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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.

Case No. IPR2018-00322

U.S. Patent No. 9,708,358

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 9,708,358**

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1001	Exhibit number not used.
1002	U.S. Patent No. 9,708,358 (“Ju”) – (Claim 1 is a cytosine claim)
1003	Exhibit number not used.
1004	Exhibit number not used.
1005	2014-03-06 IPR2012-00007, Paper 140, Final Written Decision
1006	2014-03-06 IPR2012-00006, Paper 128, Final Written Decision
1007	2014-03-06 IPR2013-00011, Paper 130, Final Written Decision
1008	2015-07-17 Federal Circuit Opinion Affirming IPR2012-00006, IPR2012-00007 and IPR2013-00011
1009	Exhibit number not used.
1010	U.S. Patent No. 7,790,869 (“Ju”)
1011	Alberts, et al., “Molecular Biology of the Cell”, Third Edition, Garland Publishing Inc., New York (1994)
1012	Exhibit number not used.
1013	WO 91/06678 (“Tsien”)
1014	Prober, <i>et al.</i> , “A System for Rapid DNA Sequencing with Flourescent Chain-Terminating Dideoxynucleotides”, Science, 238:336-341 (1987) (“Prober”)
1015	U.S. Patent No. 5,547,839 (“Dower”)
1016	Metzker, <i>et al.</i> , “Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphosphates”, Nucleic Acids Research, 22:4259-67 (1994) (“Metzker”)

Exhibit No.	Description
1017	Wu and Metzker, et al., “Termination of DNA synthesis by N6-alkylated, not 3’-O-alkylated, photocleavable 2’-deoxyadenosine triphosphates”, Nucleic Acids Research, 35:6339-6349 (2007) (“Wu and Metzker”)
1018	Sanger et. al., “DNA sequencing with chain-terminating inhibitors”, Proc. Natl. Acad. Sci. USA, 74:5463-5467 (1977) (“Sanger”)
1019	U.S. Patent No. 7,270,951 (“Stemple”)
1020	U.S. Patent No. 5,302,509 (“Cheeseman”)
1021	Pelletier, et al., “Structures of Ternary Complexes of Rat DNA Polymerase β , a DNA Template-Primer, and ddCTP”, Science, 264:1891-1903 (1994) (“Pelletier”)
1022	Exhibit number not used.
1023	Welch, et al., “Syntheses of Nucleosides Designed for Combinatorial DNA Sequencing”, Chem. Eur. J., 5:951-960 (1999) (“Welch”)
1024	Welch, et al., “Corrigenda – Syntheses of Nucleosides Designed for Combinatorial DNA Sequencing”, Chem. Eur. J., 11:7136-7145 (2005) (“Welch Corrigenda”)
1025	Exhibit number not used.
1026	Exhibit number not used.
1027	Rosenblum, et al., “New dye-labeled terminators for improved DNA sequencing patterns”, Nucleic Acid Research, 25:4500-4504 (1997) (“Rosenblum”)
1028	Excerpts from 2013-09-04 Deposition Transcript of Dr. George L. Trainor in IPR2012-00007
1029	U.S. Patent No. 5,151,507 (“Hobbs”)

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1030	Exhibit number not used.
1031	Seela, et al., “Oligonucleotide Duplex Stability Controlled by the 7-Substituents of 7-Deazaguanine Bases”, <i>Bioorganic & Mechanical Chemistry Letters</i> , 5:3049-3052 (1995) (“Seela 1995”)
1032	Exhibit number not used.
1033	Exhibit number not used.
1034	2013-06-25 Declaration of Dr. George L. Trainor from IPR2012-00006
1035	Boss, et al., “Cleavage of Allyl Ethers with Pd/C”, <i>Angew. Chem. Int. Ed. Engl.</i> , 15:558-559 (1976) (“Boss”)
1036	Qian, et al., “Unexpected Enzymatic Fucosylation of the Hindered Tertiary Alcohol of 3-C-Methyl-N-Acetylactosamine Produces a Novel Analogue of the LeX-Trisaccharide”, <i>Journal of the American Chemical Society</i> , 120:2184-2185 (1998) (“Qian”)
1037	Kamal, et al., “A Miled and Rapid Regeneration of Alcohols from their Allylic Ethers by Chlorotrimethylsilane/Sodium Iodide”, <i>Tetrahedron Letters</i> , 40:371-372 (1999) (“Kamal”)
1038	Excerpts from Prosecution History of U.S. Patent No. 9,725,480 (“Ju”)
1039	Vollhardt, et al., “Organic Chemistry”, Second Edition, W.H. Freeman and Co., New York (1994) (“Vollhardt”)
1040	Yu, et al., “Cyanine dye dUTP analogs for enzymatic labeling of DNA probes”, <i>Nucleic Acids Research</i> , 22:3226-3232 (1994) (“Yu”)
1041	Livak, et al., “Detection of single base differences using biotinylated nucleotides with very long linker arms”, <i>Nucleic Acids Research</i> , 20:4831-4837 (1992) (“Livak”)

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1042	Watson, et al., “Genetical Implication of the Structure of Deoxyribonucleic Acid”, Nature, 171:964-967 (1953) (“Watson & Crick”)
1043	Zavgorodny, et al., “1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry”, Tetrahedron Letters, 32:7593-7596 (1991) (“Zavgorodny”)
1044	2015-02-11 Final Written Decision in IPR2013-00517
1045	2016-05-09 Federal Circuit Opinion Affirming IPR2013-00517
1046	Gigg, et al., “The Allyl Ether as a Protecting Group in Carbohydrate Chemistry Part II”, J. Chem. Soc. (C), 1903-1911 (1968) (“Gigg”)
1047	2013-08-30 Substitute Columbia Patent Owner Response in IPR2012-00007, Paper 77
1048	2014-07-25 Final Written Decision in IPR2013-00128, Paper 92
1049	2014-10-28 Final Written Decision in IPR2013-00266, Paper 73
1050	2016-01-29 Federal Circuit Opinion Affirming IPR2013-00128 and IPR2013-00266
1051	Greenberg, et al., “Optimization and Mechanistic Analysis of Oligonucleotide Cleavage from Palladium-Labile Solid-Phase Synthesis Supports”, J. Org. Chem., 63:4062-4068 (1998) (“Greenberg”)
1052	Seitz, et al., HYCRON, an Allylic Anchor for High-Efficiency Solid Phase Synthesis of Protected Peptides and Glycopeptides”, J. Org. Chem., 62:813-826 (1997) (“Seitz”)
1053	Gullier, et al., “Linkers and Cleavage Strategies in Solid-Phase Organic Synthesis and Combinatorial Chemistry”, Chem. Rev., 100:2091-2157 (2000) (“Gullier”)

Exhibit No.	Description
1054	U.S. Patent No. 8,088,575 (“Ju”)
1055	Stryer, “Biochemistry”, Fourth Edition, W.H. Freeman and Co., New York (1995) (“Stryer”)
1056	Exhibit number not used.
1057	<i>Curriculum Vitae</i> of Floyd Romesberg, Ph.D.
1058	List of documents considered by Floyd Romesberg, Ph.D.
1059	Sears, et al., “CircumVent Thermal Cycle Sequencing and Alternative Manual and Automated DNA Sequencing Protocols Using the Highly Thermostable VentR (exo) DNA Polymerase”, <i>BioTechniques</i> , 13:626-633 (1992) (“Sears”)
1060	Columbia’s complaint for U.S. 9,708,358
1061	Exhibit number not used.
1062	Exhibit number not used.
1063	Exhibit number not used.
1064	Exhibit number not used.
1065	Excerpts from Prosecution History of U.S. Patent No. 9,708,358
1066	Declaration of Jingyue Ju from Prosecution History of U.S. Patent No. 9,708,358
1067	Declaration of Floyd Romesberg, Ph.D. for ’358

Illumina v. Columbia
IPR Petition – U.S. Patent No. 9,708,358

Illumina, Inc. requests *inter partes* review of Claim 1 of U.S. 9,708,358 (“’358 patent,” Ex-1002) purportedly owned by The Trustees of Columbia University (“Columbia”).

I. INTRODUCTION

In three previous IPRs the Board held all challenged claims in related Columbia patents unpatentable over the prior art Tsien reference, or obvious over Tsien in view of Prober, as shown in the following table:

Previous IPR Final Written Decision	Columbia’s Patent	Result
IPR2012-00007, Paper 140 (Ex-1005)	7,790,869 (“’869 patent”)	All challenged claims held unpatentable.
IPR2012-00006, Paper 128 (Ex-1006)	7,713,698 (“’698 patent”)	
IPR2013-00011, Paper 130 (Ex-1007)	8,088,575 (“’575 patent”)	

The Federal Circuit unanimously affirmed the Board’s decisions. *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 Fed. Appx. 916, 927-28, 934 (Fed. Cir. 2015) (Ex-1008).

Undeterred by these results, Columbia improperly sought additional bites at the apple by filing four patent applications directed to the same unpatentable subject matter. These applications issued as the ’358 patent, U.S. 9,718,852, U.S. 9,719,139, and U.S. 9,725,480. Illumina is filing IPR petitions for each of these patents.

The '358 patent issued with a single claim: Claim 1. During prosecution of the '358 patent, the Examiner rejected Claim 1 as patentably indistinct over claims held unpatentable from Columbia's '869 patent. Columbia did not disagree, and made no effort to substantively distinguish Claim 1 from the '869 patent. Instead, Columbia filed a terminal disclaimer to sidestep the rejection. ***It stands un rebutted that Claim 1 is patentably indistinct over unpatentable claims from the '869 patent.***

Claim 1 of the '358 patent is directed to a nucleotide analogue with: (1) a “small” 3'-OH capping group, and (2) a removably-labeled, cytosine-substituted base. During prosecution, Columbia's sole argument for nonobviousness was that it invented a nucleotide with a “small” 3'-O-capping group. Columbia made this argument while knowing that the Board had previously held Claim 31 of the '869 patent unpatentable, which recited “wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.” Any argument that the size or “smallness” of the 3'-O-capping group is inventive was fully and finally rejected by the Board.

Columbia relied on a concept adjudicated by the Board to be non-inventive and filed a terminal disclaimer over claims already held to be unpatentable. This clearly violates the patent owner estoppel provisions of 37 C.F.R. §42.73(d)(3)(i). Pursuant to this regulation, a “patent applicant or owner is precluded from taking

action inconsistent with [an] adverse judgment, including obtaining in any patent...

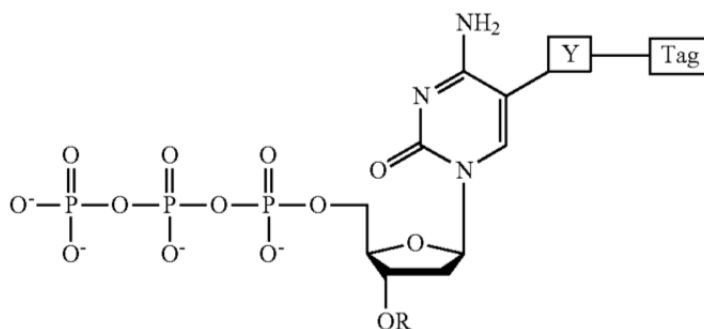
[a] claim that is not patentably distinct from a finally refused or canceled claim.” The Board should rectify Columbia’s disregard of the Board’s previous final written decisions and §42.73(d)(3)(i), and cancel Claim 1 of the ’358 patent.

II. BACKGROUND REGARDING THE ’358 PATENT

The ’358 patent claims priority to the ’869 and ’575 patents via continuation applications. Ex-1002 at Title Page. The ’358, ’869, ’575, and ’698 patents contain the same specification.

Claim 1 of the ’358 patent, the only claim, recites:

1. A cytosine deoxyribonucleotide analogue having the structure:



wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue, (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase, (c) is stable during a DNA polymerase reaction, and (d) does not contain a ketone group;

wherein OR is not a methoxy group or an ester group;

wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction;

wherein tag represents a detectable fluorescent moiety;

wherein Y represents a chemically cleavable, chemical linker which

(a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction; and

wherein the cytosine deoxyribonucleotide analogue: i) is recognized as a substrate by a DNA polymerase, ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction, iii) produces a 3'-OH group on the deoxyribose upon cleavage of R, iv) no longer includes a tag on the base upon cleavage of Y, and v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue.

A. Prosecution History and Patent Owner Estoppel

During prosecution, the Examiner issued an office action rejecting Columbia's claim for double patenting, lack of written description support, and obviousness. Ex-1065 at 93-103.

1. The double patenting rejection and patent owner estoppel

The Examiner issued an obviousness-type double patenting rejection finding Columbia's present claim was patentably indistinct from Claims 17 and 28 of the '869 patent in view of Tsien. Ex-1065 at 100. Claims 17 and 28 were previously held unpatentable by the Board and Federal Circuit. Ex-1005 at 49; Ex-1008 at 33. Under 37 C.F.R. §42.73(d)(3)(i), Columbia was bound by patent owner estoppel to refrain from taking any action to prosecute the present claim unless and until it

convinced the Examiner to withdraw the patentably indistinct finding. Instead of addressing the Examiner’s finding, Columbia evaded it with a terminal disclaimer, which improperly led the Examiner to remove the rejection. Ex-1065 at 24. The Examiner’s patentably indistinct finding was never addressed and remains intact today.

2. Lack of written description support

The Examiner rejected the functional language recited for “Y” and “R” for lack of written description support. Ex-1065 at 93-96.

Columbia asserted that Claim 1 is supported because it covers the same subject matter as the previously issued claims “cited in the Office Action in the obviousness-type double patenting rejection” that are presumed to be supported by the same specification. *Id.* at 21, n.3. The previously issued claims Columbia relied on include the patentably indistinct and now cancelled Claims 17 and 28 of the ’869 patent. The judicial estoppel rule prevents Columbia from embracing the Examiner’s patentably indistinct finding to establish written description support during prosecution without also accepting the patent owner estoppel ramifications that come with the Examiner’s finding. *New Hampshire v. Maine*, 532 U.S. 742, 749 (2001) (“Where a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position.... This rule, known as judicial

estoppel, generally prevents a party from prevailing in one phase of a case on an argument and then relying on a contradictory argument to prevail in another phase.”).

3. Columbia incorrectly asserted “small” was inventive, and did not address Tsien

The Examiner issued an obviousness rejection over Stemple in view of Tsien. Ex-1065 at 96-98. Columbia’s response focused solely on Stemple and argued nonobviousness over Stemple’s disclosure of a “large” 3’-O-2-nitrobenzyl capping group. Ex-1065 at 22-24. Columbia improperly asserted its inventive insight was the 3’-OH capping group being “small” (*id.* at 24), which contradicts the Board’s decision in IPR2012-00007 holding unpatentable Claim 31 of Columbia’s ’869 patent that recited “wherein the cleavable chemical group capping the 3’ OH group is a small chemical moiety.”¹ Ex-1005 at 11; Ex-1010 at 34:48-50. The Examiner withdrew the obviousness rejection based on Columbia’s arguments regarding Stemple and the “small” limitation. Columbia never attempted to distinguish its claim over Tsien.

¹ Emphasis supplied unless otherwise noted.

III. THE BOARD SHOULD PRECLUDE COLUMBIA FROM PARTICIPATING IN THIS PROCEEDING

Columbia should be barred from participating in the present proceeding under the Board's patent owner estoppel regulation. 37 C.F.R. §42.73(d)(3)(i). The prosecution history of the '358 patent contains an un rebutted finding by the Examiner that Claim 1 is patentably indistinct from canceled Claims 17 and 28 of the '869 patent. Columbia embraced and benefited from that finding to overcome the Examiner's rejection for lack of written description support. Columbia then sidestepped the merits of the Examiner's finding of patentable indistinctness by filing a terminal disclaimer, thereby undermining the Board and Federal Circuit's prior rulings. Columbia thus prosecuted the '358 patent in contempt of the Board's patent owner estoppel regulation to improperly obtain issuance of Claim 1. Columbia should not be permitted to take further action inconsistent with the Board and Federal Circuit's prior rulings and, under 37 C.F.R. §42.73(d)(3)(i), the Board should preclude Columbia from participating in this proceeding.

IV. CLAIM CONSTRUCTION

The claim is given its broadest reasonable construction in light of the specification. For the purposes of this proceeding, no claim term requires express construction to evaluate patentability. Illumina's position in this proceeding should not be taken as an assertion regarding the appropriate claim scope in other adjudicative forums where a different standard may apply.

