estoppel applies at all, it applies to Columbia, not Illumina; Columbia relied on the disclosures by Metzker and Kamal to persuade the Patent Office to grant its patent and is now seeking to rescind its previous position.

IV. GROUND 2

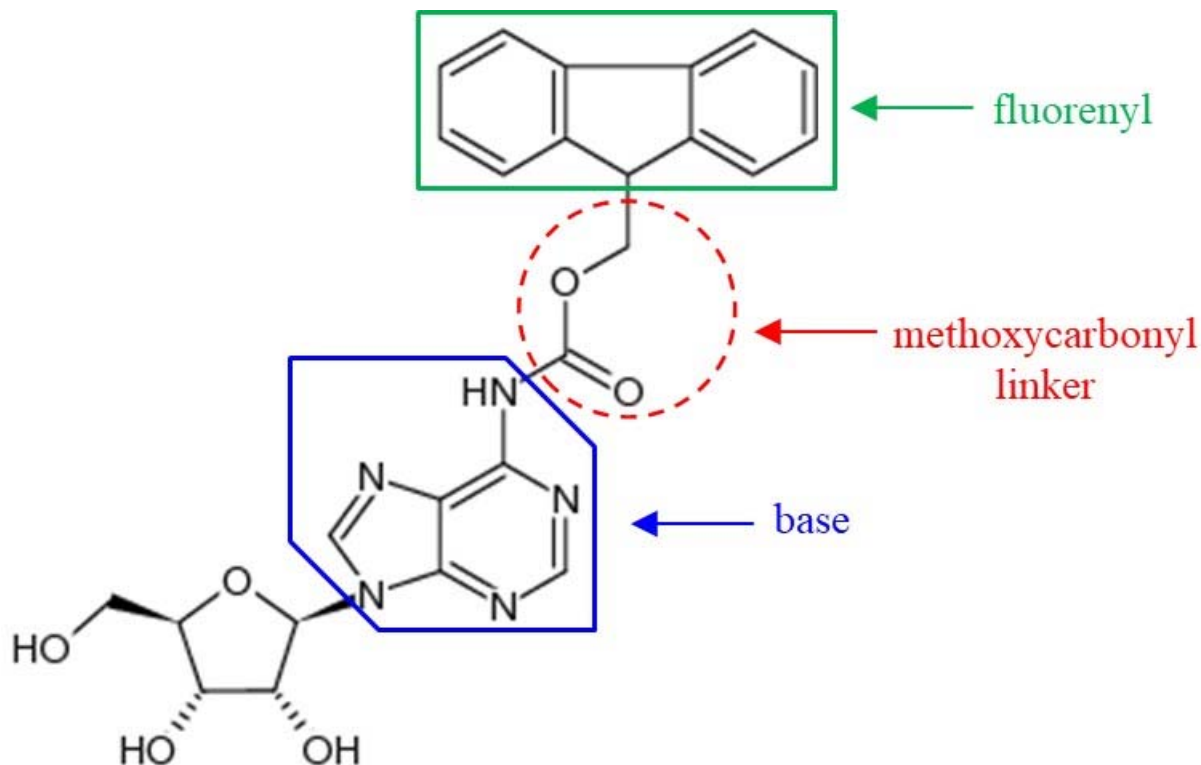
A. Ground 2 is distinct from Ground 1

Columbia asserts, without any explanation, that Petitioner's Ground 2 challenge "fails for the same reasons" as Ground 1. Columbia is wrong.

Dower does not recite the incorporation efficiency criteria of Tsien, and Dower discloses that inefficient polymerase incorporation can be addressed by permanently capping DNA chains with ddNTPs. Ex. 1015, 26:13-18. Dower does not recite Tsien's "quantitative" or "rapid" cleavage criteria. Therefore, Columbia's arguments about 3'-O-allyl-dNTPs supposedly being inefficient polymerase substrates and lacking efficient cleavage conditions should not be applied to Dower. The Petition's Ground 2 challenge, and the Board's detailed analysis in the Institution Decision, remain unaddressed.

