ILLUMINA, INC. v.
THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Case IPR2018-00291 (Patent 9,718,852)
Case IPR2018-00318 (Patent 9,719,139)
Case IPR2018-00322 (Patent 9,708,358)
Case IPR2018-00385 (Patent 9,725,480)
Case IPR2018-00797 (Patent 9,868,985)

Illumina's Demonstratives For Oral Hearing

Judge James A. Worth
Judge Michelle N. Ankenbrand
Judge Brian D. Range
March 5, 2019

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Columbia Ex. 2017
Illumina, Inc. v. The Trustees of Columbia University in the City of New York
IPR2020-01177

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Judge James A. Worth
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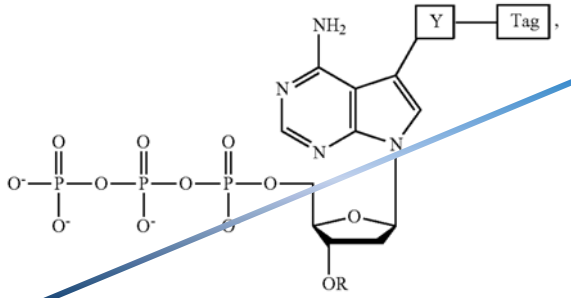
Illumina Ex. 1139
Illumina v. Columbia
IPR2018-00291, -00318, -00322, -00385, and -00797

Columbia disputes two limitations

What is claimed is:

1. An adenine 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 adenine 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 thymine or a thymine nucleotide analogue.

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,

Ex. 1001[1] at 34:2-35:4

[1]All citations are to exhibits and papers from IPR2018-00291 unless otherwise indicated.

Columbia's incorrect arguments

- Tsien does not disclose the 3'-O-allyl capping group
- Metzker would have led a POSA to believe that 3'-O-allyl is inefficiently incorporated
- It was not possible to cleave the allyl ether under SBS-compatible conditions

Reply at 6-22

Tsien's 3'-O-allyl capping group

A wide variety of hydroxyl blocking groups are cleaved selectively using chemical procedures other than base hydrolysis. 2,4-Dinitrobenzenesulfenyl groups are cleaved rapidly by treatment with nucleophiles such as thiophenol and thiosulfate (Letsinger et al., 1964). Allyl ethers are cleaved by treatment with Hg(II) in acetone/water (Gigg and Warren, 1968). Tetrahydrothiofuranyl ethers are removed under neutral conditions using Ag(I) or Hg(II) (Cohen and Steele, 1966; Cruse et al., 1978). These protecting groups, which are stable to the conditions used in the synthesis of dNTP analogues and in the sequence incorporation steps, have 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
Petition at 21-22

Dr. Menchen's Testimony

Q. And there Tsien is referring to allyl ethers; is that correct? That's how a person of ordinary skill in the art would understand this disclosure?

MR. SCHWARTZ: Objection, form.

A. So a person with ordinary skill in the art would understand that the -- that allyl ethers in general had some advantages, that they wouldn't be cleaved by base hydrolysis when deblocking occurs.

Ex. 1113 at 326:5-17

Reply at 5

3'-O-allyl meets all claim requirements for 'R'

Dr. Ju's testimony

a. Only a limited number of 3'-O capping groups meet the standard of "small" along with the other structural and functional features recited in the claim. I estimate the number of such groups would be less than 10 and 2 examples of such groups were provided.

Ex. 1022 at ¶22a

Dr. Menchen's testimony

Q. At some point it was demonstrated that allyl would work as a capping group for the claimed inventions of the Ju patents, correct?

A. That's -- that's correct.

Ex. 1112 at 296:22-297:3

Reply at 8; Petition at 22, 24, 25

"Allyl" means "-CH_2-CH=CH_2"

IUPAC Definition

3.5—The names of univalent radicals derived from unsaturated acyclic hydrocarbons have the endings "-enyl", "-ynyl", "-dienyl", *etc.*, the positions of the double and triple bonds being indicated where necessary. The carbon atom with the free valence is numbered as 1.

Examples:

Ethynyl	$CH{\equiv}C-$
2-Propynyl	$CH{\equiv}C-CH_2-$
1-Propenyl	$CH_3-CH{=}CH-$
2-Butenyl	$CH_3-CH{=}CH-CH_2-$
1,3-Butadienyl	$CH_2{=}CH-CH{=}CH-$
2-Pentenyl	$CH_3-CH_2-CH{=}CH-CH_2-$
2-Penten-4-ynyl	$CH{\equiv}C-CH{=}CH-CH_2-$

Exceptions:

The following names are retained:

Vinyl (for ethenyl)	$CH_2{=}CH-$	
Allyl (for 2-propenyl)	$CH_2{=}CH-CH_2-$	
Isopropenyl (for 1-methylvinyl)	$CH_2{=}C(CH_3)-$	(for unsubstituted radical only)

Ex. 1099 at 13
Reply at 4

Greene and Wuts

Allyl Ether (Allyl-OR): $CH_2=CHCH_2$-OR (Chart 1)

The use of allyl ethers for the protection of alcohols is common in the literature on carbohydrates because allyl ethers are generally compatible with the various methods for glycoside formation.[1] Obviously, the allyl ether is not compatible with powerful electrophiles such as bromine and catalytic hydrogenation, but it is stable to moderately acidic conditions (1 *N* HCl, reflux, 10 h).[2] The ease of formation, the many mild methods for its cleavage in the presence of numerous other protective groups, and its general stability have made the allyl ether a mainstay of many orthogonal sets. The synthesis of perdeuteroallyl bromide and its use as a protective group in carbohydrates has been reported. The perdeutero derivative has the advantage that the allyl resonances in the NMR no longer obscure other, more diagnostic resonances, such as those of the anomeric carbon in glycosides.[3] The use of the allyl protective group primarily covering carbohydrate chemistry has been reviewed.[4]

Ex. 1101 at 67;
Reply at 4, 19

Gigg and Warren

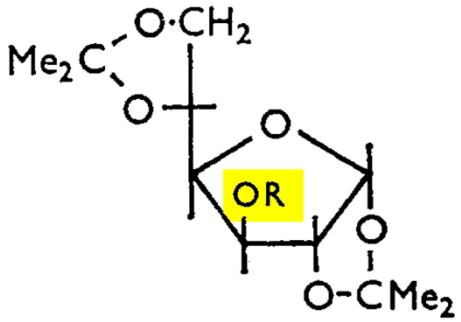
The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part II [1a]

By **Roy Gigg** • and **C. D. Warren**, National Institute for Medical Research, Mill Hill, London N.W.7

Ex. 1046 at title

The 2-methylallyl ether (XLIX) of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose was prepared and the rates of isomerisation of this compound and of the allyl ether (LI) were compared. The allyl ether was isomerised about twenty times more quickly than compound (XLIX) which was converted into the crystalline ether (L).

We have shown [10] that γ-substituted allyl ethers are eliminated to give dienes by treatment with potassium t-butoxide in dimethyl sulphoxide and this has been confirmed by others.[25] The action of these basic conditions on the 3-methylallyl (crotyl) ether (LII) [26] of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose was investigated.



(XLIX) R = CH_2–C(Me)=CH_2
(L) R = CH=CMe_2
(LI) R = CH_2–CH=CH_2
(LII) R = CH_2–CH=CH–CH_3

Ex. 1046 at 1906-07

Reply at 5;
Sur-reply at 9

Metzker

Improvements to the Sanger protocols are being sought to meet the increasing demands of large scale sequencing of whole genomes (14). We and others (15–18) have independently conceived a radically different, gel-free alternative to the Sanger scheme for DNA sequencing. This method, called the Base Addition Sequencing Scheme (BASS), is based on novel nucleotide analogs that terminate DNA synthesis. BASS involves repetitive cycles of incorporation of each successive nucleotide, *in situ* monitoring to identify the incorporated base, and deprotection to allow the next cycle of DNA synthesis, (Figure 1). Compared to Sanger sequencing, BASS has two major advantages: base resolution would not require gel electrophoresis and there is a tremendous capacity for simultaneous analyses of multiple samples. The complete scheme demands nucleotide analogs that are tolerated by polymerases, spectroscopically distinct for each base, stable during the polymerization phase, and deprotected efficiently under mild conditions in aqueous solution. These stringent requirements are formidable obstacles for the design and synthesis of the requisite analogs.

REFERENCES

15. Tsien, R. Y., Ross, P., Fahnestock, M., and Johnston, A. J., PCT number WO 91/06678, *'DNA sequencing.'*, filed: October, 26, 1990, published: May 16, 1991.

Ex. 1016 at 4259, 4267; Petition at 23, 62

Metzker

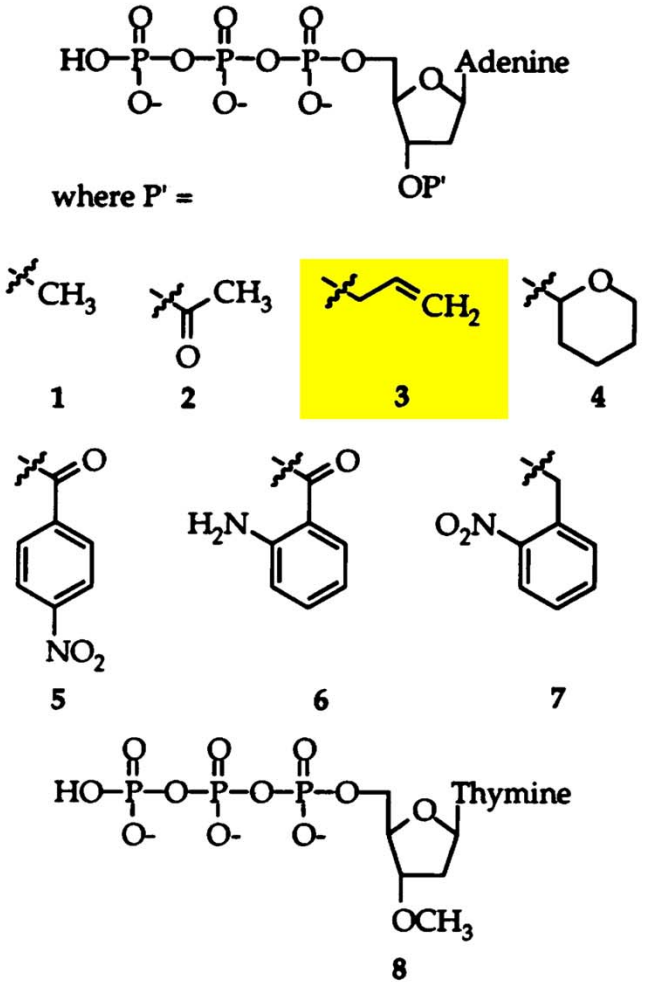


Figure 2. Chemical structures of the 3′-modified-nucleotides. Details of the chemical syntheses are described in the Materials and Methods section.