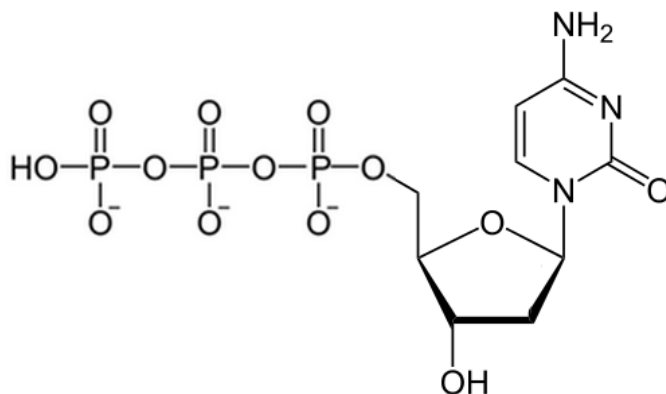
V. LEVEL OF ORDINARY SKILL IN THE ART

Illumina submits that the person of ordinary skill in the art (“POSA”) would have been a member of a team of scientists developing nucleotide analogues, researching DNA polymerases, and/or addressing DNA sequencing techniques. Such a person would have held a doctoral degree in chemistry, molecular biology, or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience. Thus, a POSA includes a person having a doctoral degree in a field related to chemistry, and at least five years of laboratory experience directed toward the research and development of nucleotide analogues, DNA polymerases, and/or DNA sequencing.

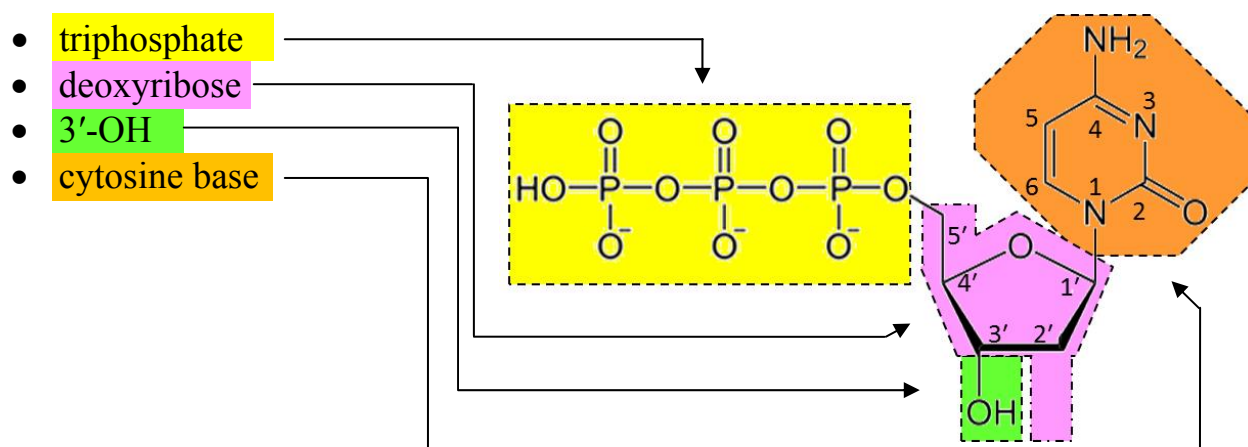
VI. STATE OF THE ART

A. Deoxyribonucleotides Were Known

Deoxyribonucleotides are found in nature and make up the building blocks of DNA. The chemical formula, nomenclature, and uses of deoxyribonucleotides were well known. Ex-1011 at 46-47, 58-60, 98-103. The arrangement of atoms comprising the naturally occurring cytidine deoxyribonucleotide triphosphate were known to be:

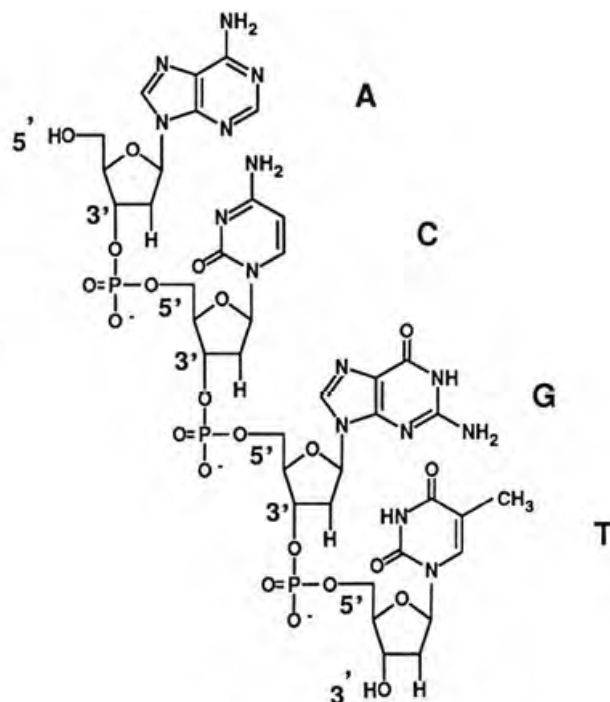


Cytidine deoxyribonucleotide triphosphate was commonly referred to by its acronym: “dCTP.” This nucleotide has several well-known features: a triphosphate, a deoxyribose, a 3'-OH, and a cytosine base. These features are highlighted in the following diagram, along with the conventional numbering of deoxyribose carbon atoms from 1' to 5' and the numbering of cytosine atoms from 1 to 6:



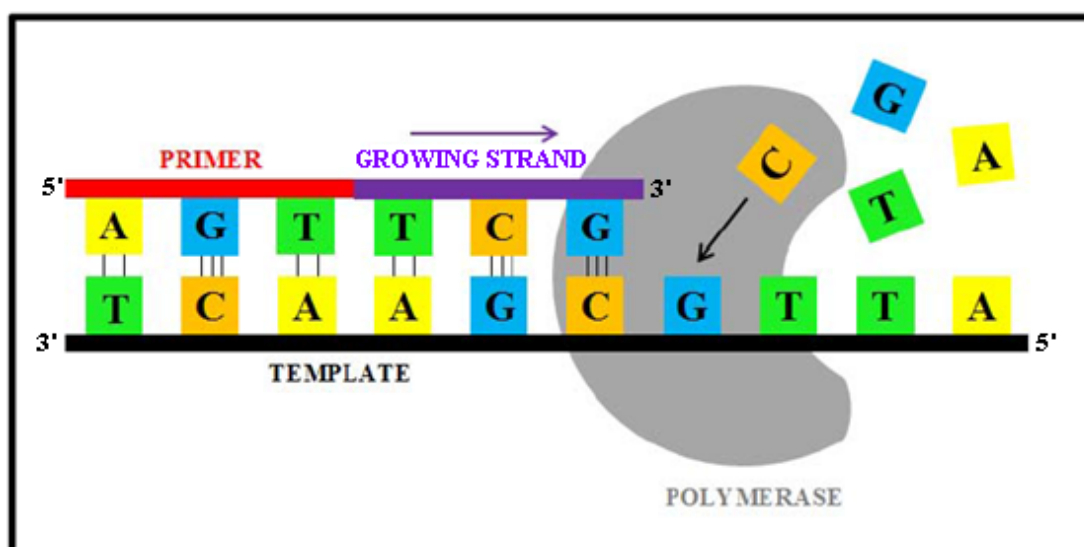
Ex-1011 at 58-59; Ex-1067 ¶31.

A strand of DNA consists of deoxyribonucleotides in which the 5'-phosphate of one nucleotide is attached to the 3'-oxygen of the adjacent nucleotide:



Ex-1067 ¶34; Ex-1011 at 98-101.

When DNA is synthesized (or copied), a single strand of DNA serves as a “template.” A polymerase enzyme incorporates nucleotides into a new strand of DNA having bases that are complementary to the template:



Ex-1067 ¶35; Ex-1011 at 98-103. If the 3'-OH group of the last nucleotide is blocked (also known as “capped”) with a protecting group, the polymerase cannot incorporate another nucleotide until the protecting group is removed (also referred to as “deblocked” or “uncapped”). Ex-1013 at 12:22-13:29; Ex-1016 at 4259-60; Ex-1002 at 7:51-58, 3:4-17; Ex-1067 ¶35.

B. Nucleotide Analogues Were Known

Several prior art methods were known for determining the sequence of DNA, including Sanger sequencing (Ex-1018; Ex-1014) and sequencing-by-synthesis (“SBS”). Ex-1013; Ex-1015; Ex-1016; Ex-1020; Ex-1067 ¶36. Sanger sequencing and SBS use a polymerase enzyme to incorporate modified nucleotides (i.e., “nucleotide analogues”) containing a detectable label into DNA. The label on the incorporated nucleotide analogue is “read” to determine the DNA sequence. Several labeled nucleotide analogues were known, including nucleotide analogues containing: (1) removable 3'-OH capping groups, and (2) labels attached to the base through a linker.

1. Nucleotide analogues having a 3'-OH cap and a labeled base were known

The Board and Federal Circuit found that Tsien and Dower disclose nucleotide analogues for DNA sequencing having **both** a removable 3'-OH cap and a detectable label attached to the base. Ex-1005 at 6; Ex-1008 at 13-15.

Tsien discloses sequencing using fluorescently labeled nucleotides having a 3'-OH blocking group. Ex-1013 at 10:17-18:33. Tsien also discloses labeling the nucleotide base. *Id.* at 27:35-28:6. Dower discloses using nucleotide analogues having a removable fluorescent label linked to the base and a removable 3'-OH blocking group. Ex-1015 at 14:50-53, 15:33-40, 15:52-56, 18:64-19:10, Fig. 9.

a. Small 3'-capping groups were desirable

Dower disclosed the desirability of nucleotides having “small blocking groups” on the 3'-OH. Ex-1015 at 25:48-51. Dower was filed in 1990 and provides blocking groups that were considered small at that time: “acetyl, tBOC, NBOC, and NVOC.” *Id.* at 25:48-51. The crystal structure of DNA polymerase was published in 1994 by Pelletier. Ex-1021 at 1897, 1903. 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:

The POSA would also have understood that Pelletier et al. disclosed, on page 1903, the precise coordinates of the structure of the polymerase in “References and Notes” 101 and, in Table 3 on page 1897, the distances between the sugar of the nucleotide analogue and the key amino acids in the active site of the polymerase....

The POSA in October 2000 would have readily known whether any given R when present as OR (a 3'-O capping group) was small by this

standard using the published coordinates and available software such as Chem3D Pro.

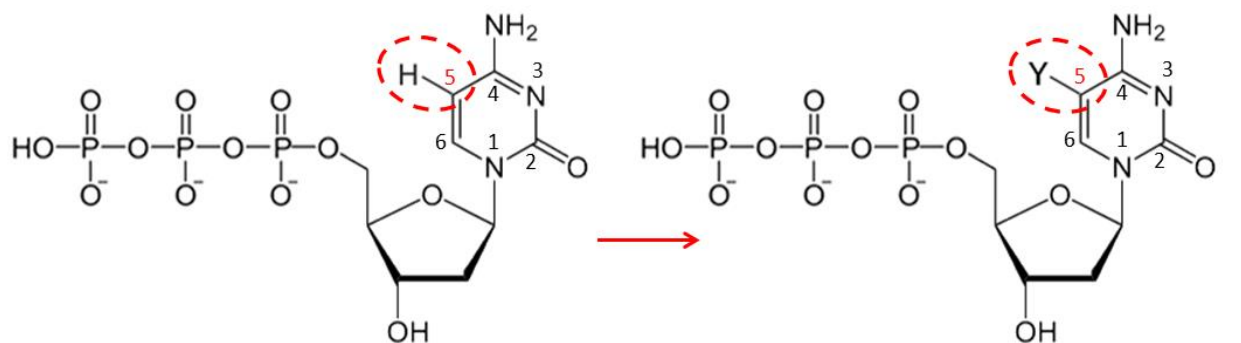
Ex-1065 at 16; Ex-1066 ¶¶11-16;² *id.* at 31-33 (Exhibit C); Ex-1002 at 2:63-3:3.

b. 5-Substituted pyrimidine labels were common

Tsien and Dower disclose base-labeled nucleotide analogues. Ex-1013 at 27:35-28:2, 28:5-6, 30; Ex-1015 at 14:50-53, 15:33-40, 15:52-56, 18:64-19:10, Fig. 9. By 1999, base-labeled nucleotide analogues were favored over nucleotides having labels at the 3'-position because labels at the 3'-position did not fit within the polymerase active site. Ex-1023 at 956; Ex-1024; Ex-1002 at 2:47-57; Ex-1066 ¶¶13-15.

Particularly preferred bases were 5-substituted pyrimidines having a label attached at the 5-position. A 5-substituted cytosine nucleotide analogue has a substituent at the 5-position instead of a hydrogen atom:

² Exhibit 1066 is a copy of the Rule 132 Declaration by Dr. Jingyue Ju that Columbia submitted during prosecution of the '358 patent.



cytosine nucleotide

5-substituted cytosine nucleotide analogue

Ex-1014 at 337-38; Ex-1067 ¶¶44-45.

Attaching a label through a linker at the 5-position of cytosine for nucleotide sequencing with DNA polymerase was disclosed in 1987 by Prober. Ex-1014 at 337-38. By 1999, 5-substituted labeled cytosine nucleotide analogues were widely and commercially available. Ex-1027 at 4501. Columbia's witness (Dr. Trainor) in IPR2012-00007 conceded that the 5-position of pyrimidines was the preferred attachment position. Ex-1028 at 280:23-281:3.

The preference for 5-substituted pyrimidines stemmed from several well-known benefits. Labels attached to the 5-position of pyrimidines “places the linker and reporter in the major groove” and “minimize[s] interference with hybridization and other processes.” Ex-1029 at 27:52-65; Ex-1067 ¶47. Furthermore, 5-substituents on pyrimidines stabilize the duplex structure of DNA. Ex-1031 at 3051.

VII. THERE IS A REASONABLE LIKELIHOOD THAT THE CHALLENGED CLAIM IS UNPATENTABLE

Illumina requests cancellation of Claim 1 as obvious in view of the asserted prior art.

A. The Asserted References Are Prior Art

The earliest claimed priority date for the '358 patent is October 6, 2000.

The asserted references are all §102(b) prior art to the '358 patent.

Asserted Reference	Publication Year	Exhibit No.
1. WO 91/06678 (“Tsien”)	1991	Ex-1013
2. U.S. 5,547,839 (“Dower”)	1996	Ex-1015
3. Prober, 238 Science 336-41, 1987 (“Prober”)	1987	Ex-1014
4. Metzker, 22 Nucleic Acids Research 4259-67, 1994 (“Metzker”)	1994	Ex-1016

B. Grounds Of Challenges

IPR is requested for the following grounds of unpatentability:

Ground	References	Basis	Challenged Claim
1	Tsien	§103(a)	1
2	Dower in view of Prober and Metzker	§103(a)	1

Illumina submits the declaration of Dr. Floyd Romesberg in support of this Petition. Ex-1067.

VIII. GROUND 1: OBVIOUSNESS OVER TSIEN

A. Introduction to Tsien

The Board and Federal Circuit previously held claims from Columbia's '869 patent were rendered unpatenable by Tsien. Ex-1005 at 8-11; Ex-1008 at 33. Tsien contains disclosures that meet all limitations of Columbia's present claim.

Tsien discloses DNA sequencing using nucleotide analogues having a 3'-OH blocking group and a fluorescent label. Tsien discloses a 3'-O-allyl blocking group that meets all "R" limitations of Columbia's present claim.

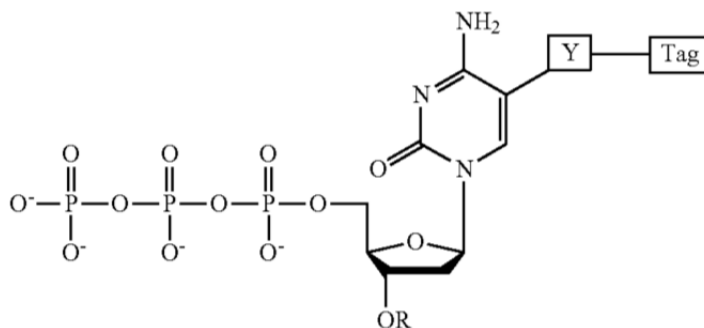
Tsien discloses attaching a fluorescent label to the 5-position of a cytosine base. Tsien further discloses using a cleavable linker to attach fluorescent labels to the base. These disclosures meet all "Y" and "Tag" limitations of Columbia's present claim.