B. Dower discloses a linker

The only Dower-specific argument raised by Columbia is that Dower allegedly lacks a chemical linker. POR, 62. Columbia argues that Dower's FMOC label is attached directly to the base. *Id.* This is wrong. An FMOC label has a cleavable methoxycarbonyl linker that connects the fluorenyl moiety to the base:



Ex. 1119 ¶108. Fmoc was known to be cleaved at the methoxycarbonyl site, not at the fluorenyl moiety. *Id.* ¶¶109-110.

Further, any argument that the claimed linker provides patentability over Dower is disingenuous. Columbia's patent has no disclosure of an exemplary chemically cleavable linker. Ex. 1067 ¶73, n.4. The Columbia patent merely says that the linker can be chemically cleaved. Ex. 1002, 14:17-21. Dower has a comparable disclosure. Ex. 1015, 15:52-59.

Faced with its sparse disclosure and a §112 rejection during prosecution, to obtain its patent Columbia argued that a POSA was able to pick an appropriate linker based on their own general knowledge. Ex. 1065, 19. Columbia should not be permitted to take a contrary position now, or hold Dower's essentially identical

disclosure to Columbia's own to be insufficient. The Board should cancel Claim 1 under Ground 2.

V. ESTOPPEL APPLIES TO COLUMBIA

The issues raised by Columbia in this IPR were addressed in the prior IPRs. While Columbia obfuscates what elements of the claim it suggests Tsien does not obviate in this IPR, it appears to be a “small, chemically cleavable, chemical group capping the oxygen at the 3' position” and maybe “does not interfere with recognition of the analogue as a substrate by a DNA polymerase.” The Board previously ruled Tsien disclosed these elements. Ex. 1005, 8-11; Ex. 1007, 16-17. This is true of most of the claim elements in this IPR, including rejecting a claim specifically reciting the 3-carbon allyl protecting group over Tsien. Ex. 1127, 11-12; Ex. 1128, 3; Ex. 1005, 46-47.

The same is true of the underlying sub-issues. Reasonable expectation of polymerase incorporation was at issue in the prior IPRs. Ex. 1007, 29-31; Ex. 1005, 17-18. Tsien meeting the small chemically cleavable capping group claim element through its allyl ether disclosure was also raised. Ex. 1127, 11-12; Ex. 1128, 3.

The patents involved in the decided and present IPRs have the same disclosure, the same claimed priority, and the same **contested** claim elements. The prior art at issue in the IPRs is identical. The only difference is Columbia found a new expert that would disagree with its prior expert. Ex. 1098, 107:12-108:20,

154:10-156:6. However, the new expert repeatedly disclaimed awareness of the POSA's knowledge at the relevant time on the very issues on which he was opining. Ex. 1112, 141:19-142:9, 143:10-18. Estoppel is designed to prevent this gamesmanship.

The Board's rules prevent a party from "taking action inconsistent with [an] adverse judgement." 37 C.F.R. §42.73(d)(3). But Columbia is doing just that. Whether this re-litigation is excluded by C.F.R. or by traditional issue preclusion, it should be excluded. Petition, 2-3, 7; *MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1376-77 (Fed. Cir. 2018).

Columbia tries to obfuscate estoppel by showing a claim with lots of underlining. However, not everything underlined is new. Most underlined elements were in claims found invalid over Tsien. Ex. 1005 (invalidating claims 12, 13, 15, 16, 17, 28, 31 and denying motion to amend); Ex. 1137 (Appx. A at 4, substitute claim 40 to allyl); Ex. 1010; Ex. 1007 (invalidating claims 1, 3, 6); Ex. 2004.

Further, the C.F.R. and issue preclusion apply to decided issues. Petition, 2-3, 7. That Columbia created a claim with new language that they had the opportunity to (but did not) argue was absent in Tsien does not prevent preclusion as to the decided claim elements (and decided sub-issues), because the validity questions are the same. *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1342 (Fed. Cir. 2013).

VI. CONCLUSION

Columbia's claim should be cancelled.

Respectfully submitted,

Dated: January 22, 2019

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that foregoing **PETITIONER’S REPLY**, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a), contains 5,599 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 **PETITIONER'S
REPLY** is being served on January 22, 2019, via e-mail to counsel for the Trustees of Columbia University, at the email addresses below:

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