Ex. 1016 at 4260
Petition at 59

Dr. Menchen's 1998 patent

United States Patent [19]
Benson et al.

[11] **Patent Number: 6,111,116**
[45] **Date of Patent: Aug. 29, 2000**

[54] **DIBENZORHODAMINE DYES**

[75] Inventors: **Scott C. Benson; Joe Y. L. Lam; Steven Michael Menchen**, all of Foster City, Calif.

[73] Assignee: **The Perkin-Elmer Corporation**, Foster City, Calif.

[21] Appl. No.: **09/199,402**
[22] Filed: **Nov. 24, 1998**

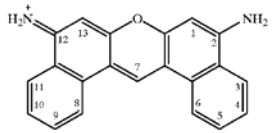
Related U.S. Application Data

Sun et al., "Synthesis of Fluorinated Fluoresceins," J. Org. Chem. 62(19) 6469–6475 (1997).

Primary Examiner—Zinna Northington Davis
Attorney, Agent, or Firm—Paul D. Grossman; Alex Andrus

[57] **ABSTRACT**

Dibenzorhodamine compounds having the structure



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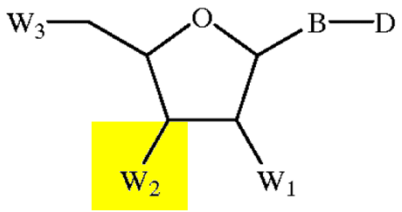
Exemplary sugar analogs include but are not limited to 2'- or 3'-modifications where the 2'- or 3'-position is hydrogen, hydroxy, alkoxy, e.g., methoxy, ethoxy, allyloxy, isopropoxy, butoxy, isobutoxy and phenoxy, amino or alkylamino, fluoro, chloro and bromo.

37. The compound of claim **1** wherein the nucleoside, nucleotide or analog comprises the structure:



wherein D is a dibenzorhodamine dye, B is a nucleobase; and B is connected to D by a linkage;

W_1 is OH, H, F or a group capable of blocking polymerase-mediated template polymerization;

W_2 is OH, H, F or a group capable of blocking polymerase-mediated template polymerization; and

W_3 is OH, monophosphate, diphosphate, triphosphate, or phosphate analog.

Ex. 1091 at 5:56-61, 27:35-52

Note: 3'-allyloxy is 3'-O-allyl

Ex. 1119 at ¶26
Ex. 1112 at 49:25-50:6

Reply at 6-7

Dr. Menchen's 1999 patent

(12) **United States Patent**
Lam et al.

(10) **Patent No.: US 6,248,884 B1**
(45) **Date of Patent: Jun. 19, 2001**

(54) **EXTENDED RHODAMINE COMPOUNDS USEFUL AS FLUORESCENT LABELS**

(75) Inventors: **Joe Y. L. Lam**, Castro Valley; **Scott C. Benson**, Alameda; **Steven M. Menchen**, Fremont, all of CA (US)

(73) Assignee: **The Perkin-Elmer Corporation**, Foster City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

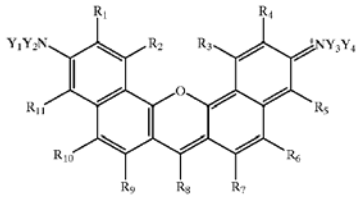
(21) Appl. No.: **09/325,243**

(22) Filed: **Jun. 3, 1999**

(74) *Attorney, Agent, or Firm*—Alex Andrus

(57) **ABSTRACT**

Extended rhodamine compounds exhibiting favorable fluorescence characteristics having the structure



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Exemplary modified pentose portions include but are not limited to 2'- or 3'-modifications where the 2'- or 3'-position is hydrogen, hydroxy, alkoxy, e.g., methoxy, ethoxy, allyloxy, isopropoxy, butoxy, isobutoxy and phenoxy, azido, amino or alkylamino, fluoro, chloro, bromo and the like.

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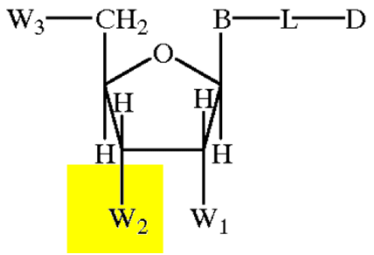
Nucleotide terminators also include reversible nucleotide terminators (Metzker et al., *Nucleic Acids Research,* 22(20): 4259 (1994)).

Particularly preferred nucleosides/tides of the present invention are shown below wherein



B is a nucleoside/tide base, e.g., uracil, cytosine, deazaadenine, or deazaguanosine; W_1 and W_2 taken separately are H or a group capable of blocking polymerase-mediated template-directed polymerzation, e.g., —H, fluorine and the like; W_3 is OH, or mono-, di- or triphosphate or phosphate analog; D is a dye compound of the present invention; and L is a covalent linkage linking the dye and the nucleoside/tide.

Ex. 1092 at 10:40-45, 11:22-24, 52:17-35
Reply at 6-7

Dr. Menchen's Testimony

Q. I didn't mean to exclude anything. My question to you is in your '116 patent you proposed allyloxy as a synthetic modification at the 3' location; is that correct?

A. That's correct.

Ex. 1112 at 64:8-13

Q. I'm just saying if it was some -- the mere fact that you can make something if you knew it would be completely disruptive of DNA sequencing, you wouldn't have listed it here, how about that? Let me ask the easy question.

A. I don't think -- yeah. If we knew it was going to fail you probably wouldn't make it.

Ex. 1112 at 80:14-23

Reply at 6-7

Dr. Menchen's Testimony

Q. How come you still identified allyl groups as a suitable modifier for 3' position in your patents?

A. Because that's what Metzker calls it. But he definitely refers to the structure of propenyl in that paper. He calls it allyl in the paper.

Ex. 1112 at 189:5-13

Reply at 15

Hiatt

United States Patent [19]

Hiatt et al.

[11] **Patent Number: 5,808,045**

[45] **Date of Patent: *Sep. 15, 1998**

[54] **COMPOSITIONS FOR ENZYME CATALYZED TEMPLATE-INDEPENDENT CREATION OF PHOSPHODIESTER BONDS USING PROTECTED NUCLEOTIDES**

[75] Inventors: **Andrew C. Hiatt**, 660 Torrance St., San Diego, Calif. 92103; **Floyd Rose**, Del Mar, Calif.

[73] Assignees: **Andrew C. Hiatt**, San Diego; **Floyd D. Rose**, Del Mar, both of Calif.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,763,594.

[21] Appl. No.: **486,897**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 300,484, Sep. 2, 1994, abandoned.

5,348,868 9/1994 Reddy et al. .
5,362,866 11/1994 Arnold, Jr. .
5,367,066 11/1994 Ureda et al. .
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5,436,143 7/1995 Hymann et al. .

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55-38324 3/1980 Japan .

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Deng and Wu, *Meth. Enzymol.*, 100: 96–116 (1983).
Kaufmann et al., *Eur. J. Biochem*, 24:4–11 (1971).
Hinton and Gumport, *Nucleic Acid Res.*, 7:453–464 (1979).
Modak, *Biochemistry*, 17, 3116–3120 (1978).
England and Uhlenbeck, *Biochemistry*, vol. 17, 11:2069–2076 (1978).
Chang and Bollum, *Biochemistry*, vol. 10, 3:536–542 (1971).
Bennett et al., *Biochemistry*, vol. 12, 20:3956–3960 (1973).
Kossel and Roychoudrury, *Eur J. Biochem.*, 22:271–276 (1971).
Flugel et al., *Biochem. Biophys. Acta*, 308:35–40 (1973).

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An alternative type of removable blocking moiety utilizes an ether linkage which forms the structure nucleotide—3'-O—R'. In this instance R'_1 can be methyl, substituted meythyl, ethyl, substituted ethyl, butyl, allyl, cinnamyl, benzyl, substituted benzyl, anthryl or silyl.

Ex. 1106 at 11:55-59
See also Ex. 1106 at 12:39, 30:8; Reply at 6

The criteria disclosed in Tsien and Columbia's patents

Tsien

Blocking Groups and Methods for Incorporation

The coupling reaction generally employs 3'hydroxyl-blocked dNTPs to prevent inadvertent extra additions.

The criteria for the successful use of 3'-blocking groups include:

(1) the ability of a polymerase enzyme to accurately and efficiently incorporate the dNTPs carrying the 3'-blocking groups into the cDNA chain,

(2) the availability of mild conditions for rapid and quantitative deblocking, and

(3) the ability of a polymerase enzyme to reinitiate the cDNA synthesis subsequent to the deblocking stage.

Ex. 1013 at 20:24-21:3

Columbia's patents

1. The Sequencing by Synthesis Approach

Sequencing DNA by synthesis involves the detection of the identity of each nucleotide as it is incorporated into the growing strand of DNA in the polymerase reaction. The fundamental requirements for such a system to work are: (1) the availability of 4 nucleotide analogues (aA, aC, aG, aT) each labeled with a unique label and containing a chemical moiety capping the 3'-OH group; (2) the 4 nucleotide analogues (aA, aC, aG, aT) need to be efficiently and faithfully incorporated by DNA polymerase as terminators in the polymerase reaction; (3) the tag and the group capping the 3'-OH need to be removed with high yield to allow the incorporation and detection of the next nucleotide; and (4) the growing strand of DNA should survive the washing, detection and cleavage processes to remain annealed to the DNA template.

Ex. 1001 at 21:2-18

Petition at 24, 36; Reply at 1, 8, 18

Dr. Menchen's Testimony

Q. Why don't you go through them one at a time and state whether you think the fundamental requirements for sequencing by synthesis disclosed in Ju are the same as those described in the prior art. Why don't you go through -- do it by number and break it down, that will be easier.