B. Claim 1 is Obvious Over Tsien

Tsien discloses all limitations of Claim 1 and renders the claim obvious. Below is a detailed obviousness analysis that begins by exposing Columbia's claimed structure for what it is: a pictorial representation of the same nucleotide previously held unpatentable by the Board in IPR2012-00007. Next, each claim limitation is demonstrated to be disclosed by Tsien, along with a motivation to combine and a reasonable expectation of success.

1. The structure depicted in Claim 1 is not new

Claim 1 recites: “A cytosine deoxyribonucleotide analogue having the structure:

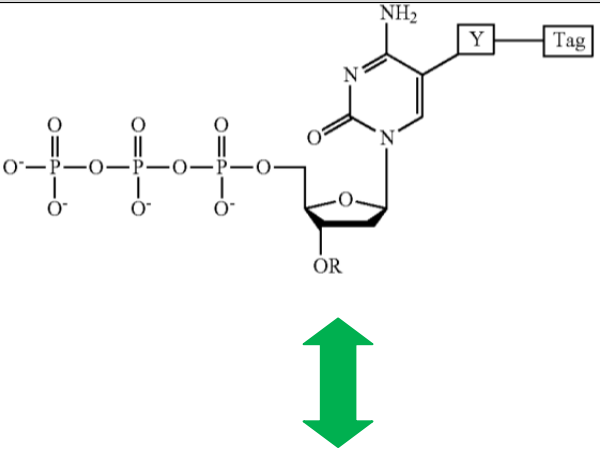


Ex-1002 at 34:3-17.

Columbia's specification does not contain a single image showing this structure. During prosecution, Columbia relied on language contained in paragraph [0093] of the specification to assert support for the claimed structure. Ex-1065 at 79. This paragraph corresponds to Ex-1002 at 10:64-66, which describes nucleotide features in prose. Every atom and group depicted in Claim 1's structure is fully described using standard nucleotide vocabulary as “a cytosine deoxyribose nucleotide triphosphate having an R group capping the 3'-OH group and a Tag attached through a cleavable linker (Y) to the 5-position of the base.” Ex-1067 ¶¶52-53.

In IPR2012-00007, the Board held unpatentable Claim 21 of Columbia's '869 patent that claimed a cytosine deoxyribonucleotide having a 3'-OH capping group and a tag attached through a cleavable linker to the base. Ex-1005 at 8-11.

The Federal Circuit affirmed. Ex-1008 at 33. In this case, Columbia merely repackaged the same unpatentable nucleotide into a “structural” format. The equivalence between the unpatentable nucleotide of Claim 21 and the present claim is evident in the following side-by-side comparison of the claims:

Claim 1 structure with equivalent nomenclature	Unpatentable Claim 21 (and Claim 12 from which it depends) from IPR2012-00007
 A cytosine deoxyribonucleotide having a 3'-OH capping group (R) and a Tag attached through a cleavable linker (Y) to the base.	21. The nucleotide of claim 12 wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine. 12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a 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.

As shown above, present Claim 1 and unpatentable Claim 21 from IPR2012-00007 recite the same cytosine deoxyribonucleotide having a 3'-OH capping group and a Tag (i.e., label) attached through a cleavable linker to the base. This

nucleotide was held unpatentable by the Board and the Federal Circuit. Columbia's tactic of changing the format in which the nucleotide is presented does not convert the unpatentable nucleotide into a patentable one. Tsien still renders the nucleotide unpatentable.

a. Tsien renders obvious the nucleotide depicted in Claim 1

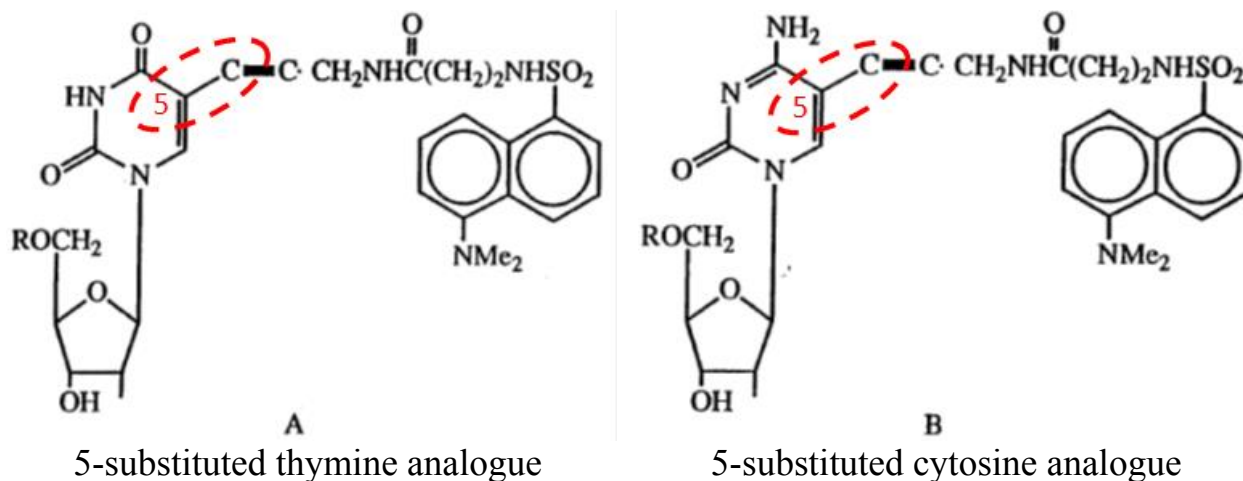
Tsien discloses deoxyribonucleotide triphosphate (dNTP) analogues. An exemplary cytosine analogue is provided in Tsien's Figure 2 as "3'-BLOCKED dC"TP." Ex-1013 at Fig. 2. This cytosine analogue is a deoxyribonucleotide having a 3'-blocking group and a tag attached to the cytosine base (as indicated by the apostrophes). *Id.* at 9:30-10:15, 12:22-27; Ex-1005 at 22-23; Ex-1067 ¶55.

Tsien discloses a cleavable linker attaching the tag to the base. Ex-1013 at 28:5-8 (disclosing "the use of a fluorescent tag attached to the base moiety" and "[t]he tag may be chemically cleaved"); *id.* at 27:35-28:35. Tsien discloses exemplary chemical linkers of silyl, allyl, and 2,4-dinitrophenylsulfenyl. *Id.* at 28:19-29.

Columbia's witness (Dr. Trainor) in IPR2012-00007 conceded that Tsien discloses each of these features. Ex-1028 at 106:4-8, 113:19-115:14, 227:2-228:4; Ex-1034 ¶28. Tsien's disclosure of a nucleotide having a 3'-OH capping group and a Tag attached through a cleavable linker to the base was confirmed by the

Board and affirmed by the Federal Circuit. Ex-1005 at 10, 22-23, 5-6; Ex-1008 at 13, 31.

Tsien further discloses 5-substituted pyrimidines:



Ex-1013 at 30 (annotated). Tsien's Structure B is a cytosine deoxyribose nucleotide having a fluorescent label attached through a linker to the 5-position of the base. Ex-1067 ¶57. Tsien discloses the advantages of labeling pyrimidines at the 5-position:

A number of approaches are possible to produce fluorescent derivatives of thymidine and deoxycytidine. One quite versatile scheme is based on an approach used by Prober et al. (1987) to prepare ddNTPs with fluorescent tags. Structures A, B, C and D below illustrate the type of fluorescent dNTPs that result from these synthetic approaches. The synthetic routes have a great flexibility in that the linker can be varied with respect to length or functionality. The terminal fluorescent moiety can also be varied according to need.

Ex-1013 at 29:10-19. Thus, Tsien discloses that Structure B is advantageous because it provides great flexibility for the linker length and functionality. Ex-1067 ¶57. Tsien’s disclosure is consistent with the known advantages of using 5-substituted pyrimidines, which “places the linker and reporter in the major groove” (Ex-1029 at 27:58-59), “minimize[s] interference with hybridization and other processes” (*id.* at 27:60-51), and stabilizes the DNA duplex. Ex-1031 at 3051; Ex-1067 ¶58. Columbia’s witness (Dr. Trainor) in IPR2012-00007 admitted that the 5-substituted pyrimidines disclosed on page 30 of Tsien were attractive nucleotide reagents. Ex-1028 at 220:25-221:2 (“I think [Tsien] gives a very nice set of reagents on page 30.”).

In summary, Tsien discloses the desirability of using the 3'-O-allyl capping group in Tsien’s sequencing methods. Tsien further discloses the desirability of a cytosine deoxyribose nucleotide having a fluorescent label attached through a linker to the 5-position of the base, as well as the desirability of attaching the label to the base via a cleavable linker. Tsien’s disclosure therefore renders obvious a cytosine deoxyribonucleotide having a 3'-OH capping group and a tag attached through a cleavable linker at the 5-position, which is the nucleotide depicted in Claim 1.

2. **Limitation R(a): “wherein R(a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3’ position of the deoxyribose of the deoxyribonucleotide analogue”**

Tsien discloses a “3'-BLOCKED dC"TP,” which is a cytosine deoxyribonucleotide analogue having a blocking group capping the 3'-oxygen of the deoxyribose. Ex-1013 at Fig. 2, 12:27-29; Ex-1067 ¶61. Tsien describes 3'-blocking groups, including chemical groups that can be removed using chemical conditions such as acid or base hydrolysis and other removal conditions. Ex-1013 at 20:24-25:34. Tsien specifically discloses the 3'-O-allyl blocking group. *Id.* at 24:29-30.

Tsien discloses 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—deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized.” *Id.* at 24:25-25:3; *id.* at 24:29-30 (“Allyl ethers are cleaved by treatment with Hg(II) in acetone/water (Gigg and Warren, 1968).”). It was known that allyl groups are chemically cleaved using palladium. Ex-1035 at 559; Ex-1036 at 2184; Ex-1067 ¶64.

A POSA would have recognized that Tsien’s allyl group is advantageous for another reason: it has a geometric configuration compatible with the active site of DNA polymerase. In 1994, Pelletier published the crystal structure of DNA

polymerase showing that the active site is spatially constrained where it binds to the 3'-group of a nucleotide substrate. Ex-1021 at 1897, 1903 (note 101). Based on Pelletier, a POSA knew only small 3'-capping groups could fit into the active site. Columbia admitted during prosecution that the POSA “would have readily known whether any given R when present as OR (a 3'-O capping group) was small by this standard using [Pelletier's] published coordinates and available software such as Chem3D Pro.” Ex-1065 at 16; Ex-1066 ¶¶11-16; *id.* at 31-33 (Exhibit C); Ex-1002 at 2:63-3:3. Dr. Ju admitted that allyl would have been recognized as small and one of “[o]nly a limited number of 3'-O capping groups [that] meet the standard of ‘small’ along with the other structural and functional features” for polymerase compatibility. Ex-1066 ¶¶22a, 16; Ex-1065 at 21. Tsien discloses the same allyl capping group that Dr. Ju admitted meets the claim term “small” along with the other requirements of R. Ex-1066 ¶19.

In 1994, Metzker demonstrated that Tsien's 3'-O-allyl group is compatible with polymerase, as conceded by Columbia's '358 patent. Ex-1002 at 3:26-30 (citing Ex-1016); Ex-1016 at 4263. The obviousness of using 3'-O-allyl is confirmed by Columbia's '358 patent, which admits “[i]t is known that ... allyl (-CH₂CH=CH₂) groups can be used to cap an -OH group, and can be cleaved chemically with high yield.” Ex-1002 at 3:39-44 (citing Ex-1037); *id.* at 26:22-33 (citing Ex-1016 & Ex-1037). Columbia's admission is binding for determining

obviousness. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) (“Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.”).

Tsien’s disclosure of small, chemically cleavable 3’-capping groups was previously settled by the Board and affirmed by the Federal Circuit. The Board found “Tsien teaches using nucleotides with 3’-OH capping groups and methods for removing the capping group and thus describes a cleavable chemical group capping the 3’-OH group.” Ex-1005 at 8-9; *id.* at 10-11. The Board also determined that Tsien rendered Claim 31 of Columbia’s ’869 patent unpatentable, and Claim 31 recited “wherein the cleavable chemical group capping the 3’ OH group is a small chemical moiety.” Ex-1005 at 11; Ex-1010 at 34:47-50; Ex-1008 at 33. Tsien therefore discloses limitation R(a).

3. Limitation R(b): “wherein R ... (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase”

Tsien discloses that a “criteria for successful use of 3’-blocking groups include[s]: (1) the ability of a polymerase enzyme to accurately and effectively incorporate the dNTPs carrying the 3’-blocking groups into the cDNA chain.” Ex-1013 at 20:28-32; *id.* at 19:4-18, 12:11-18, 24:1-2. A POSA would have known that Tsien’s 3’-O-allyl group does not interfere with recognition by a DNA polymerase because Metzker demonstrated polymerase recognition in 1994. Ex-1016 at 4263; Ex-1067 ¶¶63, 66. Columbia’s specification concedes that the 3’-O-

allyl group had been “shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994).” Ex-1002 at 3:28-30; *id.* at 3:22-26.

Dr. Ju admitted during prosecution that Tsien’s 3’-O-allyl meets this limitation and all other claimed limitations of the “R” group. Ex-1066 ¶¶22a (admitting allyl is one of “[o]nly a limited number of 3’-O capping groups [that] meet the ... structural and functional features recited in the claim”). Columbia’s witness in IPR2012-00007, Dr. Trainor, admitted Tsien discloses polymerase incorporation of 3’-capped and base-labeled nucleotides. Ex-1013 at 27:33-28:18; Ex-1028 at 449:3-20. Columbia admitted Tsien “explicitly disclosed” this limitation during prosecution of related U.S. 9,725,480 (“’480 patent”). Ex-1038 at 10.

Tsien’s disclosure of this limitation was settled when the Board held unpatentable Claim 28 from Columbia’s ’869 patent. Ex-1005 at 11. Claim 28 recited “wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.” Ex-1010 at 34:40-42; Ex-1008 at 33. Tsien therefore discloses limitation R(b).

4. **Limitations “wherein R ... (c) is stable during a DNA polymerase reaction” and “wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction”**

Tsien discloses the stability of 3'-capping groups during DNA polymerase incorporation. Ex-1013 at 19:4-18, 12:11-13:13, 23:28-32. Tsien discloses that the allyl capping group is particularly advantageous because “deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized.” *Id.* at 24:24-25:3. Tsien’s stated “incorporation” refers to DNA polymerase incorporation. *Id.* at 20:28-32; Ex-1067 ¶¶68. The overall stability disclosed by Tsien for the 3'-O-allyl group includes stability at the bond between the 3'-oxygen and the rest of the blocking group. Ex-1067 ¶¶68.

Columbia admitted Tsien discloses these two limitations during prosecution of the related '480 patent. Ex-1038 at 10-11 (citing Tsien at 23:28-32). Dr. Ju admitted the 3'-O-allyl group meets all claimed “R” limitations. Ex-1066 ¶¶22a. Tsien therefore discloses limitation R(c) and that the 3'-oxygen to R bond is stable during a polymerase reaction.

5. **Limitations “wherein R ... (d) does not contain a ketone group” and “wherein OR is not a methoxy group or an ester group”**

Tsien discloses the advantages of the 3'-O-allyl capping group (Ex-1013 at 24:24-25:3, 24:5-7), and this group does not contain a ketone group, as shown below:

-CH ₂ -CH=CH ₂ allyl Ex-1039 at 502-504	-C(=O)- ketone Ex-1039 at 43
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Tsien’s 3’-O-allyl capping group is not a methoxy or an ester group:

-O-CH ₂ -CH=CH ₂ -O-allyl	-O-CH ₃ methoxy	-O-C(=O)-CH ₃ an ester
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Ex-1067 ¶70. Tsien’s disclosure of a 3’-O-allyl capping group meets and render obvious limitations R(d) and wherein OR is not a methoxy group or an ester group.