***

Q. Start with two again.

A. Two, "The four nucleotide analogs, AA, AC, AG, AT, need to be efficiently and faithfully incorporated by DNA polymerase as terminators of the polymerase reaction." That's a common requirement.

Ex. 1112 at 258:5-259:13

Q. What's a high yield in SBS according to you?

A. Well, quantitative.

Ex. 1112 at 124:2-4; *id.* at 138:4-9

Reply at 8, 18

Columbia relied on Metzker

BACKGROUND OF THE INVENTION

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If small chemical moieties that can be easily cleaved chemically with high yield can be used to cap the 3'-OH group, such nucleotide analogues should also be recognized as substrates for DNA polymerase. It has been reported that 3'-O-methoxy-deoxynucleotides are good substrates for several polymerases (Axelrod et al. 1978). 3'-O-allyl-dATP was also shown to be incorporated by Ventr(exo-) DNA polymerase in the growing strand of DNA (Metzker et al. 1994).

Ex. 1001 at 3:22-30;
Petition at 23, 24, 59-62, 65-66, 72

Dr. Menchen's Testimony

Q. What did Ju teach about the incorporation efficiency of the allyl groups?
MR. SCHWARTZ: Objection, form.
A. He taught that they should be incorporated efficiently.
Q. Did he teach how that should be done?
MR. SCHWARTZ: Objection, scope.
A. Yeah, I don't -- I don't remember seeing that.

Ex. 1112 at 284:6-18

Reply at 9, 23

Ju provides no new incorporation or cleavage chemistry

United States Court of Appeals
for the Federal Circuit

TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK,
Appellant

v.

ILLUMINA, INC.,
Appellee

2014-1547

However, as already explained, if novel and nonobvious chemistry was needed to practice the claimed inventions, Dr. Ju would have been obligated to disclose this chemistry in the patent. *See* 35 U.S.C. § 112(1) (2000).

Ex. 1008 at 31;
Petition at 36-37, 73; Reply at 2, 9, 23

3’-O-allyl dATP efficiently competes with natural dATP

Metzker

concentration dependent. Thus, minimum dNTP concentrations that gave efficient incorporation, but no apparent misincorporation were first defined in this assay. These dNTP concentrations were then used to determine the minimum ddNTP concentration that yielded complete termination. *Pfu* (exo$^-$) DNA polymerase was excluded from the Oligo-template assay since a ddNTP concentration that yielded complete termination for this enzyme [1] by AMV-RT. In addition to termination, some readthrough was also observed due to the presence of contaminating dATP. All RP-HPLC purified 3′-modified-dATPs (compounds [1]−[7]) showed approximately 1% dATP contamination, and these trace levels could not be removed by subsequent RP-HPLC.

3′-*O*-Methyl-dATP [1] was also incorporated by M-MuLV-RT and inhibited DNA syntheses by r*Tth* and Vent$_{R^{®}\ (exo^-)}$

Table 2. Activity matrix of RP-HPLC purified 3′-protecting dNTPs challenged against commercially available polymerases

3'-modified-dATP (except compound [8])	AMV-RT	M-MuLV-RT	Klenow fragment	Sequenase®	*Bst* DNA polymerase	AmpliTaq® DNA polymerase	Vent$_R$(exo$^-$)® DNA polymerase	r*Tth* DNA polymerase
[1] *O*-methyl	Termination	Termination*	-	-	-	-	Inhibition	Inhibition*
[2] *O*-acyl	-	-	-	-	-	-	Inhibition	-
[3] *O*-allyl	-	-	-	-	-	-	Termination*	-
[4] *O*-tetrahydropyran	-	-	-	-	-	-	-	-
[5] *O*-(4-nitrobenzoyl)	-	-	-	-	-	-	-	-
[6] *O*-(2-aminobenzoyl)	-	-	-	-	-	-	-	-
[7] *O*-(2-nitrobenzyl)	-	-	-	Inhibition	Termination	Termination*	Termination*	-
[8] 3'-*O*-methyl-dTTP	-	Inhibition	-	Inhibition	Termination	Termination	Termination	Termination

All compounds were assayed at a final concentration of 250 μM according to the conditions specified in Table 1. ‘−’ means no activity was detected, ‘Termination’ means that the termination bands mimic ddNTP termination bands, and ‘Inhibition’ means the rate of DNA synthesis is reduced in a nonspecific manner. ‘*’ means the activity was incomplete at a final concentration of 250 μM .

Ex. 1016 at 4263
Petition at 23; Reply at 9-10

Metzker and Columbia disclose the same polymerases

Metzker

Table 2. Activity matrix of RP-HPLC purified 3′-protecting dNTPs challenged against commercially available polymerases

3'-modified-dATP (except compound [8])	AMV-RT	M-MuLV-RT	Klenow fragment	Sequenase®	*Bst* DNA polymerase	AmpliTaq® DNA polymerase	Vent$_R$(exo$^-$)® DNA polymerase	r*Tth* DNA polymerase
[1] *O*-methyl	Termination	Termination*	-	-	-	-	Inhibition	Inhibition*
[2] *O*-acyl	-	-	-	-	-	-	Inhibition	-
[3] *O*-allyl	-	-	-	-	-	-	Termination*	-

Ex. 1016 at 4263

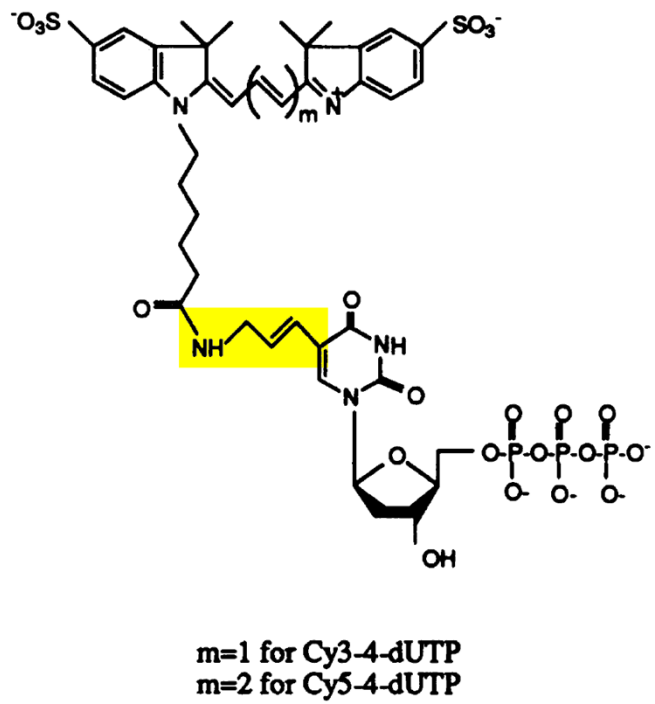
Columbia's Patents

Possible DNA polymerases include Thermo Sequenase, Taq FS DNA polymerase, T7 DNA polymerase, and Vent (exo-) DNA polymerase.

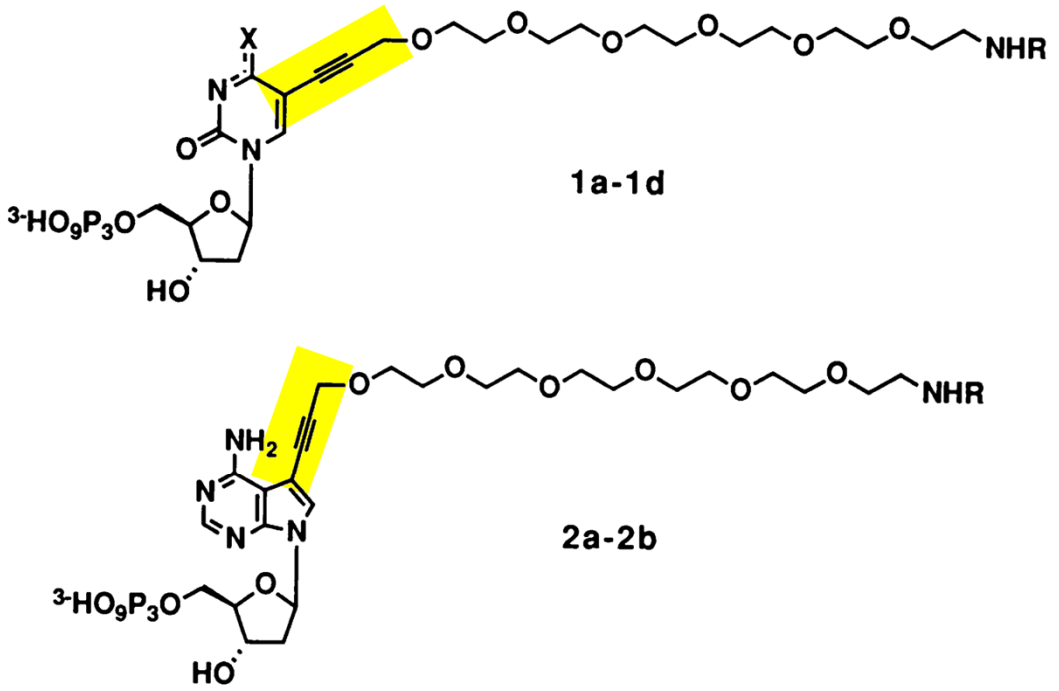
Ex. 1001 at 22:4-6

Reply at 9

Vent polymerase incorporation of labeled nucleotides



Ex. 1040 at 3228



1a	X = O, R = H_2^+.	dUTP-22.
1b	X = O, R = 3.	Biotin-36-dUTP.
1c	X = NH_2, R = H_2^+.	dCTP-22.
1d	X = NH_2, R = 3.	Biotin-36-dCTP.
2a	X = O, R = H_2^+.	dc^7ATP-22.
2b	X = O, R = 3.	Biotin-36-dc^7ATP.

Ex. 1041 at 4833

Petition at 30; Reply at 17, 22-23

Metzker

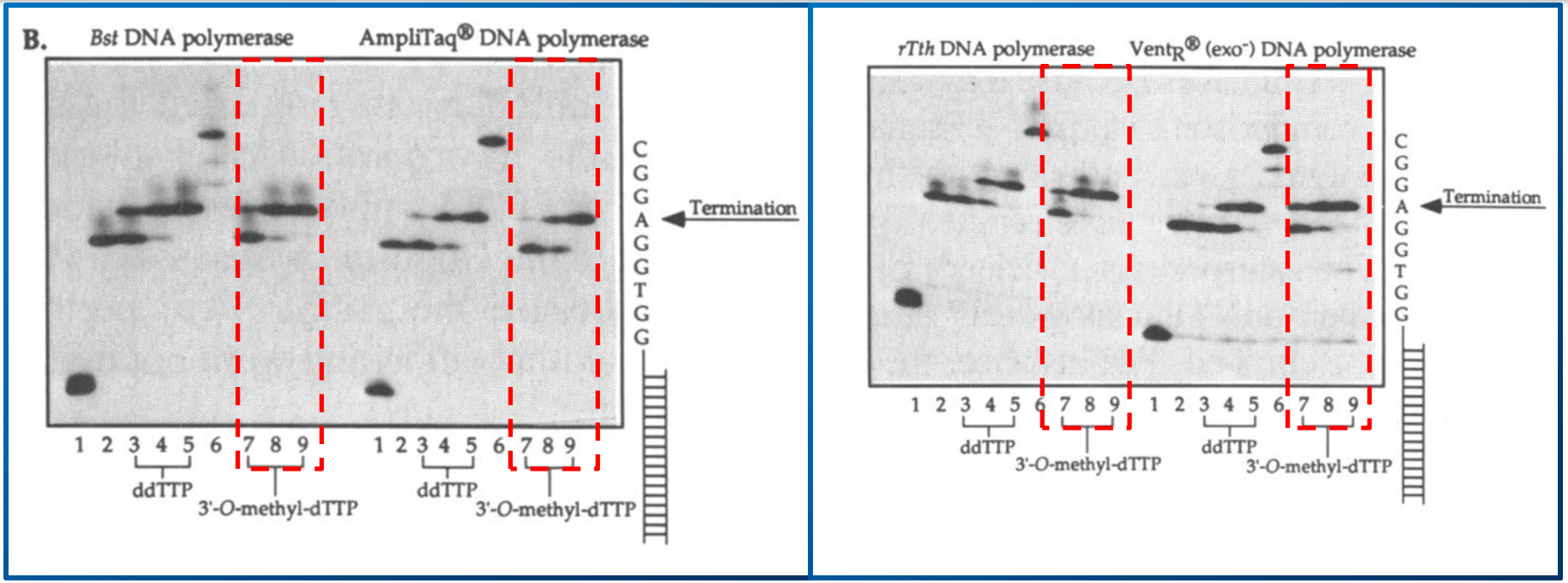
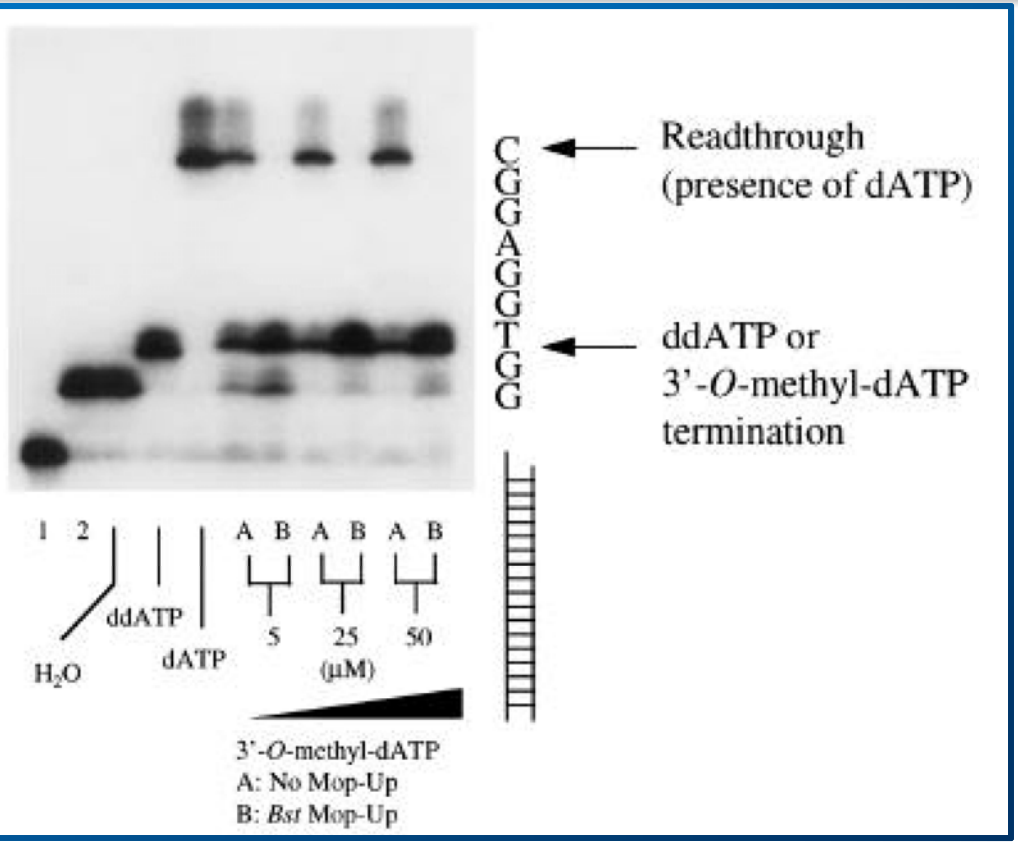


Figure 4. Incorporation of 3′-*O*-methyl-dTTP by *Bst*, AmpliTaq® , r*Tth* , and $Vent_R$® (exo⁻) DNA polymerases.

(B) Conditions for the Oligo-template assay were used for *Bst*, AmpliTaq® , r*Tth* , and $Vent_R$® (exo⁻) DNA polymerases. Lane 1 contained no dNTPs or ddNTPs. Lanes 2−7 contained dATP, dCTP and ddGTP. In addition, lanes 3−5 contained (*Bst*) 0.1 μM, 0.5 μM and 2.5 μM ddTTP; (AmpliTaq®) 1.0 μM, 5.0 μM and 25 μM ddTTP; (r*Tth*) and ($Vent_R$® (exo⁻)) 4 μM, 20 μM, and 100 μM ddTTP, respectively; lane 6 contained dTTP; and lanes 7−9 contained (*Bst*) 4 μM, 20 μM, and 100 μM of 3′-*O*-methyl-dTTP; (AmpliTaq®), (r*Tth*), and ($Vent_R$® (exo⁻)) 20 μM, 100 μM, and 500 μM of 3′-*O*-methyl-dTTP, respectively.

Ex. 1016 at Fig 4(B); Reply at 13

Metzker 1998



Following enzymatic mop-up, the incorporation of 3′-*O*-methyl-dATP by AMV-RT shows complete termination without natural nucleotide read-through (Figure 3, lanes B).

Ex. 2131 at 816; Reply at 12, 14

Metzker's Reaction Time

Polymerase incorporation assays

***

For each reaction, 5 μL aliquots of the annealed primer-template samples were dispensed into separate tubes containing 5 μL mixtures of each enzyme and nucleotides in their specific buffers. The final buffer conditions, concentrations of nucleotides, enzymatic units, and incubation temperatures are given in Table 1. The reactions were incubated for 10 min. and then stopped by the addition of 5 μL of stop solution containing 98% D.I. formamide, 10 mM EDTA, pH 8.0, 0.025% bromophenol blue, and 0.025% xylene cyanol.

76. Finally, a skilled artisan would have appreciated that extending the reaction time would have likely increased the degree of incorporation, and termination, for a particular 3'-O-modified dNTP. This is underscored by the fact that Metzker 1994 appears to run the incorporation reactions for 10 minutes. Ex. 1016 (Metzker 1994) at 4262 (reaction time for Table 1 termination is 10 minutes).

Ex. 1016 at 4262; Ex. 1119 ¶76; Reply at 13

Dr. Menchen's Testimony

Q. Are you an enzymologist?
A. No, I'm not.
Q. Do you know which polymerases would work with allyl just based on your technical expertise in the field?
MR. SCHWARTZ: Objection, scope.
A. Yeah. I'm not -- I don't have the background to -- to say that or determine that.
Q. Do you have any idea which enzymes would work with MOM?
MR. SCHWARTZ: Same objection.
A. I -- I have no idea.

Q. Have you personally worked with Vent(exo-) DNA polymerase?
MR. SCHWARTZ: Objection to form.
A. I have never worked with any polymerase myself.

Q. My question isn't that. My question is whether it's meaningful information?
A. I can't comment on that.
Q. Why not?
MR. SCHWARTZ: Objection to scope to all those questions. Just give me a chance to object Dr. Menchen.
THE WITNESS: Okay.
A. Because I'm -- I'm not a crystallographer and I'm not an expert on polymerases. So I can't really evaluate, yeah, that analysis myself.

Ex. 1112 at 141:19-142:9, 193:13-18, 270:2-16
Reply at 11; Motion to Exclude at 2-3, 5-6

5-substituted pyrimidines and 7-substituted 7-deaza-purines

The alkynylamino linker-containing nucleotides of this invention have distinct advantages such as: the small steric bulk of the alkynylamino-linker minimizes perturbation of the nucleotide; positioning the linker on the 5-position of pyrimidine nucleotides and the 7-position of 7-deazapurine nucleotides eventually places the linker and reporter in the major groove when the nucleotide is incorporated into double-stranded DNA (this will serve to minimize interference with hybridization and other processes, which require that a double-stranded conformation be possible); and alkynylamino-nucleotides with a reporter attached are excellent substrates for AMV reverse transcriptase.

Ex. 1029 at 27:52-65

See also Ex. 1030 at 1087; Ex. 1031 at 3051; Petition at 14

Escalating efficiency expectations in mid-to-late 2000's

"The Race for the $1000 Genome," Science, 311:1544, 2006

The race is on

The first group to produce a technology capable of sequencing a human genome sequence for $1000 will get instant gratification, as well as potential future profits: In September 2003, the J. Craig Venter Science Foundation promised $500,000 for the achievement. That challenge has since been picked up by the Santa Monica, California–based X Prize Foundation, which is expected to up the ante to between $5 million and $20 million. But the competition really began in earnest in 2004, when the National Institutes of Health launched a $70 million grant program to support researchers working to sequence a complete mammal-sized genome initially for $100,000 and ultimately for $1000. That program has had an "amazing" effect on the field, encouraging researchers to pursue a wide variety of new ideas, says Church. That boost in turn has led to a miniexplosion of start-up companies, each pursuing its own angle on the technology (see table, p. 1546).