6. Limitation “wherein tag represents a detectable fluorescent moiety”

Tsien discloses an exemplary cytosine analogue: “3’-BLOCKED dC”TP.” Ex-1013 at Fig. 2; *id.* at 10:4-15. The apostrophes indicate a fluorescent tag. *Id.* at 10:7-10 (“When [the dNTPs] are each tagged or labeled with different reporter groups, such as different fluorescent groups, they are represented as dA’TP, dC”TP, dG””TP and dT”””TP.”). The “fluorescent tag [is] attached to the base moiety” and “[t]he tag may be chemically cleaved.” *Id.* at 28:5-8; *id.* at 28:19-23, 27:36-28:12, 26:17-36, 13:4-13. Tsien’s fluorescent tags “are detected by conventional analytical methods” and provide “a major advantage of the present method.” *Id.* at 31:1-5.

The Board previously held unpatentable Claim 17 of Columbia’s ’869 patent that recited “wherein the detectable label is a fluorophore.” Ex-1005 at 11; Ex-1010 at 34:17-18; Ex-1008 at 30-31. Tsien therefore discloses this limitation.

7. Limitation Y is a “chemically cleavable, chemical linker”

Tsien discloses “cleavable tethers” (Ex-1013 at 28:23-29) that link the fluorescent tag to the base moiety. *Id.* at 28:5-8 (disclosing “the use of a fluorescent tag attached to the base moiety” and “[t]he tag may be chemically cleaved”); Ex-1005 at 10, 21-22. Tsien discloses exemplary chemical linkers (such as allyl, silyl, and 2,4-dinitrophenylsulfenyl), along with exemplary chemical cleavage conditions. Ex-1013 at 28:19-29; Ex-1067 ¶74.

The Board previously determined that Tsien discloses a chemically cleavable linker. Ex-1005 at 10, 21-22; Ex-1008 at 13, 31. Columbia’s witness in IPR2012-00007 (Dr. Trainor) confirmed that Tsien discloses a chemically cleavable linker attaching a tag to the base. Ex-1028 at 106:4-8, 113:19-115:14, 227:2-228:4. Columbia admitted during prosecution that Tsien discloses chemically cleavable chemical linkers. Ex-1065 at 19 (“[T]he Examiner refers to Stemple and Tsien as disclosing examples of chemically cleavable, chemical linkers. Applicant agrees.”); Ex-1066 ¶20. Tsien therefore discloses this limitation.

8. Limitation Y(a): “wherein Y ... (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase”

Tsien discloses exemplary “cleavable tethers” that attach the fluorescent tag to the base moiety. Ex-1013 at 28:23-29, 28:5-12. Such tethers “do not interfere with the binding of the dNTP to the polymerase.” *Id.* at 28:31-35; Ex-1067 ¶76. Tsien discloses that fluorescent tags and tethers are “innocuous,” meaning that their physical and chemical properties “do not interfere with either the enzymatic addition of the marked nucleotide to the cDNA, or the subsequent deblocking to yield a viable 3'-OH terminus.” Ex-1013 at 26:2-12. These disclosures meet limitation Y(a). Ex-1067 ¶76.

The '358 patent admits “it is known that modified DNA polymerases (Thermo Sequenase and Taq FS polymerase) are able to recognize nucleotides with extensive modifications with bulky groups such as energy transfer dyes at the 5-position of the pyrimidines (T and C)”. Ex-1002 at 2:57-63. This admission is confirmed by Tsien’s discussion of Structure B (which is a cytosine analogue having a label linked at the 5-position), and this discussion cites to Prober for “show[ing] enzymatic incorporation.” Ex-1013 at 28:16-18, 29:12-16; *id.* at 30. Tsien is correct that Prober shows polymerase incorporation of 5-substituted cytosine analogues. Ex-1014 at 337, 340; *see also* Ex-1040 at 3228, 3230 (demonstrating Vent DNA polymerase incorporation); Ex-1041 at 4832-33 (same); Ex-1067 ¶77.

Columbia “agreed” that Tsien discloses examples of the claimed linkers. Ex-1065 at 19; Ex-1066 ¶20. Columbia admitted in a related application that Tsien discloses this limitation. Ex-1038 at 12. Tsien therefore discloses limitation Y(a).

9. Limitation Y(b): “wherein Y ... (b) is stable during a DNA polymerase reaction”

Tsien discloses that “[t]he tether can be cleavable if desired to release the fluorophore or other label on demand.” Ex-1013 at 28:19-23. Tsien discloses exemplary chemically cleavable tethers “that permit removing the fluorescent group before the next successive nucleotide is added.” Ex-1013 at 28:23-25. The “successive nucleotide” addition refers to a DNA polymerase reaction. *Id.* at 28:31-35. The removal of the fluorescent group from the nucleotide analogue *after* incorporation and *before* the addition of next nucleotide indicates the linker is stable during the polymerase reaction. Ex-1067 ¶79.

Columbia “agreed” that Tsien discloses examples of the claimed linkers. Ex-1065 at 19; Ex-1066 ¶20. Columbia admitted in a related application that Tsien discloses this limitation. Ex-1038 at 12. Tsien therefore discloses limitation Y(b).

10. Limitation i): “wherein the cytosine deoxyribonucleotide analogue: i) is recognized as a substrate by a DNA polymerase”

Tsien discloses polymerase recognition of a nucleotide analogue having a small chemically cleavable 3'-capping group (such as Tsien's 3'-O-allyl group) and a chemically cleavable linker attached to the base. *Supra* Sections VIII.B.3 and 8.

Tsien further discloses a “3'-BLOCKED dC"TP” analogue is added to a reaction zone with the three other labeled and blocked dNTPs where a polymerase brings “about addition of the one, and only the one, of the four labeled blocked dNTPs which is complementary to the first available template nucleotide following the primer.” Ex-1013 at 12:22-27, Fig. 2. This polymerase addition discloses recognition of a cytosine deoxyribonucleotide having a 3'-OH capping group and a detectable tag attached to the base. Ex-1067 ¶¶81-82; *see also* Ex-1013 at 19:4-18, 20:28-32. Tsien's cleavable linkers “do not interfere with the binding of the dNTP to the polymerase” (Ex-1013 at 28:31-35) and the fluorescent tag and tethers are “innocuous” to the polymerase. *Id.* at 26:2-12. It was known that Vent polymerase incorporates 3'-O-allyl nucleotide analogues (Ex-1016 at 4263), as well as 5-substituted cytosine nucleotide analogues. Ex-1040 at 3228, 3230; Ex-1041 at 4832-33; Ex-1059 at 632; Ex-1067 ¶82. Tsien's disclosures therefore meet limitation i).

11. Limitation ii): “wherein the cytosine deoxyribonucleotide analogue ... ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction”

As discussed in Sections VIII.B.3, 8 and 10, Tsien discloses DNA polymerase recognition and incorporation of nucleotide analogues having a small chemically cleavable 3'-capping group and a chemically cleavable linker. This incorporation is depicted in Tsien's Figure 1B:

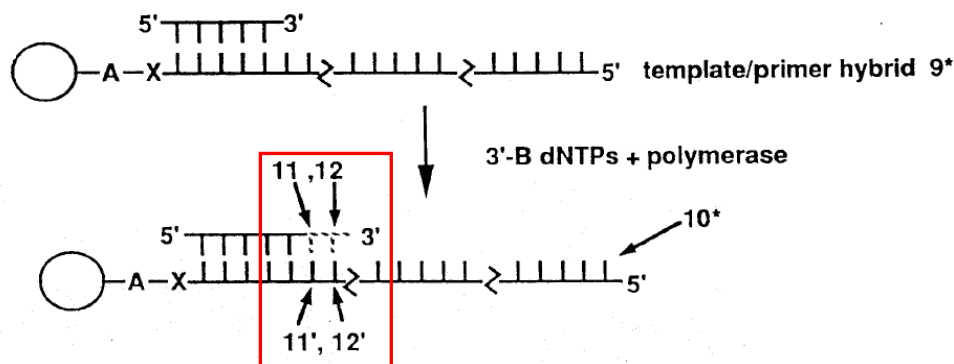


FIG. 1B

Ex-1013 at Figure 1B (annotated). In Figure 1B, dNTP analogues are added by DNA polymerase, with “11 and 12 represent[ing] the first two such dNTPs incorporated into the growing molecule.” Ex-1013 at 11:5-9. Nucleotide analogues 11 and 12 are added at the 3'-end of the growing chain. Ex-1013 at 12:22-13:29; Ex-1067 ¶¶84-85. Tsien therefore discloses limitation ii).

12. **Limitation iii): “wherein the cytosine deoxyribonucleotide analogue ... iii) produces a 3'-OH group on the deoxyribose upon cleavage of R”**

Tsien discloses that 3'-blocking group removal “generates an active 3' hydroxyl.” Ex-1013 at 13:14-22. Tsien discloses conditions for chemical cleavage of 3'-O-allyl ethers. *Id.* at 24:29-30. Columbia's '358 patent admits it was known that the “allyl (-CH₂CH=CH₂) group is used to cap the 3'-OH group using well-established synthetic procedures” and “can be removed chemically with high yield.” Ex-1002 at 26:22-33 (citing Ex-1016 & Ex-1037); *id.* at 3:39-44; Ex-1067 ¶87; *see also* Ex-1035 at 559 (demonstrating cleavage of allyl groups using

palladium); Ex-1036 at 2184 (demonstrating quantitative allyl cleavage). Tsien discloses limitation iii).

13. Limitation iv): “wherein the cytosine deoxyribonucleotide analogue ... iv) no longer includes a tag on the base upon cleavage of Y”

As discussed in Section VIII.B.7, Tsien discloses a cleavable linker that removes the tag from the base upon cleavage of the linker. Tsien discloses that “[t]he tether can be cleavable if desired to release the fluorophore or other label on demand.” Ex-1013 at 28:19-23. The fluorophore is removed from the nucleotide via chemical cleavage of the tether. *Id.* at 28:23-29; Ex-1067 ¶89; Ex-1005 at 21-22; Ex-1008 at 13. Tsien therefore discloses limitation iv).

14. Limitation v): “wherein the cytosine deoxyribonucleotide analogue ... v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue”

Tsien discloses that each nucleotide analogue should pair with its complementary nucleotide. A “key” feature of Tsien’s disclosure is “direct identification of the dNTPs as they are incorporated into the growing complementary DNA chain.” Ex-1013 at 7:19-24; *id.* at 28:31-35 (disclosing “proper base pairing during complementary chain growth”). Tsien discloses that four labeled and 3’-blocked dNTP analogues (A, T, G, and C analogues) are added to a reaction zone such that polymerase “bring[s] about addition of the one, and only the one, of the four labeled blocked dNTPs which is complementary to the

first available template nucleotide following the primer.” *Id.* at 12:22-27. A cytosine nucleotide analogue forms three hydrogen bonds with its complementary nucleotide, guanosine. Ex-1011 at 99; Ex-1042 at 966; Ex-1067 ¶92.

Tsien discloses Structure B, which is a cytosine analogue having a label linked at the 5-position. Ex-1013 at 30. Tsien cites to Prober for showing enzymatic incorporation of 5-labeled cytosine analogues. *Id.* at 29:12-16 (“Prober et al. (1987) [prepared] ddNTPs with fluorescent tags. Structures A, B, C and D below illustrate the type of fluorescent dNTPs that result from these synthetic approaches.”); *id.* at 28:16-18 (“Prober et al. (1987) show[s] enzymatic incorporation of fluorescent ddNTPs”). Tsien is correct that Prober shows polymerase incorporation of 5-substituted cytosine analogues. Ex-1014 at 337, 340. Prober discloses DNA polymerase maintains fidelity during incorporation of 5-labeled cytosine analogues. *Id.* Maintenance of fidelity indicates that the 5-labeled cytosine analogue forms hydrogen bonds with its complementary guanine nucleobase. Ex-1067 ¶91. A POSA would therefore have expected Tsien’s 5-substituted cytosine nucleotide analogues to form hydrogen bonds with guanine. Tsien thus renders obvious limitation v).

15. There was motivation to combine disclosures within Tsien

Tsien discloses all features of Claim 1. The Board and Federal Circuit determined a POSA reading Tsien would clearly envisage a nucleotide having a

fluorescent label attached via a cleavable linker to a base and a 3'-OH capping group. Ex-1005 at 10; Ex-1008 at 31.

Tsien discloses that a 3'-O-allyl is an advantageous capping group because “deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized.” Ex-1013 at 24:29-25:3. Tsien’s disclosure of the desirability of the allyl protecting group would have motivated a POSA to select and use the 3'-O-allyl capping group on the nucleotide analogues disclosed by Tsien.

Tsien discloses a cytosine analogue (Structure B) having a fluorescent label attached through a linker to the 5-position of the base. Ex-1013 at 30. Tsien discloses the advantages of labeling cytosine at the 5-position because it provides “great flexibility in that the linker can be varied with respect to length or functionality.” *Id.* at 29:16-19. It was well-known that attaching substituents to cytosine nucleotide analogues was advantageous because substitution at the 5-position “places the linker and reporter in the major groove” (Ex-1029 at 27:58-59), “minimize[s] interference with hybridization and other processes” (*id.* at 27:60-51), and stabilizes the DNA duplex. Ex-1031 at 3051; Ex-1067 ¶96. Tsien cites to Prober for “show[ing] enzymatic incorporation” of fluorescently labeled nucleotide analogues (Ex-1013 at 28:16-18), including cytosine analogues having a label attached via a linker of the 5-position of the base. *Id.* at 29:12-16 (discussing

Structure B and citing Prober). Tsien is correct that Prober shows polymerase incorporation of 5-substituted and labeled cytosine analogues. Ex-1014 at 337, 340. Columbia’s witness (Dr. Trainor) in IPR2012-00007 admitted Tsien’s 5-substituted cytosine analogue was an attractive nucleotide reagent. Ex-1028 at 220:25-221:2 (“I think [Tsien] gives a very nice set of reagents on page 30.”). Thus, there was motivation within Tsien itself and in the art to label cytosine with a linker at the 5-position.

Combining the favorable disclosures within Tsien “does not require a leap of inventiveness.” *Boston Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009); Ex-1067 ¶¶94-95. Thus, a POSA would have been motivated to combine Tsien’s disclosures to arrive at a cytosine nucleotide analogue having a 3'-O-allyl group and a tag attached through a cleavable linker at the 5-position of the base.

a. The motivation here was not present in IPR2013-00517

Tsien discloses the desirability of using the 3'-O-allyl group in Tsien’s sequencing methods, which provides express motivation to use a 3'-O-allyl group in Tsien’s methods. In *Intelligent Bio-Systems v. Illumina*, IPR2013-00517, the Board found there was no motivation to combine Tsien with disclosures from Zavgorodny (Ex-1043). Ex-1044 at 7-18. Here, Tsien *itself* expressly encourages using the allyl group, which is a markedly different situation than IPR2013-00517

where disclosures *outside of Tsien* from Zavgorodny failed to provide motivation to combine Zavgorodny's 3'-O-azidomethyl group with Tsien's methods. Columbia may argue that a POSA would not have been motivated to use Tsien's 3'-O-allyl group in view of Tsien's criteria for a 3'-blocking group. Such an argument would directly contradict Tsien's express encouragement to use the 3'-O-allyl group. Ex-1013 at 24:29-25:3. Tsien's express encouragement provides a motivation to use the 3'-O-allyl group in Tsien's nucleotide analogues. *See Boston Sci.*, 554 F.3d at 991.

16. There was a reasonable expectation of success

The Board determined that a POSA would have had a reasonable expectation of success in making 3'-capped nucleotide analogues having a label cleavably linked to the base. Ex-1005 at 26-35. The Federal Circuit affirmed, explaining that Columbia's specification does not provide novel or nonobvious chemistry to practice the claimed nucleotides. Ex-1008 at 31. Each step of the synthetic process for preparing the nucleotide analogues disclosed by Tsien was within the level of ordinary skill. Columbia's witness (Dr. Trainor) in IPR2012-00007 confirmed the level of ordinary skill included:

- Adding an alkynylamino group to a nucleotide base. Ex-1028 at 177:13-178:15, 179:7-23.

- Attaching a fluorescent label to the alkynylamino group via a cleavable linker. *Id.* at 191:23-192:5, 170:7-171:5, 166:3-168:4, 342:19-343:9, 387:5-388:23.