Ex. 1120 at 1544; Reply at 15

Columbia relied on Kamal

BACKGROUND OF THE INVENTION

***

However, the procedure to chemically cleave the methoxy group is stringent and requires anhydrous conditions. Thus, it is not practical to use a methoxy group to cap the 3'-OH group for sequencing DNA by synthesis. An ester group was also explored to cap the 3'-OH group of the nucleotide, but it was shown to be cleaved by the nucleophiles in the active site in DNA polymerase (Canard et al. 1995). Chemical groups with electrophiles such as ketone groups are not suitable for protecting the 3'-OH of the nucleotide in enzymatic reactions due to the existence of strong nucleophiles in the polymerase. It is known that MOM (—CH_2OCH_3) and allyl (—$CH_2CH{=}CH_2$) groups can be used to cap an —OH group, and can be cleaved chemically with high yield (Ireland et al. 1986; Kamal et al. 1999).

Ex. 1001 at 3:31-44;
Petition at 23, 32, 50, 60

Columbia repeatedly relied on Metzker and Kamal

The MOM ($—CH_2OCH_3$) or allyl ($—CH_2CH═CH_2$) group is used to cap the 3'-OH group using well-established synthetic procedures (FIG. **13**) (Fuji et al. 1975, Metzker et al. 1994). These groups can be removed chemically with high yield as shown in FIG. **14** (Ireland, et al. 1986: Kamal et al. 1999). The chemical cleavage of the MOM and allyl groups is fairly mild and specific, so as not to degrade the DNA template moiety. For example, the cleavage of the allyl group takes 3 minutes with more than 93% yield (Kamal et al. 1999), while the MON group is reported to be cleaved with close to 100% yield (Ireland, et al. 1986).

Ex. 1001 at 26:22-33

The MOM ($—CH_2OCH_3$) or allyl ($—CH_2CH═CH_2$) group is used to cap the 3'-OH group using well-established synthetic procedures (FIG. **13**) (Fuji et al. 1975, Metzker et al. 1994). These groups can be removed chemically with high yield as shown in FIG. **14** (Ireland, et al. 1986: Kamal et al. 1999). The chemical cleavage of the MOM and allyl groups is fairly mild and specific, so as not to degrade the DNA template moiety.

Ex. 1001 at 28:15-22

Petition at 23, 32, 37, 50, 60, 68, 72

Dr. Menchen's Testimony

Q. What would a person of ordinary skill in the art conclude as to whether or not Ju is stating that MOM and allyl can be used for his inventions that are claimed?

A. They would conclude that he doesn't really show that, you know -- he doesn't show here that he has cleavage conditions that are compatible with SBS.

Ex. 1112 at 235:19-236:4

Reply at 18

The Board, Federal Circuit, and Supreme Court

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2012-00007
Patent 7,790,869 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

The court concluded that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *Baxter*, 952 F.2d at 392.

Ex. 1005 at 38 (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991))

326 U.S. 242

GENERAL ELECTRIC CO. v. JEWEL INCANDESCENT LAMP CO. et al.

No. 46.

Argued Oct. 18, 19, 1945.

Decided Nov. 5, 1945.

Rehearing Denied Dec. 3, 1945.

See 326 U.S. 810, 66 S.Ct. 227.

It is not invention to perceive that the product which others had discovered had qualities they failed to detect.

Gen. Elec. Co. v. Jewel Incandescent Lamp Co., 326 U.S. 242, 249 (1945)

Reply at 8

Palladium-based cleavage of the allyl group

Columbia's '852 patent admits it was known that the "allyl (-$CH_2CH{=}CH_2$) group is used to cap the 3′-OH group using well-established synthetic procedures" and "can be removed chemically with high yield." Ex-1001 at 26:22-33 (citing Ex-1016 & Ex-1037); *id.* at 3:39-44; Ex-1012 ¶87; *see also* Ex-1035 at 559 (demonstrating cleavage of allyl groups using palladium); Ex-1036 at 2184 (demonstrating quantitative allyl cleavage).

Petition at 32

It was known that allyl groups are chemically cleaved using palladium. Ex-1035 at 559; Ex-1036 at 2184; Ex-1012 ¶64.

Petition at 22

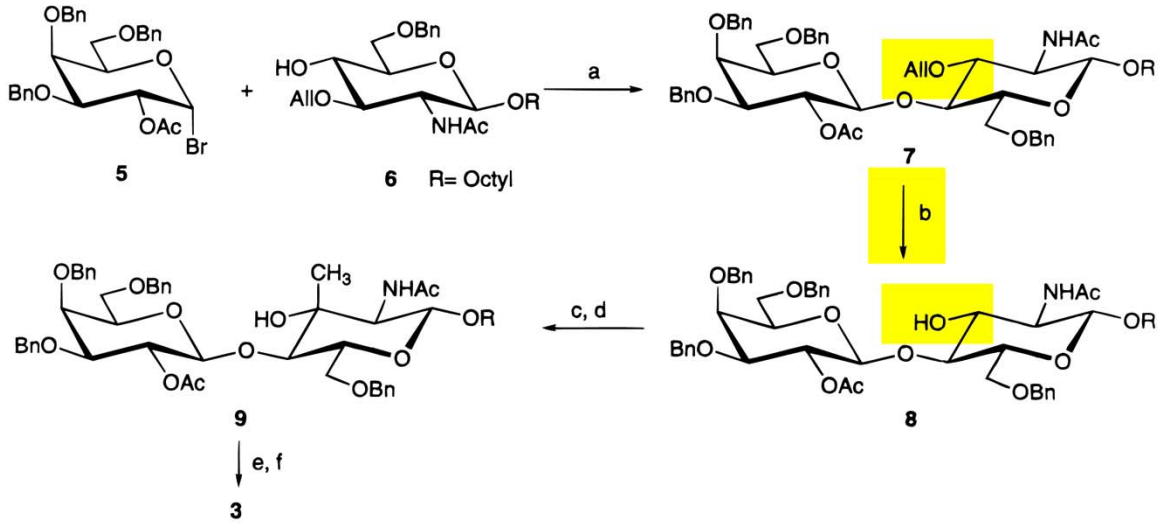
It was also known that allyl groups were generally efficiently removed using palladium, including under aqueous conditions. Ex-1035 (Boss) at 559, Table 1; Ex-1036 (Qian) at 2184 ("The O-allyl group was then removed using $PdCl_2$, providing [the deprotected compound] in quantitative yield.").

Ex. 1012 ¶64

Palladium-based cleavage of the allyl group

Qian – quantitative allyl ether removal at room temperature

Scheme 2[a]



[a] Reagents and Conditions: (a) **3** (1.5 equiv), AgOTf (2 equiv), 4 Å molecular sieves, CH_2Cl_2, −30 to 0 °C, 3 h, 81%; (b) $PdCl_2$ (0.5 equiv), MeOH, room temperature (rt), 2 h, quantitative; (c) DMSO, Ac_2O, rt, 4 h; (d) MeLi (1.5 equiv), THF, −78 °C, 2 h, 20% (two steps); (e) NaOMe, MeOH, rt, 27 h, 92%; (f) H_2, 20% $Pd(OH)_2/C$, MeOH, 20 h, 85%.

Ex. 1036 at 2184-85;
Petition at 22, 32

Palladium-based cleavage of the allyl group

Boss – aqueous palladium removal of the allyl group

Table 1. Converted allyl ethers.

Allyl ether	Reaction conditions [a]	Product	Yield [%] [b]
(4) C_6H_5–O–	Pd/C methanol/H_2O/H^+ 6 h reflux	(4a) C_6H_5–OH	>95
(5) n-C_8H_{17}–O–	Pd/C methanol/H_2O/H^+ 6 h reflux	(5a) n-C_8H_{17}–OH	>95
(6) 	Pd/C H_2O/H^+ 6 h 80°C	(6a) 	>95

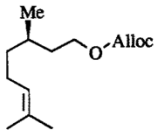
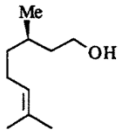
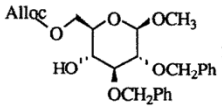
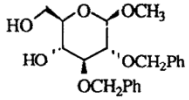
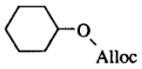
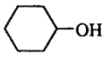
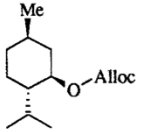
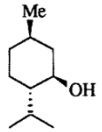
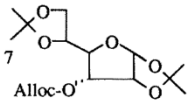
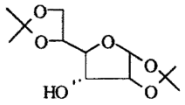
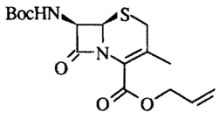
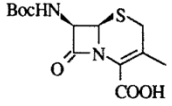
Ex. 1035 at 559;
Petition at 22, 32

Palladium-based cleavage of the allyl group

Genet – aqueous palladium removal of the allyl group

Deprotective method of Alloc in aqueous media

Table I : Palladium Mediated Deprotection of Alcohols with $Pd(OAc)_2$ / TPPTS, Et_2NH.

entry	substrates	NuH (eq)	product	Pd(0) (mol%)	solvent	time /r.t.	yield %
1		Et_2NH 5		2	CH_3CN/H_2O	5min	94
2	"" ""	HCOOH 3.5	"" ""	2	CH_3CN/H_2O	2.5h	51
3	"" ""	Et_2NH 5	"" ""	2	CH_2Cl_2/H_2O	3min	76
4		2.2		2	CH_3CN/H_2O	20min	99
5		2.2		2	CH_3CN/H_2O	10min	80
6		2.2		2.2	C_3H_7CN/H_2O	30min	100
7		2.2		2	CH_3CN/H_2O	10min	99
8		10		2	$CH_3CN/MeOH/H_2O$	1h	93

Ex. 1094 at 499;
See also Ex. 1114 at 8784;
Ex. 1115 at 249
Reply at 20-21

Dr. Menchen's Testimony

Q. And let me show you this. It's marked as Exhibit 1094.

(Exhibit 1094, Genet reference from 1994, marked for identification, as of this date.)

***

Q. And if you look at page 499, do you see that Table 1? And do you understand this table?

A. I understand the table.

***

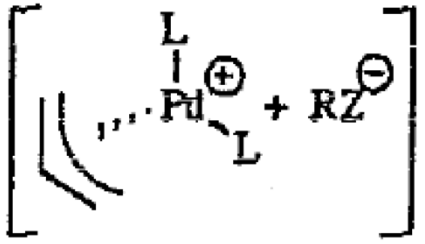
Q. My question is just is this method described on page 499, this was within the level of ordinary skill in the art in the mid-1990s for deprotection; is that correct?

A. I would say so.

Ex. 1113 at 359:7-11, 360:6-9, 360:25-361:6
Reply at 21

Dr. Romesberg's Testimony

The π-allyl methodology was also well known for the removal of an allyloxycarbonyl groups, for example in the presence of diethylamine as an allyl scavenger, in aqueous media. Ex 1115 (Lemaire-Audoire 2) at 248. Regardless of the particular allyl derivative, the π-allyl methodology proceeds through the intermediate shown below (the intermediate is formed after the nucleophilic Pd^0 displaces the RZ group from the allyl group).



Ex 1115 (Lemaire-Audoire 2) at 248

Ex. 1119 ¶41; *see also id.* ¶¶40-43; Ex. 2140 at 187:8-25; Reply at 21

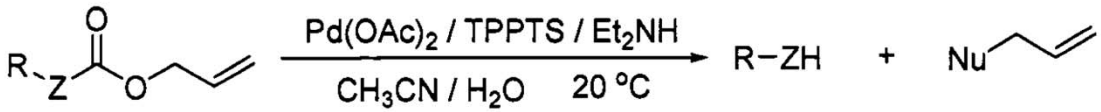
Palladium-based cleavage of the allyl group

Dr. Ju's Laboratory

In the past decades, chemists have developed efficient catalysts to cleave allyl groups from allyl ethers, allyl carbonates or allyl carbamates; these are composed of palladium (0) or (II) combined with suitable ligands or other reagents.

Ex. 1116 at 163

Genet – aqueous palladium removal of the allyl group



Z = O or NH or CH_2 5~15 min, 70~100%

Substrate : $Pd(OAc)_2$: TPPTS : Et_2NH = 1: 0.02 : 0.04 : 2.5

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

Ex. 1116 at 164
Reply at 20-21

The Board previously cancelled Columbia's claims

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2012-00007
Patent 7,790,869 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

***

With respect to claims 13, 17, 20-26, 28, 29, 31, and 33, Illumina identified specific disclosure in Tsien where each limitation is found (Petition 22-26). We find Illumina's assertions to be supported by a preponderance of the evidence.

***

X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 are cancelled;

28. The nucleotide of claim **12**, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.

31. The nucleotide of claim **12**, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.

Ex. 1005 at 1, 11, 49
Ex. 1010 at 34:40-42, 48-50
Petition at 23, 25

Columbia's incorrect arguments

- The Dower-based ground fails for the same reasons as the Tsien-based ground
- Dower does not disclose a cleavable linker

Reply at 25-26

Dower

Examples of these compounds are deoxynucleotide triphosphates with small blocking groups such as acetyl, tBOC, NBOC and NVOC on the 3'OH. These groups are easily and efficiently removed under conditions of high or low pH, exposure to light or heat, etc.

Ex. 1015 at 25:48-53
Petition at 58

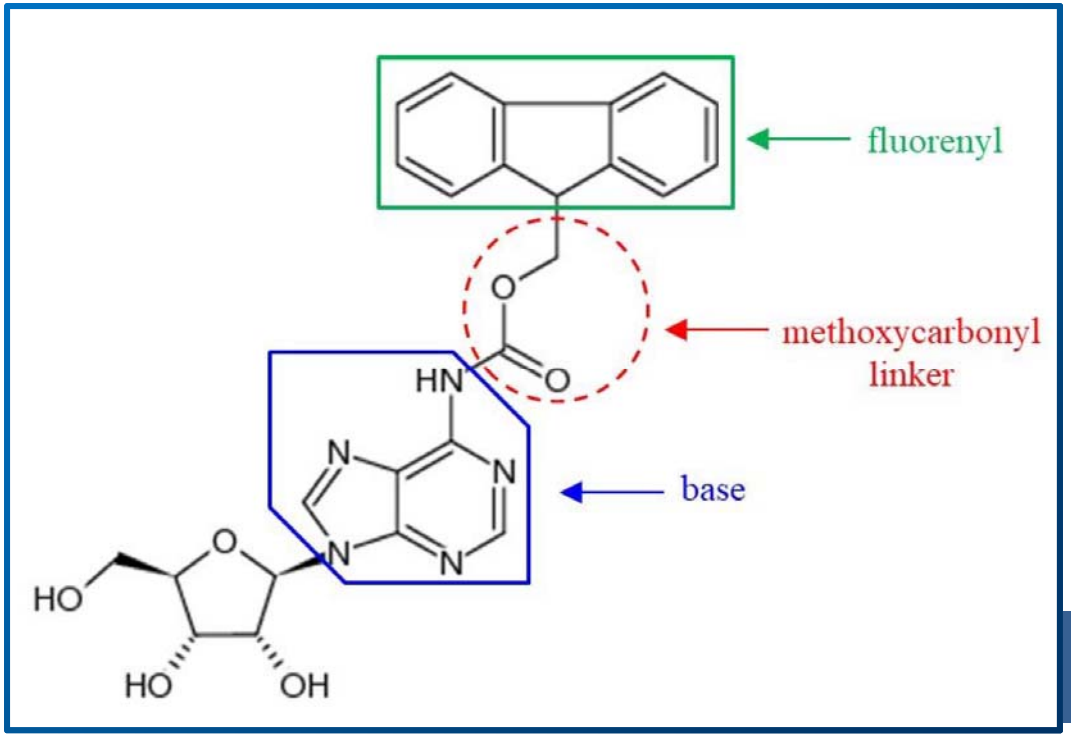
Dower

The structures of the fluorescently labeled and reversible terminator base analogs are selected to be compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension. For example, where two different chain terminators are used, they may be utilized by two different polymerases that are both present during the chain extension step.

Step 5: An optional step is the permanent capping of chain extension failures with high concentrations of dideoxynucleotide triphosphates. This step serves to reduce the background of fluorescence caused by addition of an incorrect base because of inefficient chain extension (termination) at an earlier step.

Ex. 1015 at 26:6-18
Petition at 60-61; Reply at 25

Dower



Reply at 26

Instead, Dr. Romesberg now says that FMOC's cleavable linker could be attached to the carbon in the challenged claim via "***an additional linker***[.]" Ex. 2140, 197:16-198:8. No such theory exists in Illumina's Petition. And, Illumina's double-linker is excluded from the claim, which requires one linker (Y), not two linkers (Y Y).

Sur-reply at 24

The double-linker theory includes a propargyl amine linker

Q. But Dower doesn't teach attaching Fmoc to the three bases that he teaches attaching it to through any kind of additional linker, correct?

A. Dower gives an example where he uses Fmoc to attach directly to the three of the four that you could directly attach to. T is not. But Dower cites to Prober consistently throughout, six times, and I think expressly says four linkers. Look to Prober. And Prober published T analogs with exocyclic amines that would have been suitable and, in fact, cites -- uses them in the example that we used -- included in my dec for exactly that, a propargylamine linker to attach a linker to it, which he attached a fluorophore to.

He didn't attach the Fmoc directly, but it would be an exocyclic amine that you would exactly be able to do that if you chose. Or you would be able to choose an additional linker between them. And that's what Seitz did.

Ex. 2140 at 197:16-198:8; Sur-reply at 24

The propargyl amine (alkynylamino) theory was in the Petition

Petition on Dower

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.

Petition Section VIII.B.16

Each step of the synthetic process for preparing the nucleotide analogues disclosed by the combination of Tsien and Prober were within the level of ordinary skill. Columbia's witness (Dr. Trainor) in IPR2012-00007 confirmed the level of ordinary skill included:

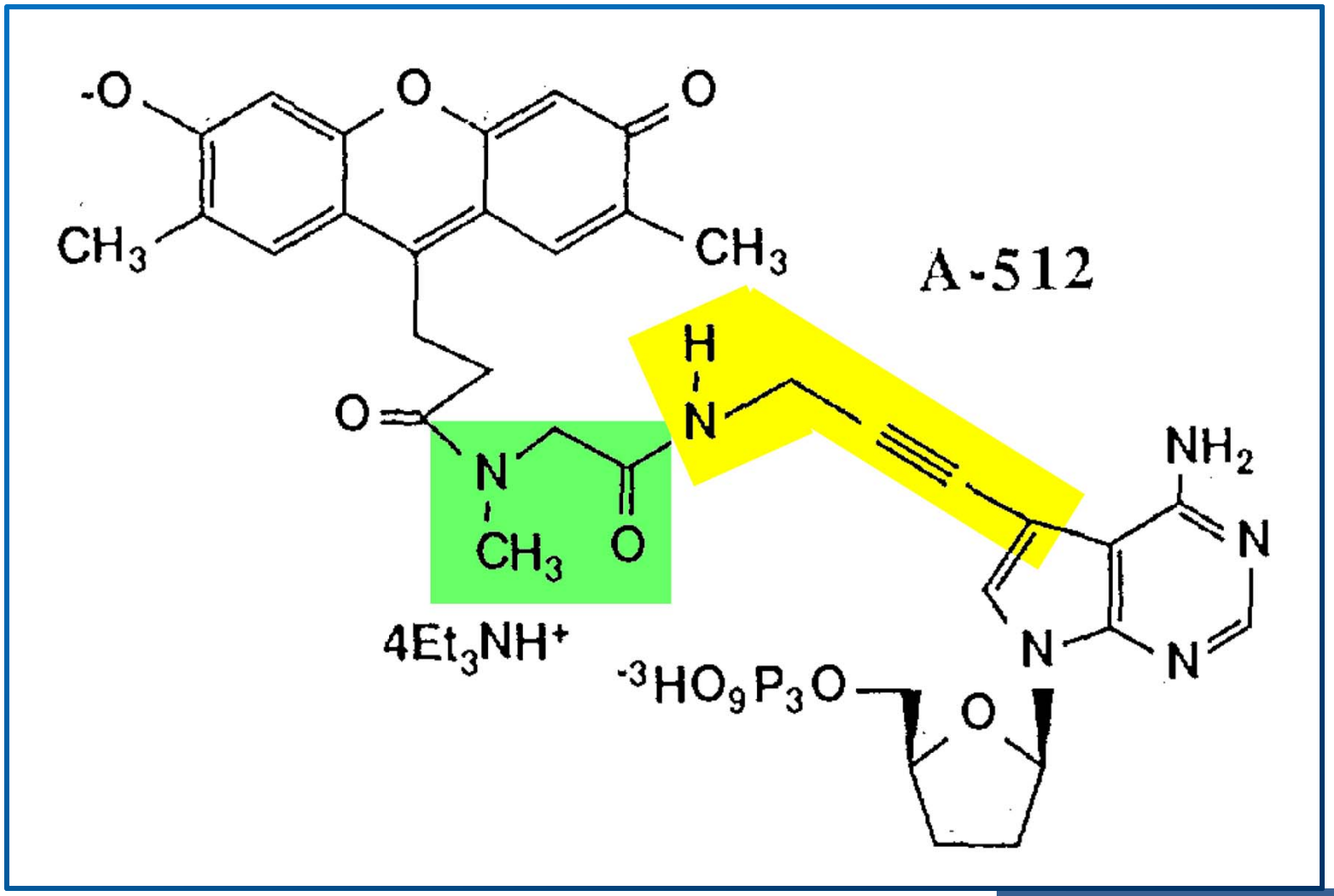
- Adding an alkynylamino group to a 7-iodide deaza-adenine. Ex-1028 at 177:13-178:15, 179:7-23.
- Attaching a fluorescent label to the alkynylamino group via a cleavable linker. *Id.* at 191:23-192:5, 170:7-171:5, 166:3-168:4, 342:19-343:9, 387:5-388:23.