See also Ex-1029 at 28:3-29:1; Ex-1028 at 243:8-244:2. Dr. Romesberg agrees. Ex-1067 ¶97.

Tsien cites to Gigg, which provides methods for preparing allyl ethers. Ex-1013 at 24:29-30 (citing Ex-1046). Columbia admitted that the allyl group is added using well-established synthetic procedures. Ex-1002 at 26:23-25 (citing Ex-1016); Ex-1016 at 4261; Ex-1067 ¶98.

Tsien cites to Prober for “produc[ing] fluorescent derivatives of thymidine and deoxycytidine.” Ex-1013 at 29:10-29; *id.* at 28:5-18. Prober discloses a “highly convergent and general” synthetic scheme for preparing a 5-labeled cytosine analogue. Ex-1014 at 337.

The '358 patent acknowledges that the claimed nucleotides could be made using “well-established” procedures taught by Prober and Hobbs. Ex-1002 at 24:47-49. The specification “does not provide additional guidance with respect to chemical procedures.” Ex-1008 at 24. Accordingly, a POSA would have reasonably expected to make a 3'-O-allyl capped cytosine nucleotide analogue with a cleavable linker attached to the 5-position of the base in accordance with Claim 1.

A POSA would have expected the cytosine nucleotide analogue disclosed by Tsien to meet each of the recited functional limitations recited in Claim 1, as previously discussed. *Supra* Sections VIII.B.2-4, 6-14. The Board previously determined there was an expectation of success. Ex-1005 at 33-35. The Federal Circuit affirmed. Ex-1008 at 24.

For all these reasons, a POSA would have been motivated to make the nucleotide analogue recited in Claim 1 with a reasonable expectation of success. Consequently, Claim 1 is obvious over Tsien.

C. The Pharmaceutical “Lead Compound” Analysis Does Not Apply

Columbia may argue that a pharmaceutical “lead compound” analysis is required to demonstrate obviousness of its claim. Columbia advocated for a “lead compound” approach in IPR2012-00007 (Ex-1047 at 11), but the Board did not agree with Columbia then, and it should not now.

In IPR2012-00007, the Board held (and the Federal Circuit affirmed) that nucleotide analogues recited in Columbia’s claims were obvious using the standard four-factor *Graham*-based obviousness analysis. Ex-1005 at 19-46; Ex-1008 at 9; *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-407 (2007). The unpatentable nucleotide analogues at issue in IPR2012-00007 were recited in prose. Here, Columbia presents nucleotides in pictorial format. But presenting nucleotides in prose versus in pictorial format does not fundamentally change the obviousness

analysis. The same *Graham*-based obviousness analysis applied to the nucleotide analogues claimed in IPR2012-00007 also applies to the nucleotide analogue claimed by the '358 patent.

The Board and Federal Circuit followed the standard *Graham*-based analysis to determine obviousness of Columbia's and Illumina's nucleotide claims in all six previous final written decisions and all three corresponding Federal Circuit affirmances:

IPR / Appeal No.	Board / Federal Circuit Decision	Obviousness analysis
1. IPR2012-00007	Ex-1005 at 35-36	Standard <i>Graham</i> analysis
2. IPR2012-00006	Ex-1006 at 28	Standard <i>Graham</i> analysis
3. IPR2013-00011	Ex-1007 at 32	Standard <i>Graham</i> analysis
4. IPR2013-00128	Ex-1048 at 11	Standard <i>Graham</i> analysis
5. IPR2013-00266	Ex-1049 at 9-10	Standard <i>Graham</i> analysis
6. IPR2013-00517	Ex-1044 at 9-10	Standard <i>Graham</i> analysis
7. Appeal of IPR2012-00006/00007/00011	Ex-1008 at 9	Standard <i>Graham</i> analysis
8. Appeal of IPR2013-00128/00266	Ex-1050 at 8	Standard <i>Graham</i> analysis
9. Appeal of IPR2013-00517	Ex-1045 at 1366	Standard <i>Graham</i> analysis

The nucleotide subject matter of Columbia's present claim should be evaluated under the same *Graham*-based obviousness analysis as these previous cases.

1. A pharmaceutical “lead compound” analysis compares compounds having specific arrangements of atoms

The pharmaceutical “lead compound” obviousness analysis is based on two steps: (1) comparing the specific arrangement of atoms between a prior art lead compound and a claimed compound, and (2) confirming a motivation exists to modify the prior art arrangement of atoms to arrive at the claimed arrangement. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012). Obviousness of compounds may be shown in other contexts, such as when a compound arises “from theoretical considerations rather than from attempts to improve on [particular] prior art compounds.” *Id.* at 1291. A lead compound analysis is not the exclusive test for obviousness. *Ex parte Cao*, Appeal No. 2010-004081 at 9 (B.P.A.I. Sept. 21, 2011); M.P.E.P. §2143(I)(B) at Example 10.

2. Claim 1 does not define a compound having a specific arrangement of atoms

The structure drawn in Claim 1 depicts an arrangement of several specific atoms, *along with three functional groups that have no specific arrangement of atoms*: “R,” “Y” and “Tag.” The specifically depicted atoms simply describe cytosine deoxyribonucleotide triphosphate, which is not new. Ex-1011 at 58; Ex-1067 ¶52.

Columbia chose to define the three remaining groups (R, Y, and Tag) using functional language that “define[s] something (in this case, a composition) by what

it *does* rather than by what it is (as evidenced by specific structure or material, for example).” *In re Swinehart*, 439 F.2d 210, 212 (C.C.P.A. 1971) (emphases in original). In other words, Columbia chose to claim R, Y and Tag without defining any specific atoms, much less any specific arrangement of atoms.

Columbia’s Y group is defined functionally as “a chemically cleavable, chemical linker.” The R group is defined functionally as a “chemically cleavable, chemical group.” Both Y and R are further defined functionally as “not interfer[ing] with recognition” and “stable during a DNA polymerase reaction.” The claim contains negative limitations that prevent R from containing a ketone, methoxy, or an ester. These negative limitations are carve-outs that Columbia added to avoid prior art. The negative limitations do not require any particular atoms or arrangement of atoms. Claim 1 requires that R be “small,” but this limitation merely excludes R groups according to one property (dimension) without defining any particular arrangement of atoms.

Columbia defined its claim functionally, without claiming any specific arrangement of atoms. Columbia cannot turn around and require more specificity from the prior art. The obviousness analysis for Columbia’s functionally claimed subject matter should not be cabined within the specific atom-by-atom comparison confines of a “lead compound” analysis when that level of specificity does not exist in the claim.

3. Columbia’s §112 arguments cut against a “lead compound” analysis

The specification of Columbia’s patent does not disclose any specific chemical group that meets the recited linker Y. The only linker disclosed in the specification is a 2-nitrobenzyl linker, but Columbia disclosed that this is a *photocleavable* linker, not a *chemically* cleavable linker. Ex-1002 at 11:16-18, 14:21-23.

The Examiner rejected the recited linker Y for indefiniteness and lack of written description support. Ex-1065 at 93-96. In response, Columbia and Dr. Ju relied on the prior art disclosure of Tsien and Stemple for their disclosure of linkers. *Id.* at 19; Ex-1066 ¶20 (“A POSA would have been familiar with many such chemical linkers from the prior art as of October 2000 including such linkers described by Tsien and Stemple.”). Columbia thus availed itself of Tsien’s disclosure for §112 purposes. Columbia cannot now invoke a lead compound analysis to argue that Tsien’s disclosure lacks appropriate specificity to render the claim obvious.

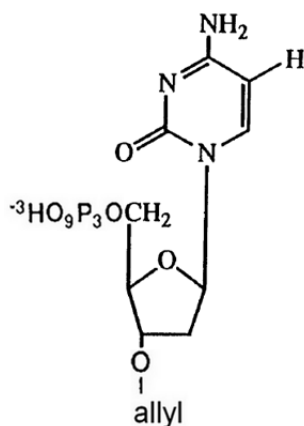
D. Tsien’s 3’-O-allyl dCTP is a Lead Compound

Although the Board should not require a “lead compound” analysis, Columbia’s claim is nevertheless obvious under the “lead compound” approach.

The first step in a “lead compound” analysis is identifying a lead compound. A lead compound need not be the single best compound in the prior art. *Altana*

Pharma AG v. Teva Pharms. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009). A lead compound need not have been tested nor have demonstrated activity through comparative data. *Ex parte Dong*, Appeal No. 2011-010047 at 6-7 (P.T.A.B. 2013); M.P.E.P. §2143(I)(B) at Example 9. There merely needs to be a reason for a POSA to have “selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.” *Otsuka*, 678 F.3d at 1291.

Tsien discloses that 3'-O-allyl is one of three advantageous 3'-blocking groups “used in the synthesis of dNTP analogues and in the sequence incorporation steps.” Ex-1013 at 24:25-25:3. The “dNTP analogues” refer to the four nucleotide analogues: dATP, dCTP, dGTP, and dTTP. *Id.* at 9:35-10:3 (“dNTPs’ of these materials are abbreviated as dATP, dCTP, dGTP, and dTTP”). Based on Tsien’s specific and finite disclosure of 3'-O-allyl dNTPs, a POSA would at once envisage a 3'-O-allyl dCTP nucleotide analogue as if Tsien had drawn its structural formula or written its name:



In re Petering, 301 F.2d 676, 681-82 (C.C.P.A. 1962) (“[O]ne skilled in this art would, on reading the [prior art] patent, at once envisage *each member* of this limited class ... as fully as if [the prior art] had drawn each structural formula or had written each name.”) (emphasis in original); Ex-1067 ¶101.

A POSA would have recognized Tsien’s 3’-O-allyl dCTP disclosure as a natural starting point for further development efforts because Tsien discloses that the 3’-O-allyl blocking group on dNTPs has “some advantages over groups cleavable by base hydrolysis—deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized.” Ex-1013 at 24:24-25:3; Ex-1067 ¶102. Thus, Tsien’s 3’-O-allyl dCTP nucleotide was a lead compound.

Other researchers were actually using 3’-O-allyl nucleotides as promising lead compounds before 2000. Metzker and colleagues used the 3’-O-allyl dATP nucleotide as a lead compound for DNA sequencing development and demonstrated that this nucleotide was incorporated by DNA polymerase. Ex-1016 at 4263. Metzker’s experimental validation of Tsien’s 3’-O-allyl nucleotide analogues provides significant and independent confirmation that such analogues were lead compounds. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 974 (Fed. Cir. 2014) (affirming lead compound selection where “researchers at the time treated [the compound] as a promising compound”).

1. Tsien's 3'-O-acetyl dTTP also qualifies as a Lead Compound

If Columbia argues that Tsien does not disclose a 3'-O-allyl dCTP with sufficient clarity for a lead compound, such an argument should be rejected. Columbia's '358 patent does not disclose any specific chemical compound falling within the claim, and Columbia cannot require a more specific disclosure from the prior art than it disclosed within its own specification. *Supra* Section VIII.C.3. Furthermore, Tsien discloses an alternative lead compound: 3'-O-acetyl dTTP (compound 6). Ex-1013 at Fig. 5, 22:1-16. Tsien's 3'-O-acetyl dTTP would have been a natural starting point for further development efforts because it is specifically disclosed as a representative 3'-blocked nucleotide for use in Tsien's methods. *Id.* at 21:32-22:20, 9:4-7; Ex-1067 ¶¶104-105; *Altana*, 566 F.3d at 1008 (the prior art need not point to a single lead compound). Tsien discloses that the 3'-O-allyl ether is one of three capping groups that are advantageous over ester groups because allyl has "some advantages over groups cleavable by base hydrolysis—deblocking occurs only when the specific deblocking reagent is present and premature deblocking during incorporation is minimized." Ex-1013 at 24:25-25:3; Ex-1067 ¶107; *supra* Section VIII.B.2. Tsien discloses that the synthetic procedure for synthesis of 3'-O-acetyl dTTP is applicable to the other three bases, including 3'-O-acetyl dCTP. Ex-1013 at 22:17-20. Thus, even if

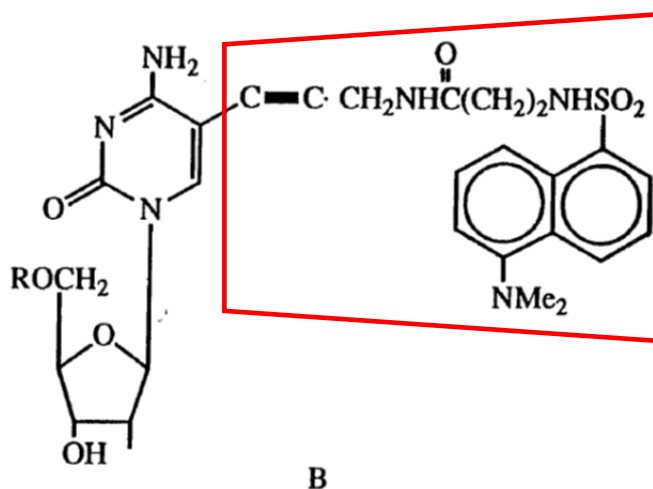
Tsien's 3'-O-acetyl dTTP nucleotide is selected as the starting compound, a POSA would have been motivated to modify this nucleotide to arrive at 3'-O-allyl dCTP.

2. Motivation to use Tsien's 5-substituted cytosine base having a linker and label

A POSA would have been motivated to modify Tsien's 3'-O-allyl dCTP by substituting the cytosine base at the 5-position with a fluorescent label attached through a linker.

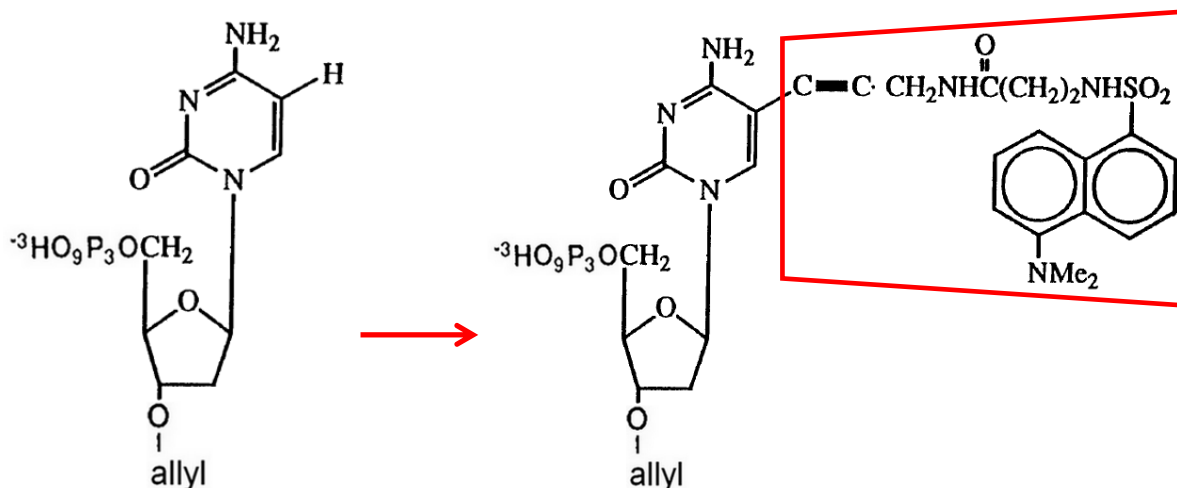
The Board and Federal Circuit determined that Tsien provides an anticipatory disclosure of a nucleotide having a linker attaching a fluorescent label to the base and a 3'-OH capping group. Ex-1005 at 10-11; Ex-1008 at 31.

Tsien discloses a cytosine analogue having a fluorescent label attached through a linker to the 5-position:



Ex-1013 at 30 (Structure B). Tsien discloses the desirability of labeling cytosine at the 5-position (*id.* at 29:16-19), and the advantages of 5-substituted cytosine bases were well-known in the art. *Supra* Section VIII.B.15; Ex-1067 ¶109. Tsien

therefore provides explicit encouragement to add a fluorescent label attached through a linker at the 5-position of the cytosine base:



Ex-1067 ¶¶108-109; *Bristol-Myers*, 752 F.3d at 975.

3. Motivation to use a cleavable allyl linker

A POSA would have been motivated to use a cleavable allyl linker to attach the fluorescent label to the 5-position of a cytosine nucleotide analogue. The Board and Federal Circuit determined that Tsien provides an anticipatory disclosure of a nucleotide having a cleavable linker attaching a fluorescent label to the base and a 3'-OH capping group. Ex-1005 at 10-11; Ex-1008 at 31. The Board determined that a POSA “would have been guided to use the cleavable linker [described in Tsien] to attach the fluorescent label to the base on the nucleotide.” Ex-1005 at 10.

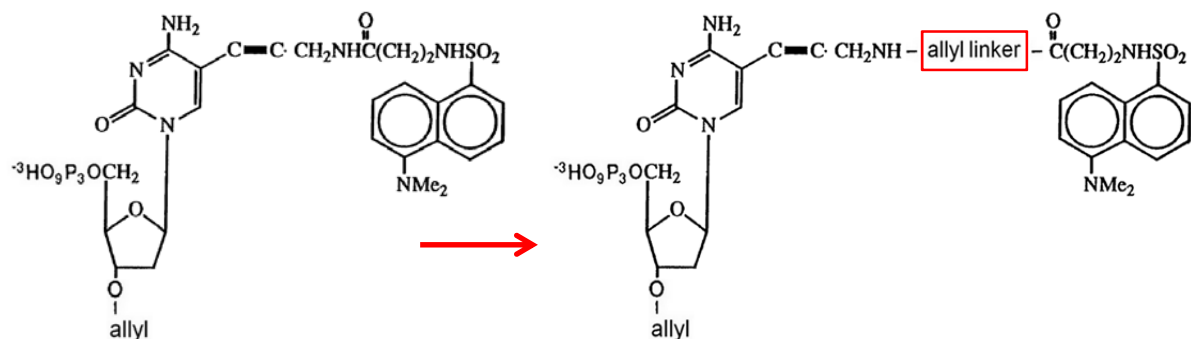
Columbia relied on Tsien’s disclosure of chemically cleavable linkers to fulfill its §112 requirements. Ex-1065 at 18-19; Ex-1066 ¶20. Tsien discloses a

cleavable allyl linker as one of three exemplary cleavable linkers for attaching the fluorescent label to the base. Ex-1013 at 28:19-29; Ex-1005 at 10; Ex-1008 at 31; *supra* Section VIII.B.7. The Federal Circuit agreed “that an embodiment comprising a 3'-OH-capped nucleotide, base-label, and cleavable linker could be envisaged clearly by one of ordinary skill in the art upon reading the Tsien disclosure.” Ex-1008 at 31.

A POSA would have been motivated to place Tsien's cleavable allyl linker on Tsein's 5-substituted cytosine following Tsien's guidance to use a cleavable allyl linker. Allyl linkers were common in the prior art. Ex-1051 at 4062-63; Ex-1052 at 813-15; Ex-1053 at 2132-33; Ex-1067 ¶¶110-113. Seitz discloses an allyl linker for attaching a fluorescent Fmoc group to a molecule having an amine group. Ex-1052 at 815. Tsien cites to Prober for its synthetic approach to produce fluorescent derivatives of cytosine analogues. Ex-1013 at 29:10-16, 28:5-18; Ex-1014 at 337 (disclosing a “highly convergent and general” synthetic scheme for preparing 5-labeled pyrimidines). The amine group disclosed by Sietz is compatible with the amine used by Prober at the 5-position of cytosine. Ex-1067 ¶109.

Following Tsien's direction to use an allyl linker, a POSA would have arrived at a cytosine deoxyribonucleotide analogue having a fluorescent group attached through a cleavable allyl linker to the 5-position of the base and a 3'-O-

allyl capping group:



This compound meets all limitations of Columbia's claim for the same reasons discussed in Section VIII.B.

4. There was a reasonable expectation of success

The Board previously determined that a POSA would have had a reasonable expectation of success in making 3'-capped nucleotide analogues with a label cleavably linked to the base. Ex-1005 at 26-35. The Federal Circuit affirmed. Ex-1008 at 31. The steps for preparing nucleotide analogues disclosed by Tsien were within the level of ordinary skill, as conceded by Columbia's witness (Dr. Trainor) in IPR2012-00007. *Supra* Section VIII.B.16.

The '358 patent acknowledges that 3'-capped nucleotide analogues having cleavable linkers on a 5-substituted cytosine base could be made using "well-established" procedures taught by Prober and Hobbs. Ex-1002 at 24:47-49.

A POSA would have known how to attach a 3'-O-allyl ether based on Tsien's disclosure. Ex-1013 at 24:29-30 (citing Ex-1046); Ex-1046 at 1904-10; Ex-1067 ¶115. Procedures for adding a cleavable allyl linker attached to a

fluorophore were established in the art. Ex-1052 at 813-15; Ex-1067 ¶116; Ex-1002 at 26:22-33, 3:41-44.

Tsien cites to Prober for “produc[ing] fluorescent derivatives of thymidine and deoxycytidine.” Ex-1013 at 29:10-29; *id.* at 28:5-18. Prober discloses a “highly convergent and general” synthetic scheme for preparing 5-labeled pyrimidines, including a 5-labeled cytosine nucleotide analogue. Ex-1014 at 337. Thus, the steps for making Tsien’s nucleotide analogues were well-known in the art.

A POSA would have expected the cytosine nucleotide analogue disclosed by Tsien to meet each of the recited functional limitations. *Supra* Sections VIII.B.1-4, 6-14.

For all these reasons, a POSA would have selected Tsien’s 3’-O-allyl dCTP as a lead compound and would have been motivated to modify the compound based on Tsien’s disclosures to make 3’-O-allyl cytosine nucleotide analogues having a fluorophore attached to the 5-position of the base via cleavable allyl linker with a reasonable expectation of success in making and using such nucleotide analogues. Consequently, Claim 1 is obvious over Tsien under a “lead compound” analysis.

IX. 35 U.S.C. §325(D) IS NOT APPLICABLE

A. Columbia’s improper prosecution tactics should not be rewarded

Columbia may request discretionary denial of institution under §325(d). Any such request should be rejected. But for Columbia ignoring the Board’s unpatentability decision from IPR2012-00007, the ’358 patent would not have issued. Columbia evaded the Board’s decision by seeking a different audience within the Patent Office—an Examiner—to re-litigate patentability. Columbia advanced arguments during prosecution that contradict the Board and Federal Circuit’s prior findings and decisions on unpatentability to mislead the Examiner into issuing an unpatentable claim.

Columbia told the Examiner it invented a small 3'-O-capping group. Ex-1065 at 24. This contradicts the Board’s holding in IPR2012-00007, where the non-inventiveness of “smallness” was fully and finally decided. *Supra* Section II.A.3. The Board held a “small” 3'-capping group was anticipated by Tsien. Ex-1005 at 11; Ex-1008 at 33. Columbia’s improper statements during prosecution appear to have caused the Examiner to fail to appreciate the smallness of Tsien’s 3'-O-allyl capping group.

Furthermore, Columbia avoided the Examiner’s finding that Claim 1 was patentably indistinct from unpatentable Claims 17 and 28 of the ’869 patent by filing a terminal disclaimer without any attempt to distinguish Claim 1 from the

unpatentable claims. Columbia's tactics, if tolerated, would provide a roadmap for future parties to circumvent a Board final written decision and the patent owner estoppel ramifications by re-litigating patentability with Examiners. Permitting Columbia's behavior would erode the public's confidence in the IPR system for securing the "just, speedy, and inexpensive" final resolution of patentability. 37 C.F.R. §42.1(b). No arguments under §325(d) should be entertained in light of Columbia's improper behavior.

B. The Petition provides arguments and evidence not cited during prosecution

This petition provides significant evidence not addressed during prosecution. *See Unified Patents Inc. v. Berman*, IPR2016-01571, Paper 10 at 12 (P.T.A.B. 2016) (Informative Decision) (encouraging petitioners to distinguish petitions from the prosecution history). During prosecution, Columbia never addressed patentability over Tsien and, in particular, never addressed patentability over Tsien's disclosure of the 3'-O-allyl capping group. This petition rectifies this significant oversight.

Furthermore, this petition is supported by Dr. Romesberg's expert testimony, which provides evidence of the knowledge present in the art, and this evidence was not available during prosecution. Dr. Romesberg considered the art available before 2000 and explains why a POSA would have understood that Tsien's 3'-O-allyl group meets the claimed small protecting group in view of the

prior art. This petition is similar to numerous previous instances in which the Board instituted trial when the same prior art was before an examiner, but the petition provided significant evidence not considered by the examiner.

For example, the Board instituted trial where, like here, a petition demonstrated that prior art cited by an examiner contains disclosures that meet the limitations of the challenged claims. *Guardian Indus. Corp. v. Pilkington Deutschland AG*, IPR2016-01635, Paper 9 at 9-10 (P.T.A.B. 2017). The Board instituted trial where, like here, the petitioner “presents the prior art in a new light” along with expert testimony not available to the examiner. *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00804, Paper 13 at 11-13 (P.T.A.B. 2017). The Board instituted trial where prior art was discussed during prosecution and, like here, the petition relied on expert testimony explaining that “several assertions made by Applicants’ attorneys during prosecution to overcome the rejection are incorrect.” *Apotex Inc. v. Novartis AG*, IPR2017-00854, Paper 11 at 13-14 (P.T.A.B. 2017); *see also Actavis LLC v. Abraxis Bioscience LLC*, IPR2017-01101, Paper 7 at 8 (P.T.A.B. 2017) (citing *Tandus Flooring, Inc. v. Interface, Inc.*, IPR2013-00333, Paper 16 at 6 (P.T.A.B. 2013) and *Chimei Innolux Corp. v. Semiconductor Energy Lab. Co.*, IPR2013-00066, Paper 10 at 8 (P.T.A.B. 2013)); *Boehringer Ingelheim Int’l GmbH v. AbbVie Biotech. Ltd.*, IPR2016-00408, Paper 9 at 7-8 (P.T.A.B. 2016); *Lupin Ltd. v. Horizon Therapeutics, Inc.*, IPR2016-00829, Paper 13 at 17

(P.T.A.B. 2016) (instituting where “Petitioner has presented new evidence, such as Dr. Vaux’s testimony, and therefore new arguments that were not before the Examiner.”); *Amerigen Pharms. Ltd. v. Janssen Oncology, Inc.*, IPR2016-00286, Paper 14 at 17-18 (P.T.A.B. 2016).

Columbia incorrectly argued nonobviousness of smallness by distinguishing the claim solely over Stemple, and completely avoided Tsien’s disclosure of the small 3’-O-allyl group and the Board’s holding that smallness is not inventive. This petition corrects the shortcomings from the prosecution via Dr. Romesberg’s expert testimony and by emphasizing key teachings of Tsien (e.g., the 3’-O-allyl group). This significant evidence was not before the Examiner, and this Petition therefore warrants institution.

X. GROUND 2: OBVIOUSNESS BASED ON DOWER IN VIEW OF PROBER AND METZKER

A. Introduction to Dower, Prober, and Metzker

Dower discloses DNA sequencing methods using nucleotide analogues with a fluorescent label and a 3’-OH blocking group. Dower discloses cleavably linking the label to the base. Dower includes several citations to Prober.

Prober discloses DNA sequencing methods using nucleotide analogues having a fluorescent label linked to the 5-position of cytosine.

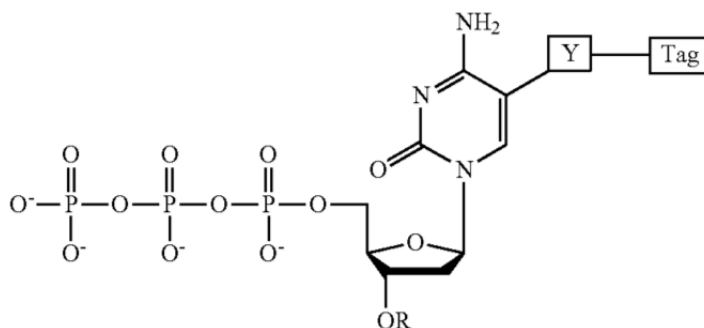
Metzker discloses nucleotide analogues having 3’-capping groups for DNA sequencing.

B. Claim 1 is Obvious Over Dower in view of Prober and Metzker

Dower in view of Prober and Metzker renders Claim 1 obvious. Below is a detailed obviousness analysis that begins by addressing the obviousness of the structure depicted in Columbia's claim, followed by a detailed demonstration that each recited claim limitation is disclosed by Dower in view of Prober and Metzker, along with a motivation to combine the references with a reasonable expectation of success.

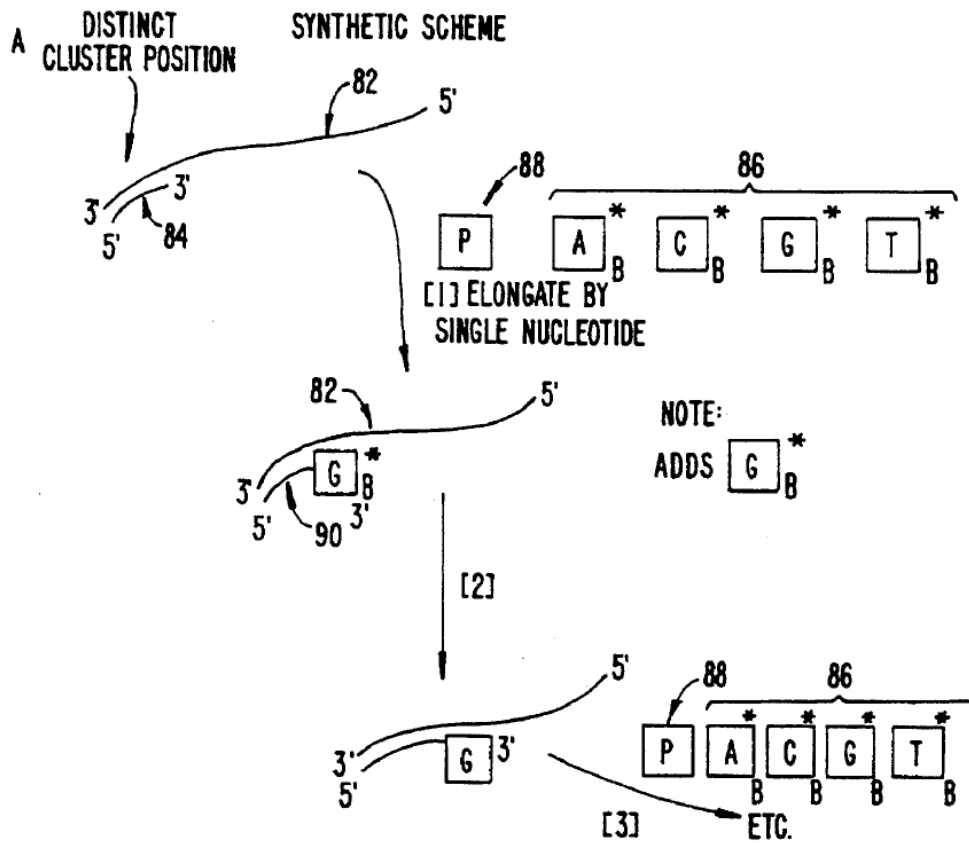
1. The structure depicted in Claim 1 is not new

The first part of Claim 1 includes the following structure:



This structure is fully described using standard nucleotide vocabulary as “a cytosine deoxyribose nucleotide triphosphate having an R group capping the 3'-OH group and a Tag attached through a linker (Y) at the 5-position of the base.” *Supra* Section VIII.B.1. Dower in view of Prober renders obvious this nucleotide.

Dower discloses sequencing using deoxyribonucleotide triphosphate analogues, including the sequencing depicted in Figure 8A:



Ex-1015 at 14:41-47, Fig. 8A. This figure includes the following cytosine analogue:



Id. This cytosine nucleotide analogue has a removable 3'-blocking group (indicated by B) and a label (indicated by the asterisk). Ex-1015 at 15:1-3, 15:35-40. The label is "a removable moiety." *Id.* at 14:56-59. Dower discloses a fluorescent label attached the base. Ex-1015 at 5:35-37, 18:64-19:10, Fig. 9; Ex-1007 at 11. Dower therefore discloses a nucleotide having a removable 3'-capping

group as well as a label removably linked to the base. Dower discloses the desirability of the 3'-blocking group being "small." Ex-1015 at 25:48-53.