See also Ex-1029 at 28:62-29:23; Ex-1028 at 243:8-244:2.

Petition at 37, 73;
Ex. 1012 ¶¶ 97, 114, 116, 124,

Prober includes a double-linker

Prober nucleotide with propargyl amine linker and second linker



Petition at 47, 58; Ex. 1012 ¶123; Ex. 1014 at 338; Sur-reply at 24

A linker (Y) theory of Dower was in the Petition

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 7-position of deaza-adenine. Ex-1012 ¶146.

Petition at 64; *id*. at 73, 37

The claimed linker does not provide patentability over Dower

Further, any argument that the claimed linker provides patentability over Dower is disingenuous. Columbia's patent has no disclosure of an exemplary chemically cleavable linker. Ex. 1012 ¶73, n.4. The Columbia patent merely says that the linker can be chemically cleaved. Ex. 1001, 14:17-21. Dower has a comparable disclosure. Ex. 1015, 15:52-59.

Reply at 26

Columbia's disclosure is similar to Dower for Linker (Y) embodiments

Dower

One important functional property of the monomers is that the label be removable. The removal reaction will preferably be achieved using mild conditions. Blocking groups sensitive to mild acidic conditions, mild basic conditions, or light are preferred.

Ex. 1015 at 15:52-56

Columbia's patents

In one embodiment, the linker between the unique label and the nucleotide analogue is cleavable 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. In a further embodiment, the cleavable linker is a photocleavable linker which comprises a 2-nitrobenzyl moiety.

Ex. 1001 at 14:17-23

Reply at 26

Examiner's rejection during reexamination

Tsien et al. do not teach explicitly teach a nucleoside 5'-triphosphate with a 3'-allyl protective group. At page 24, lines 29 - 30, Tsien et al. describes a deblocking procedure for an allyl ether. Tsien et al. also describes the use of allyl ether groups at remote positions (i.e., with respect to the ribosyl moiety) for attaching fluorescent groups to the nucleoside base at page 27, line 13 through page 28, line 4. Even though Tsien et al. does not explicitly teach an allyl group protecting the 3'-OH of the ribosyl group, by referencing the ribosyl through the use of the term "remote," the person of skill in the art would immediately envision the 3'-OH protected by an allyl group because the prior art clearly teaches allyl as a standard protecting group for hydroxyl groups. See Greene et al. at pages 22 - 45 and 413.

Therefore, the claimed 3'-OH protected nucleoside 5'-triphosphates and compositions containing them along with a buffer, an enzyme capable of forming phosphodiester bonds, an oligonucleotide or polynucleotide with a free 3'-OH group bound to a solid support would have been obvious to the person of skill in the art as taught by Tsien et al. for the purpose of sequencing the nucleic acid bound to the solid support. The use of a 3'-OH allyl protecting group that is readily removable but not only implicitly disclosed in Tsien et al. is rendered obvious by Greene et al. and the Patent Owner's admission that all of the protecting groups are known in the prior art.

Ex. 2065 at 101;
Reply at 23-24

Reexamination priority date

Reexamination Request:
No. 90/008,152, Aug. 3, 2006

Reexamination Certificate for:

Patent No.:	**6,232,465**
Issued:	**May 15, 2001**
Appl. No.:	**08/486,536**
Filed:	**Jun. 7, 1995**

Certificate of Correction issued Feb. 19, 2002.

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/300,484, filed on Sep. 2, 1994, now Pat. No. 5,990,300.

Ex. 2065 at 129

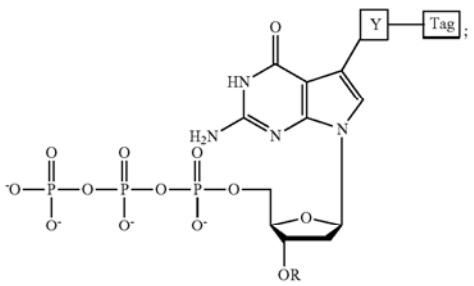
Intervening Reference	Publication Date
Metzker (Ex. 1016)	October 1994 (*see* Ex. 1097)
Qian (Ex. 1036)	1998
Kamal (Ex. 1037)	1999
Gardner (Ex. 1122)	1999

Reply at 24

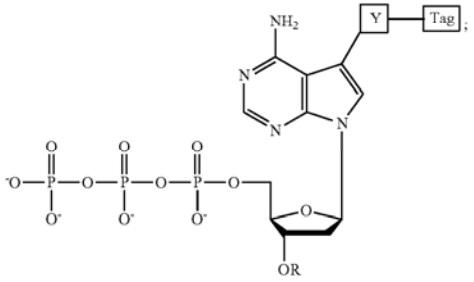
Method Case – IPR2018-00797 – Claim Construction

1. A method for sequencing a nucleic acid which comprises detecting the identity of a nucleotide analogue incorporated into the end of a growing strand of DNA in a polymerase reaction, wherein the nucleotide analogue is any of the following:

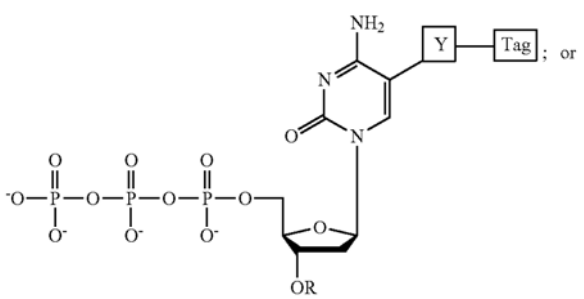
(A)



(B)

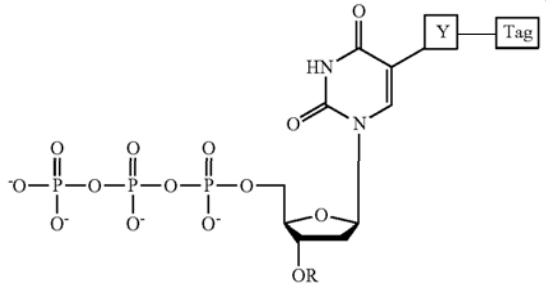


(C)



or

(D)



. . .

Ex. 1075 at 34:3-36:28

Method Case – IPR2018-00797 – Claim Construction

SUMMARY OF THE INVENTION

This invention is directed to a method for sequencing a nucleic acid by detecting the identity of a nucleotide analogue after the nucleotide analogue is incorporated into a growing strand of DNA in a polymerase reaction, which comprises the following steps:

(i) attaching a 5' end of the nucleic acid to a solid surface;

(ii) attaching a primer to the nucleic acid attached to the solid surface;

(iii) adding a polymerase and one or more different nucleotide analogues to the nucleic acid to thereby incorporate a nucleotide analogue into the growing strand of DNA, wherein the incorporated nucleotide analogue terminates the polymerase reaction and wherein each different nucleotide analogue comprises (a) a base selected from the group consisting of adenine, guanine, cytosine, thymine, and uracil, and their analogues; (b) a unique label attached through a cleavable linker to the base or to an analogue of the base; (c) a deoxyribose; and (d) a cleavable chemical group to cap an —OH group at a 3'-position of the deoxyribose;

(iv) washing the solid surface to remove unincorporated nucleotide analogues;

(v) detecting the unique label attached to the nucleotide analogue that has been incorporated into the growing strand of DNA, so as to thereby identify the incorporated nucleotide analogue;

(vi) adding one or more chemical compounds to permanently cap any unreacted —OH on the primer attached to the nucleic acid or on a primer extension strand formed by adding one or more nucleotides or nucleotide analogues to the primer;

(vii) cleaving the cleavable linker between the nucleotide analogue that was incorporated into the growing strand of DNA and the unique label;

(viii) cleaving the cleavable chemical group capping the —OH group at the 3'-position of the deoxyribose to uncap the —OH group, and washing the solid surface to remove cleaved compounds; and

(ix) repeating steps (iii) through (viii) so as to detect the identity of a newly incorporated nucleotide analogue into the growing strand of DNA;

wherein if the unique label is a dye, the order of steps (v) through (vii) is: (v), (vi), and (vii); and

wherein if the unique label is a mass tag, the order of steps (v) through (vii) is: (vi), (vii), and (v).

Ex. 1075 at 4:45-5:23; *id.* at 8:33-9:11
IPR2018-00797 Reply at 4

Method Case – IPR2018-00797 – Claim 2

Columbia's Claim 2

2. A method for simultaneously sequencing a plurality of different nucleic acids which comprises simultaneously applying the method of claim 1 to the plurality of different nucleic acids.

Pallas discloses simultaneous sequencing using Tsien's method

In another aspect, the invention includes a system for simultaneously analyzing the nucleotide sequences of a population of polynucleotides. Copies of each kind of polynucleotide in the population are sorted onto and anchored to one or more microparticles so that a population of loaded microparticles is formed.