The Board previously found Dower "describes nucleotides with a label attached to the base and a small removable chemical moiety capping the 3'-OH group." Ex-1007 at 10. The Federal Circuit agreed that Dower discloses nucleotides "that are base-labeled and contain removable 3'-OH moieties." Ex-1008 at 13-14.

Dower cites to Prober for its disclosure of labeled nucleotide analogues of dATP, dCTP, dGTP, and dTTP. Ex-1015 at 25:4-12. Dower cites to Prober six times, repeatedly directing a POSA to consider Prober's disclosure. *Id.* at 25:4-12, 25:44-47, 20:39-42, 23:16-26, 28:6-17, 17:35-36.

Prober discloses 5-substituted pyrimidines. Prober discloses nucleotides "to which succinylfluorescein has been attached via a linker to the heterocyclic base ... [t]he linker is attached to the 5 position in the pyrimidines." Ex-1014 at 337; *id.* at 338, Fig. 2A.

A POSA would have considered Prober's pyrimidine nucleobase having a tag attached through a linker at the 5-position of the base for use in Dower's nucleotide analogues based on Dower's repeated citations to Prober for labeling. Ex-1067 ¶¶122-124; *infra* Section X.B.6. Dower in view of Prober therefore renders obvious a cytosine deoxyribonucleotide having a 3'-OH capping group and

a tag attached through a cleavable linker at the 5-position, which is the nucleotide analogue depicted in Claim 1.

2. Limitation R(a)

a. Dower

Dower discloses “deoxynucleotide triphosphates with small blocking groups” on the 3'-OH. Ex-1015 at 25:48-51. Dower discloses that such small groups are removed by treatment with pH and other chemical reagents. *Id.* at 25:15-18. Thus, Dower discloses a small chemically cleavable capping group.

Dower's disclosure of small chemically cleavable 3'-capping groups was previously settled by the Board and affirmed by the Federal Circuit. The Board found “Dower describes nucleotides with a label attached to the base and a small removable chemical moiety capping the 3'-OH group.” Ex-1007 at 10. The Federal Circuit affirmed. Ex-1008 at 33.

Dower was filed in 1990 and provides blocking groups that were considered small at that time: “acetyl, tBOC, NBOC, and NVOC.” Ex-1015 at 25:48-51. The crystal structure of DNA polymerase was published in 1994 by Pelletier. Ex-1021 at 1897, 1903. Columbia admitted that “[t]he POSA in October 2000 would have readily known whether any given R when present as OR (a 3'-O capping group) was small” by using the coordinates published by Pelletier and available software such as Chem3D Pro. Ex-1065 at 16; Ex-1066 ¶¶11-16; *id.* at 31-33

(Exhibit C); Ex-1002 at 2:63-3:3. Thus, the crystal structure confirmed Dower's disclosure that the 3'-capping group should be "small." Ex-1067 ¶¶125-127. Dower therefore discloses limitation R(a).

b. Metzker

Metzker discloses 3'-ether capping groups—including the 3'-O-allyl ether—for sequencing DNA. Ex-1016 at 4261. Metzker reported that 3'-O-ethers were advantageous because they are incorporated by polymerases. *Id.* at 4265. Metzker also explored ester caps. *Id.* at 4260-61. The esters were not polymerase substrates. *Id.* at 4265, 4263; Ex-1067 ¶128. Metzker's results would have motivated a POSA to use Metzker's ether groups, such as the 3'-O-allyl ether.

A POSA would have keyed into Metzker's 3'-O-allyl group for two important reasons: (1) it was shown to be incorporated by a polymerase, and (2) it is removable. Ex-1067 ¶¶129-131.

Metzker demonstrated that a 3'-O-allyl substituted nucleotide was incorporated by a polymerase. Ex-1016 at 4265; Ex-1002 at 3:26-30 (citing Ex-1016). Thus, Metzker demonstrated that the 3'-O-allyl group is, in fact, appropriately sized to fit within the polymerase active site. Metzker was submitted for publication a mere 21 days before Pelletier published the polymerase crystal structure. Metzker and Pelletier therefore provide simultaneously converging evidence confirming Dower's disclosure that the 3'-O-capping group should be

small. Ex-1065 at 16; Ex-1066 ¶¶11-16; *id.* at 31-33 (Exhibit C); Ex-1067 ¶130.

Columbia and Dr. Ju admitted that the 3'-O-allyl capping group is small. Ex-1065 at 16-17; Ex-1066 ¶¶16-17; *id.* at 31-33 (Exhibit C).

Metzker's 3'-O-allyl group was also advantageous because it is chemically cleaved in high yield. Columbia's specification directly admitted "[i]t is known that ... allyl (-CH₂CH=CH₂) groups can be used to cap an -OH group, and can be cleaved chemically with high yield." Ex-1002 at 3:41-44 (citing Ex-1037); *id.* at 26:22-33 (citing Ex-1016 & Ex-1037); Ex-1037 at 371-72; *see also* Ex-1035 at 559 (demonstrating allyl cleavage using palladium); Ex-1036 at 2184 (demonstrating quantitative allyl cleavage). Metzker's 3'-O-allyl group therefore meets limitation R(a).

3. Limitation R(b)

Dower uses a DNA polymerase to incorporate a fluorescently labeled dCTP analogue with a 3'-OH blocking group. Ex-1015 at 24:61-25:22; Ex-1067 ¶133. Dower also discloses the label and 3'-blocking group "are selected to be compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension." Ex-1015 at 26:6-9; *id.* at 18:14-16 (nucleotide analogues "should be compatible with the selected polymerase"); *id.* at 15:62-65. A POSA understood that polymerase incorporation involves recognition by the polymerase. Ex-1067 ¶¶134-135. The Board

previously determined that Dower anticipated Claim 1 of Columbia’s ’575 patent, which recited a cytosine nucleotide analogue “wherein said small cleavable chemical group does not interfere with the recognition of the nucleotide analogue by polymerase.” Ex-1007 at 13; Ex-1054 at 33:45-44; Ex-1008 at 33.

Metzker demonstrated that a 3’-O-allyl substituted nucleotide was recognized as a substrate by DNA polymerase. Ex-1016 at 4265. Columbia’s ’358 patent admits that Metzker’s 3’-O-allyl group was “shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994).” Ex-1002 at 3:26-30.

Dower and Metzker therefore disclose limitation R(b).

4. Limitations R(c) and “wherein the covalent bond between the 3’-oxygen and R is stable during a DNA polymerase reaction”

Dower discloses sequencing using labeled and 3’-blocked nucleotides that are incorporated, detected, and then deblocked so that the 3’-OH is “made available for chain extension in the next round of polymerization.” Ex-1015 at 25:4-22. The 3’-blocking group prevents polymerase extension until the 3’-OH is made available by appropriate treatment. *Id.* The 3’-blocking group is therefore stable during the polymerase reaction. Ex-1067 ¶137. The ability of Dower’s 3’-blocking group to block further extension includes stability at the bond between the 3’-oxygen and the rest of the blocking group. *Id.* Dower therefore discloses 3’-groups that are

stable during the polymerase reaction, including stable at the 3'-oxygen and R bond.

Metzker expressly discloses that capped nucleotides should be “stable during the polymerization phase” of sequencing. Ex-1016 at 4259. Metzker demonstrated that the 3'-O-allyl group was incorporated and stable during a polymerase reaction. *Id.* at 4265 (demonstrating a 3'-O-allyl nucleotide was incorporated by polymerase and terminated the growing strand); Ex-1002 at 3:26-30 (citing Ex-1016). The stability demonstrated by Metzker included stability at the bond between the 3'-oxygen and the rest of the capping group to ensure termination of the growing strand. Ex-1016 at 4263; Ex-1067 ¶138.

Dower and Metzker therefore disclose limitations R(c) and the 3'-oxygen to R bond is stable during a polymerase reaction.

5. Limitations R(d) and “wherein OR is not a methoxy group or an ester group”

Metzker discloses a 3'-O-allyl capping group on a nucleotide analogue (Ex-1016 at 4261), and this group does not contain a ketone, a methoxy, or an ester group. *Supra* Section VIII.B.5. Metzker's allyl group therefore meets limitations R(d) and that OR is not methoxy or ester.

6. Limitation “wherein tag represents a detectable fluorescent moiety”

The cytosine nucleotide analogue shown in Dower’s Figure 8 is “labeled with a removable moiety, e.g., a fluorescent label, so that the scanning system can detect the particular nucleotide incorporated after its addition to the polymerization primer.” Ex-1015 at 14:46-59. “[A] fluorescent moiety is the preferred [label] form.” *Id.* at 20:50-53. The Board previously determined that Dower discloses a detectable fluorescent moiety. Ex-1007 at 13; Ex-1054 at 33:44-34:30, 34:36-37.

Dower cites to Prober for labeled nucleotide analogues. Ex-1015 at 25:4-12, 25:44-47, 20:39-42, 23:16-26. Prober discloses “[t]he set of four fluorescence-tagged chain-terminating reagents” in which “succinylfluorescein has been attached via a linker to the heterocyclic base ... [t]he linker is attached to the 5 position in the pyrimidines”. Ex-1014 at 337-338, Fig. 2A.

Dower and Prober therefore disclose this limitation. Ex-1067 ¶¶143-144.

7. Limitation Y is a “chemically cleavable, chemical linker”

Dower cites to Prober for labeled nucleotide analogues. Ex-1015 at 25:4-12, 25:44-47, 20:39-42, 23:16-26. Prober’s label is attached via a linker to the 5-position of cytosine. Ex-1014 at 337-38, Fig. 2A. Dower discloses “[o]ne important functional property of the [dNTP] monomers is that the label be removable.” Ex-1015 at 15:52-53. Dower specifies that the label is linked to the base and can be cleaved “chemical[ly], using acid, base, or some other, preferably

mild, reagent.” *Id.* at 21:32-40; *id.* at 15:52-56, 25:35-40, Fig. 9, 5:35-37. Dower in view of Prober therefore renders obvious a chemically cleavable linker at the 5-position of cytosine. Ex-1067 ¶146.

8. Limitations Y(a) and Y(b)

Dower discloses that the linked label “does not interfere with the nucleotide-specific chemistry or enzymology” (Ex-1015 at 20:47-49) and is “compatible with appropriate polymerization” by DNA polymerase. *Id.* at 15:56-59; *id.* at 15:3-14, Fig. 8. Dower’s disclosure of polymerase compatibility and lack of interference with polymerization indicates that the linker and label are stable during the polymerase reaction. Ex-1067 ¶¶148-149.

Dower cites to Prober for labeled nucleotide analogues. Ex-1015 at 25:4-12, 25:44-47, 20:39-42, 23:16-26. Prober discloses a label attached through a linker to the 5-position of cytosine. Ex-1014 at 337-38, Fig. 2A. Prober demonstrated that DNA polymerase recognized and incorporated a cytosine nucleotide analogue having a stable linker at the 5-position. Ex-1014 at 336-37; Ex-1067 ¶150. Columbia’s ’358 patent admits it was known that DNA polymerase recognizes nucleotides with linkers or other bulky groups at the 5-position of pyrimidines. Ex-1002 at 2:57-63:3.

Dower in view of Prober therefore disclose limitations Y(a) and Y(b).

9. Limitation i)

Dower discloses that a fluorescently labeled dCTP analogue with 3'-OH blocking group is "incorporated" by DNA polymerase. Ex-1015 at 24:61-25:22. Dower also discloses that the label and 3'-OH blocking group "are selected to be compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension." *Id.* at 26:6-9. Dower's nucleotide analogues "typically have both a labeling moiety and a blocking agent while remaining compatible with the elongation enzymology" (*id.* at 15:62-65) and "should be compatible with the selected polymerase." *Id.* at 18:14-16. In IPR2013-00011, the Board determined that Dower anticipated Claim 1 of Columbia's '575 patent, and that claim required polymerase incorporation of a cytosine nucleotide analogue having a 3'-OH capping group and a labeled base. Ex-1007 at 13; Ex-1054 at 33:35-41. A POSA would understand that polymerase incorporation and compatibility for Dower's nucleotide analogues involves recognition by the polymerase. Ex-1067 ¶153.

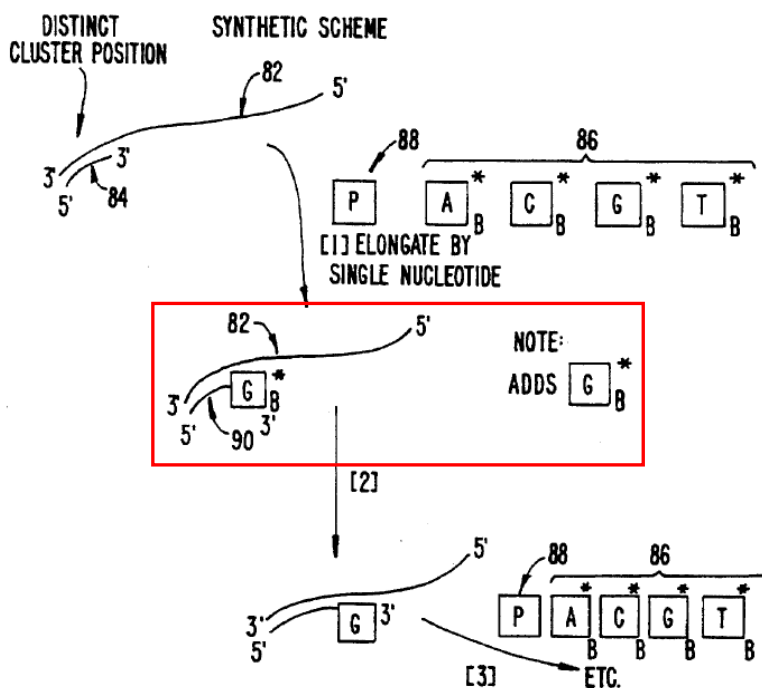
Metzker discloses that a 3'-O-allyl nucleotide analogue was incorporated by polymerase. Ex-1016 at 4263, 4265. Columbia's '358 patent concedes that Metzker's 3'-O-allyl ether had been "shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994)." Ex-1002 at 3:26-30 (citing Ex-1016).

Prober discloses that DNA polymerase maintains appropriate fidelity (i.e., recognition and incorporation) of 5-substituted cytosine analogues. Ex-1014 at 337, 340; Ex-1067 ¶155. 5-Substituted cytosine nucleotides were known to be substrates of numerous polymerases, including Vent polymerase, which incorporates Metzker's 3'-O-allyl nucleotide as a substrate. Ex-1040 at 3228, 3230; Ex-1041 at 4832-33; Ex-1016 at 4265; Ex-1002 at 2:57-63; Ex-1067 ¶77.

Dower in view of Metzker and Prober therefore renders obvious limitation i).

10. Limitation ii)

As discussed in Sections X.B.3 and 8, Dower discloses DNA polymerase recognition and incorporation of nucleotide analogues having a small chemically cleavable 3'-capping group and a chemically cleavable linker attached to the base. This incorporation is depicted in Dower's Figure 8A:



Ex-1015 at Figure 8A (annotated). In Figure 8A, polymerase 88 adds a labeled and blocked dGTP analogue to the 3'-end of the growing strand of DNA. *Id.* at 15:1-10. Dower discloses the addition of dCTP analogues, which are likewise incorporated at the 3'-end. *Id.* at 25:4-11, Fig. 8; Ex-1067 ¶157.

Metzker discloses that a 3'-O-allyl nucleotide analogue was incorporated by polymerase. Ex-1016 at 4263, 4265. Prober discloses DNA polymerase incorporation of 5-substituted cytosine. Ex-1014 at 337, 340. It was known that polymerase incorporates a nucleotide at the 3'-end of a growing strand of DNA. Ex-1011 at 252; Ex-1055 at 89; Ex-1067 ¶158.

Dower in view of Metzker and Prober therefore disclose limitation ii).

11. Limitation iii)

Dower discloses that 3'-blocking groups are cleaved by treatment with pH and other chemical reagents. Ex-1015 at 25:15-18. Dower discloses that the cleavage conditions make the 3'-OH on the terminating base available for the next round of polymerization. *Id.* at 25:19-22.

Metzker's 3'-O-allyl capping group was known to be chemically cleaved in high yield to produce a 3'-OH group. Ex-1037 at 371-72; Ex-1002 at 3:41-44 (citing Ex-1037); *id.* at 26:22-33 (citing Ex-1016 & Ex-1037); Ex-1035 at 559; Ex-1036 at 2184; Ex-1067 ¶161.

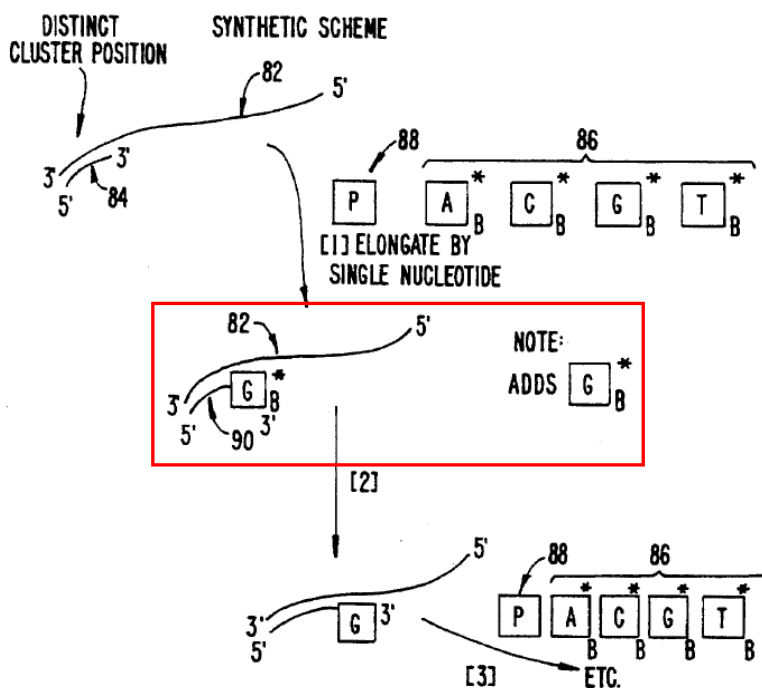
Therefore, Dower and Metzker disclose limitation iii).

12. Limitation iv)

As discussed in Section X.B.7, Dower discloses a label cleavably linked to the base. Dower discloses “[o]ne important functional property of the [dNTP] monomers is that the label be removable. The removal reaction will preferably be achieved using mild conditions.” Ex-1015 at 15:52-56; *id.* at 21:32-40. Dower therefore discloses removal of the label by cleaving the linkage to the base, which meets limitation iv). Ex-1067 ¶163.

13. Limitation v)

Dower uses a polymerase “to extend a primer complementary to a target template” as shown in Figure 8:



Ex-1015 at Figure 8A (annotated), 14:44-53. A POSA would understand that Figure 8A shows polymerase 88 adding a labeled and blocked dGTP analogue by forming hydrogen bonds with a cytosine base in the template strand. *Id.* at 15:1-10; Ex-1067 ¶165. Dower discloses the addition of dCTP analogues. Ex-1015 at 25:4-11, Fig. 8. It was firmly established that dCTP analogues form hydrogen bonds with guanine bases in a template strand. Ex-1042 at 966; Ex-1011 at 99; Ex-1067 ¶165.

Prober discloses that DNA polymerase maintains fidelity during incorporation of 5-substituted cytosine analogues. Ex-1014 at 337, 340. This indicates that the 5-substituted cytosine forms hydrogen bonds with the complementary guanine nucleobase. Ex-1067 ¶166.

Dower and Prober therefore disclose limitation v).

14. A POSA would have been motivated to combine Dower, Prober and Metzker

Dower discloses all features of Claim 1 except (1) a 5-substituted cytosine and (2) that the 3'-capping group should not be a methoxy or an ester/ketone group. Prober discloses 5-substituted cytosine, and Metzker discloses a 3'-O-allyl ether capping group that is not a methoxy or an ester/ketone. A POSA would have recognized the benefits of combining Dower, Prober and Metzker.

Dower discloses a nucleotide analogue having a cleavably linked fluorescent label and a small 3'-OH capping group. Dower expressly cites to the fluorescently labeled nucleotides described in Prober, providing direction to turn to Prober. Ex-1015 at 25:4-12, 25:44-47, 20:39-42, 23:16-26, 28:6-17, 17:35-36.

The Board previously determined that Dower does not anticipate deazapurine nucleotide analogues via incorporation-by-reference of Prober's disclosure. Ex-1007 at 13-16; Ex-1006 at 39-42. Incorporation-by-reference is a high standard that requires a host document to "identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). This Petition does not seek to disturb the Board's previous determination. This Petition asserts the more flexible obviousness standard in which "any need or problem known in the field" can provide a reason to combine the prior art. *KSR*, 550 U.S. at 420. Dower's discussion of base

labeling expressly cites to Prober, reasonably suggesting that Prober’s disclosure would be beneficial in Dower’s sequencing method. Ex-1067 ¶168.

Prober’s disclosure is beneficial in Dower’s methods for several reasons. Prober discloses the 5-position of pyrimidines were reported “to be acceptable for attaching substituents to chain-propagating substrates (that is, deoxynucleotide triphosphates) for DNA polymerases.” Ex-1014 at 340. Prober discloses DNA polymerase maintains the fidelity of 5-substituted cytosine analogues during polymerase incorporation. *Id.* at 337, 340. It was known that linking labels to the 5-position of cytosine was advantageous because this “places the linker and reporter in the major groove” (Ex-1029 at 27:58-59), “minimize[s] interference with hybridization and other processes” (*id.* at 27:60-61), and stabilizes the DNA duplex. Ex-1031 at 3051; Ex-1067 ¶169. Columbia’s ’358 patent admits polymerases were known “to recognize nucleotides with extensive modifications with bulky groups such as energy transfer dyes at the 5-position of the pyrimidines (T and C)”. Ex-1002 at 2:57-63. For these reasons it had become common place for researchers to use cytosine bases having a fluorescent label linked to the base before 2000. Ex-1027 at 4501; Ex-1028 at 280:23-281:3. Thus, a POSA would have been motivated to use Prober’s 5-substituted cytosine as the base in Dower’s fluorescently labeled nucleotide analogue.

Dower was filed in 1990 and disclosed that the 3'-capping group should be small. Columbia admitted that "[t]he POSA in October 2000 would have readily known whether any given R when present as OR (a 3'-O capping group) was small" by using the coordinates published by Pelletier and available software such as Chem3D Pro. Ex-1065 at 16; Ex-1066 ¶¶11-16; *id.* at 31-33 (Exhibit C); Ex-1002 at 2:63-3:3. In 1994, Metzker demonstrated that the 3'-O-allyl group was incorporated by polymerase. Ex-1016 at 4265, 4263; Ex-1002 at 3:26-30. Columbia and Dr. Ju admitted that allyl would be known to be small. Ex-1065 at 16-17; Ex-1066 ¶¶16-17; *id.* at 31-33 (Exhibit C). A POSA would have been motivated to use Metzker's 3'-O-allyl group as Dower's "small" group because Metzker demonstrated that the 3'-O-allyl is appropriately sized to fit within the polymerase active site. Ex-1067 ¶170. There was further motivation to use Metzker's 3'-O-allyl ether because it was known to be chemically cleaved in high yield, as admitted by Columbia. Ex-1002 at 3:37-44, 26:22-33; Ex-1037 at 371-72; Ex-1035 at 559; Ex-1036 at 2184; Ex-1067 ¶170.

A POSA would have therefore been motivated to combine Dower, Prober and Metzker to arrive at a cytosine nucleotide analogue having a 3'-O-allyl capping group and a fluorophore attached through a cleavable linker at the 5-position of the base.

15. There would have been a reasonable expectation of success

A POSA would have had a reasonable expectation of success in combining Dower, Prober and Metzker to make 3'-capped 5-substituted cytosine nucleotide analogues with cleavable linkers.

Columbia's specification does not provide novel or nonobvious chemistry to practice the claimed nucleotides. Ex-1008 at 31. The steps for preparing nucleotide analogues disclosed by the combination of Dower, Prober and Metzker were within the level of ordinary skill. *Supra* Section VIII.B.16.

The '358 patent acknowledges that the claimed nucleotides could be made using "well-established" procedures taught by Prober and Hobbs. Ex-1002 at 24:47-49.

A POSA would have expected the cytosine nucleotide analogue disclosed by Dower, Prober and Metzker to meet each of the recited functional limitations recited in Claim 1, as previously discussed. *Supra* Section X.B.1-4, 6-13; Ex-1067 ¶¶172-175.

For all these reasons, a POSA would have been motivated to make the nucleotide analogue recited in Claim 1 with a reasonable expectation of success based on Dower in view of Prober and Metzker. Consequently, Claim 1 is obvious over Dower in view of Prober and Metzker.

XI. GROUNDS 1 AND 2 ARE NOT REDUNDANT

The asserted grounds are not redundant or duplicative. Ground 1 is based on the same reference that rendered Columbia's claims unpatentable in IPR2012-00007. Columbia may raise a §325(d) challenge for Ground 1, which, as previously discussed, would not withstand scrutiny. *Supra* Section IX. There is no colorable §325(d) challenge for Ground 2.

XII. THERE IS NO EVIDENCE OF SECONDARY CONSIDERATIONS

Grounds 1 and 2 demonstrate a strong prima facie case of obviousness. There is no evidence of secondary considerations of nonobviousness. In IPR2012-00007, the Board rejected all of Columbia's nonobviousness positions. Ex-1005 at 35-46. The Federal Circuit affirmed. Ex-1008 at 24-29. Should Columbia raise new allegations regarding secondary considerations in this proceeding, Illumina will respond.

XIII. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(A)(1)

Pursuant to 37 C.F.R. §42.8(a)(1), the mandatory notices identified in 37 C.F.R. §42.8(b) are provided below as part of this Petition.

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Illumina, Inc. is the real party-in-interest for Petitioner.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Illumina is concurrently filing petitions for IPR of U.S. 9,718,852, 9,718,139, and 9,725,480 ("the '852, '139 and '480 patents"), also purportedly

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owned by Columbia. The '852, '358, '139, and '480 patents were asserted against Illumina in *Trustees of Columbia Univ. v. Illumina, Inc.*, C.A. No. 17-cv-973-GMS (D. Del.).

Columbia asserted U.S. 7,790,869, 7,713,698, and 8,088,575 (“the '869, '698 and '575 patents”) against Illumina in *Trustees of Columbia Univ. v. Illumina, Inc.*, C.A. No. 12-cv-376 (D. Del.). The Board previously held all challenged claims from the '869, '698 and '575 patents were unpatentable as follows:

- Claims 12, 13, 15-17, 20-26, 28, 29, 31 and 33 from the '869 were held unpatentable over Tsien (alone or in view of Prober) by the Board in *Illumina v. Columbia*, IPR2012-00007, Paper 140 (P.T.A.B. 2014) (Ex-1005). The unpatentable Claims 17 and 28 of the '869 patent are patentably indistinct from Claim 1 of the '358 patent. See Ex-1065 at 100. The remaining unpatentable claims are nearly identical to Claim 1 of the '358 patent.
- Claims 1-7, 11, 12, 14, 15 and 17 from the '698 patent and Claims 1-3 and 6 from the '575 patent were held unpatentable over Tsien (alone or in view of Prober) by the Board in *Illumina v. Columbia*, IPR2012-00006, Paper 128 & IPR2013-00011, Paper 130 (P.T.A.B. 2014) (Exs-1006 & 1007). The unpatentable claims from the '698 and '575 patents are nearly identical to Claim 1 of the '358 patent.

The Federal Circuit unanimously affirmed all of the Board’s unpatentability determinations from IPR2012-00006, IPR2012-00007 and IPR2013-00011 in *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 Fed. Appx. 916 (Fed. Cir. 2015) (Ex-1008).

Illumina raised counterclaims alleging infringement of U.S. 7,057,026, 8,158,346, and 7,566,537 (“the ’026, ’346, and ’537 patents”) in *Trustees of Columbia Univ.*, C.A. No. 12-cv-376. The ’026 and ’346 patents were the subject IPR2013-00128 and IPR2013-00266, respectively. The Board held all claims at issue in these IPRs unpatentable over, *inter alia*, Tsien (alone or in view of Prober) and further in view of Rabani and/or Church. See IPR2013-00128, Paper 92 (P.T.A.B. 2014) (Ex-1048); IPR2013-00266, Paper 73 (P.T.A.B. 2014) (Ex-1049). The Federal Circuit unanimously affirmed all of the Board’s unpatentability determinations from IPR2013-00128 and IPR2013-00266 in *Illumina Cambridge Ltd. v. Intelligent Bio-Systems, Inc.*, 638 Fed. Appx. 999 (Fed. Cir. 2016) (Ex-1050).

The ’537 patent was the subject of IPR2013-00517. The Board held all claims at issue in that IPR were not unpatentable over (1) Tsien in view of Zavgorodny *et al.*, 32 Tetrahedron Letters 7593-93 (1991), and (2) U.S. 6,664,079 to Ju *et al.* in view of Zavgorodny (Ex-1044). The Federal Circuit unanimously affirmed the Board’s determinations from IPR2013-00517 in *Intelligent Bio-*

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Systems, Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359 (Fed. Cir. 2016) (Ex-1045).

The '537 patent is currently the subject of two follow-on petitions filed on October 5, 2017 by Complete Genomics, Inc. in IPR2017-02172 and IPR2017-02174. Illumina's preliminary responses are due on January 23, 2018 in these two IPRs.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Illumina provides the following designation of counsel, all of whom are included in Customer No. 20,995 identified in Illumina's Power of Attorney.

Lead Counsel	Back-up Counsel
Kerry Taylor, Reg. No. 43,947 Knobbe, Martens, Olson, & Bear, LLP 2KST@knobbe.com <u>Postal and Hand-Delivery Address:</u> 2040 Main St., 14th Floor Irvine, CA 92614 Telephone: (858) 707-4000 Facsimile: (858) 707-4001	Michael L. Fuller, Reg. No. 36,516 Knobbe, Martens, Olson, & Bear, LLP 2MLF@knobbe.com <u>Postal and Hand-Delivery Address:</u> 2040 Main St., 14th Floor Irvine, CA 92614 Telephone: (858) 707-4000 Facsimile: (858) 707-4001

D. Service Information (37 C.F.R. §42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the addresses shown above. Petitioner also consents to electronic service by email to BoxIllumina@knobbe.com.

XIV. PAYMENT OF FEES PURSUANT TO 37 C.F.R. §42.103

The undersigned authorize the Office to charge the fee set forth in 37 C.F.R. §42.15(a) for this Petition to Deposit Account No. 11-1410. Review of one claim is requested. The undersigned further authorize payment for any additional fees that may be due to be charged to the above-referenced Deposit Account.

XV. REQUIREMENTS FOR REVIEW UNDER 37 C.F.R. §42.104

Illumina certifies that the '358 patent is available for IPR and that Illumina is not barred or estopped from requesting IPR challenging the patent claims on the grounds identified herein. This petition is being filed less than a year prior to service of the first complaint alleging infringement of the '358 patent (Ex-1060), and is not barred under 35 U.S.C. §315(b). *TRW Auto. US LLC v. Magna Elecs. Inc.*, IPR2014-00293, Paper 18 at 10-11 (P.T.A.B. 2014) (Informative Decision).

XVI. CONCLUSION

For the reasons provided, Claim 1 of the '358 patent is unpatentable and should be canceled.

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Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 18, 2017

By: /Kerry Taylor/

Kerry S. Taylor, Reg. No. 43,947

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

Customer No. 20,995

Attorneys for Petitioner

ILLUMINA, INC.

(858) 707-4000

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that foregoing
**PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO.
9,708,358**, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a),
contains 13,998 words and therefore complies with the type-volume limitations of
37 C.F.R. §42.24(a).

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 18, 2017

By: /Kerry Taylor/
Kerry S. Taylor, Reg. No. 43,947
Michael L. Fuller, Reg. No. 36,516
Customer No. 20,995

Attorneys for Petitioner
ILLUMINA, INC.
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,708,358** and **EXHIBITS 1002, 1005-1008, 1010-1011, 1013-1021, 1023-1024, 1027-1029, 1031, 1034-1055, 1057-1060, 1065-1067** are being served on December 18, 2017, via Federal Express overnight mail on counsel of record for U.S. Patent No. 9,708,358 as addressed below:

COOPER & DUNHAM, LLP
30 Rockefeller Plaza, 20th Floor
New York, NY 10112

Dated: December 18, 2017

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