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DNA Sequencing

Polynucleotides loaded onto microparticles may be simultaneously sequenced in the instant apparatus using a "base-by-base" DNA sequencing methodology. Such sequencing methodology permits the stepwise identification of a sequence of nucleotides in a target polynucleotide, usually one base at a time, through successive cycles of treatment and detection. Base-by-base approaches are disclosed in the following references: Cheeseman, U.S. patent 5,302,509; Tsien et al, International application WO 91/06678; Rosenthal et al, International application WO 93/21340; Canard et al, Gene, 148: 1-6 (1994); Metzker et al, Nucleic Acids Research, 22: 4259-4267 (1994); and the like.

Ex. 1080 at 2:30-33, 16:26-33
IPR2018-00797 Petition at 52-54

Issue Preclusion Applies to PTAB Proceedings

MAXLINEAR, INC., Appellant

v.

CF CRESPE LLC, Appellee

2017-1039

United States Court of Appeals,
Federal Circuit.

Decided: January 25, 2018

880 F.3d 1373, 1376 (Fed. Cir. 2018)

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2015-00592.

It is well established that collateral estoppel, also known as issue preclusion, applies in the administrative context. *See B & B Hardware, Inc. v. Hargis Indus., Inc.*, —— U.S. ——, 135 S.Ct. 1293, 1303, 191 L.Ed.2d 222 (2015). The Supreme Court has held:

> [It is] clear that issue preclusion is not limited to those situations in which the same issue is before two *courts*. Rather, where a single issue is before a court and an administrative agency, preclusion also often applies. Indeed, this Court has explained that because the principle of issue preclusion was so "well established" at common law, in those situations in which Congress has authorized agencies to resolve disputes, "courts may take it as given that Congress has legislated with the expectation that the principle [of issue preclusion] will apply except when a statutory purpose to the contrary is evident."

Id. (alteration in original) (quoting *Astoria*

Reply at 28

Issue Preclusion Applies Across Patents With Claims That Are Not Identical

The OHIO WILLOW WOOD COMPANY, Plaintiff–Appellant,

v.

ALPS SOUTH, LLC, Defendant–Cross Appellant.

Nos. 2012–1642, 2013–1024.

United States Court of Appeals, Federal Circuit.

Nov. 15, 2013.

Rehearing and Rehearing En Banc Denied Jan. 23, 2014.*

735 F.3d 1333, 1342 (Fed. Cir. 2013)

OWW seeks reversal on appeal by arguing that the mere existence of different language in the adjudicated claims of the '182 patent and unadjudicated claims of the '237 patent is sufficient to overcome collateral estoppel. We disagree. Our precedent does not limit collateral estoppel to patent claims that are identical.

Reply at 28

Issue Preclusion Applies Across Patents With Claims That Are Not Identical

The OHIO WILLOW WOOD COMPANY, Plaintiff–Appellant,

v.

ALPS SOUTH, LLC, Defendant–Cross Appellant.

Nos. 2012–1642, 2013–1024.

United States Court of Appeals, Federal Circuit.

Nov. 15, 2013.

Rehearing and Rehearing En Banc Denied Jan. 23, 2014.*

735 F.3d 1333, 1343 (Fed. Cir. 2013)

It is undisputed that the adjudicated claims of the '182 patent only require a "polymeric" gel whereas the unadjudicated claims of the '237 patent specifically require a "block copolymer" gel. OWW argues that this difference in claim scope precludes summary judgment. But OWW has not adequately supported this contention because it has not provided any explanation regarding *how* the "block copolymer" limitation is patentably significant in view of the obviousness determination regarding the claims of the '182 patent. Since OWW failed to explain how the "block copolymer" limitation changes the invalidity analysis, OWW has not met its burden of opposing summary judgment based on this distinction. Thus, summary judgment that claims 1, 2, 4, 15, 16, and 20 of the '237 patent are invalid on the basis of collateral estoppel was appropriate.

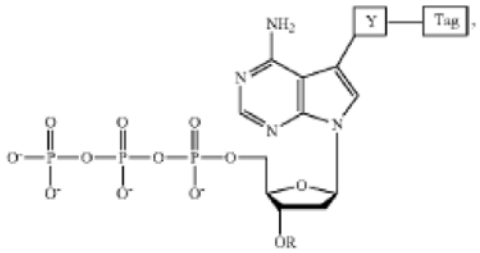
Reply at 28

Columbia Focuses Exclusively on the 3'-O-Capping Group

Patent Owner Response at i-iii

3’-O-Capping Group Claim Elements

1. An adenine 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;

Patent Owner Response at 63-64

The Board previously cancelled Columbia's claims based on Tsien

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2012-00007
Patent 7,790,869 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

***

X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 are cancelled;

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.

13. The nucleotide of claim **12**, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3'OH group is cleaved by chemical means.

Ex. 1005 at 1, 49;
Ex. 1010 at 33:40-54;
Petition at 15, 17-18

The Board previously cancelled Columbia's claims based on Tsien

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2012-00007
Patent 7,790,869 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

***

X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 are cancelled;

28. The nucleotide of claim **12**, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.

31. The nucleotide of claim **12**, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.

Ex. 1005 at 1, 11, 49;
Ex. 1010 at 34:40-42, 48-50;
Petition at 23, 25

The Board previously cancelled Columbia's claims based on Tsien

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2013-00011
Patent 8,088,575 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

***

XI. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1-3 and 6 of U.S. Patent 8,088,575 B2 are cancelled;

1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising: a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template; b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and contains a small removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, wherein said small cleavable chemical group does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate; and c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.

Ex. 1007 at 1, 13, 45;
Ex. 1054 at 33:29-34:31;
Petition at 61, 65

The Board previously cancelled Columbia's claims based on Tsien

ILLUMINA, INC.
Petitioner
v.
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
Patent Owner

Case IPR2013-00011
Patent 8,088,575 B2

Before SALLY G. LANE, RICHARD M. LEBOVITZ, and DEBORAH KATZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

***

XI. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1-3 and 6 of U.S. Patent 8,088,575 B2 are cancelled;

2. The method of claim **1**, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of the incorporated nucleotide analogue, thereby permitting the incorporation of a further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.

6. The method of claim **1**, wherein said base of at least one of said nucleotide analogues is a deazapurine.

Ex. 1007 at 1, 45;
Ex. 1054 at 34:31-35, 42-43;
Petition at 1

The Examiner found Columbia's new claims are patentably indistinct

The Examiner's Rejection

Claim 61 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 14, 17-19, 28, and 32 of U.S. Patent No. 7,790,869 in view of Tsien (WO 91/06678).

Ex. 1065 at 100

Double Patenting

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A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s).

Ex. 1065 at 99

Petition at 4-5, 6-7

Patent Owner Estoppel

(d) Estoppel.

(3) Patent applicant or owner. A patent applicant or owner is precluded from taking action inconsistent with the adverse judgment, including obtaining in any patent:

(i) A claim that is not patentably distinct from a finally refused or canceled claim;

(ii) An amendment of a specification or of a drawing that was denied during the trial proceeding, but this provision does not apply to an application or patent that has a different written description.

37 C.F.R. § 42.73(d)(3)(i);
Petition at 4-5, 6-7

Columbia's claim to 3'-O-allyl was denied in the prior IPRs

Columbia's Motion to Amend in IPR2012-00007

Claim 40 (proposed substitute for Claim 19): The nucleotide of claim [[12]] 34, wherein said cleavable chemical group comprises —$CH_2CH{=}CH_2$.

Claim 34 (proposed substitute for original Claim 15 rewritten in independent form to include features of independent Claim 12 and amended to delete member of Markush group): A nucleotide ~~of claim 12~~ having a base that is attached to a detectable label through a cleavable linker, wherein the base is a deazapurine, 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, and 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, and heat~~, and light~~.

Ex. 1137, Appx. A at 3-4; Reply at 28

Columbia's claim to 3'-O-allyl was denied in the prior IPRs

Columbia's Motion to Amend in IPR2012-00007

Claim 40 (proposed substitute for Claim 19): The nucleotide of claim [[12]] 34, wherein said cleavable chemical group comprises —$CH_2CH{=}CH_2$.

Ex. 1137, Appx. A at 4

Board's Final Written Decision

X. ORDER

In consideration of the foregoing, it is

ORDERED that claims 12, 13, 15-17, 20-26, 28, 29, 31, and 33 of U.S. Patent 7,790,869 B2 are cancelled;

FURTHER ORDERED that Columbia's motion to amend claims is denied;

Ex. 1005 at 49

Reply at 28

Columbia is re-litigating the same 3'-O-allyl incorporation efficiency issue that was raised in the previous IPRs

Illumina's Reply to Columbia's Patent Owner Response in IPR2012-00007

> Claim 49 requires only that the "cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase." *Id.* Dr. Trainor admitted that this property is met by any 3' blocking group that allows incorporation by a polymerase. Ex. 2094 at 154:10-156:22. For example, Tsien discloses an allyl 3' blocking group, which would not interfere. Ex. 1002 at 24:29-30; Ex. 2094 at 106:14-108:21.

Ex. 1128 at 3;
see also Ex. 1127 at 11-12

Reply at 27

Columbia is re-litigating the same 3'-O-allyl cleavage issue that was raised in the previous IPRs

Q. Okay. And where we were looking down before on line 29, of page 24 it says, "Allyl ethers are cleaved by treatment with Mercury 2 in acetone/water," and it cites to a reference.

Do you see that?

A. Yes, I see that.

Q. Okay. So it discloses that allyl ethers, as blocking groups, can be removable, right?

A. It doesn't specify whether they're removable without other reactions going on that would destroy the ability of the nucleotide to work, which is important to perform this invention.

Ex. 1098 at 112:8-24; Sur-reply at 30-31

Polymerase Fidelity

96. Eckert's discussion is in the context of PCR using natural dNTPs. Eckert's discussion does not include modified dNTPs that, while efficiently incorporated, have a larger Km (weaker binding). This is why higher concentrations are used for accurate and efficient incorporation, but it will also likely increase the concentration required for misinsertion. The window between efficient correct incorporation and misincorporation is shifted to higher concentrations. A person working in the field of DNA sequencing would understand Eckert's teachings indicate that the concentration required for misincorporation is higher than the concentration required for accurate and efficient incorporation.

Ex. 1119 ¶ 96;
Motion to Exclude at 11-12; Sur-reply at 13