The Trustees Of Columbia University In The City Of New York and Qiagen Sciences, LLC

v.

Illumina, Inc.

Case No. 19-1681-CFC

Illumina's Claim Construction Hearing Presentation

“Y”

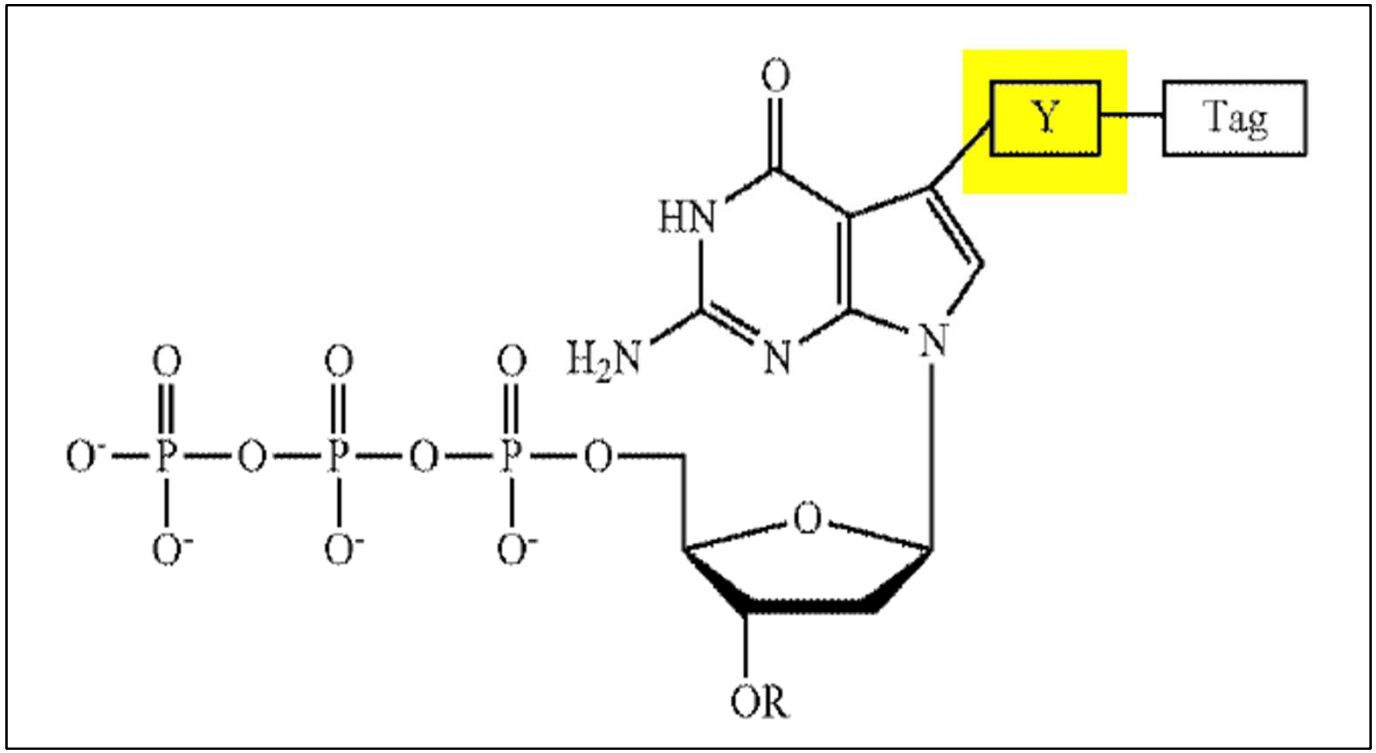
Disputed Claim Term

Claim Term	Illumina's Construction	Plaintiffs' Construction
"Y" '458 Patent: Claims 1, 2 '459 Patent: Claims 1, 2 '742 Patent: Claims 1, 2 '984 Patent: Claims 1, 2 '380 Patent: Claims 1, 3	"A single linker that directly connects the base to the label"	"Represents a part of the nucleotide analogue, attaching the base of the nucleotide analogue to a tag, as depicted in the illustration of the nucleotide analogue in the claim"

Key Dispute

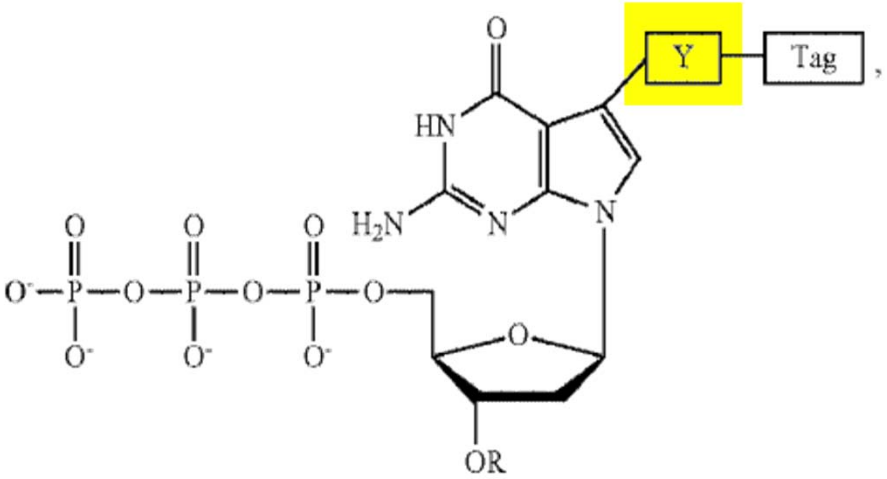
- Whether “Y” is a single linker or multiple linkers?
  - Illumina’s position: single linker
  - Plaintiffs’ position: multiple linkers

Claim Language: Only One Linker



Claim Language: Only One Linker

1. A guanine deoxyribonucleotide analogue having the structure:

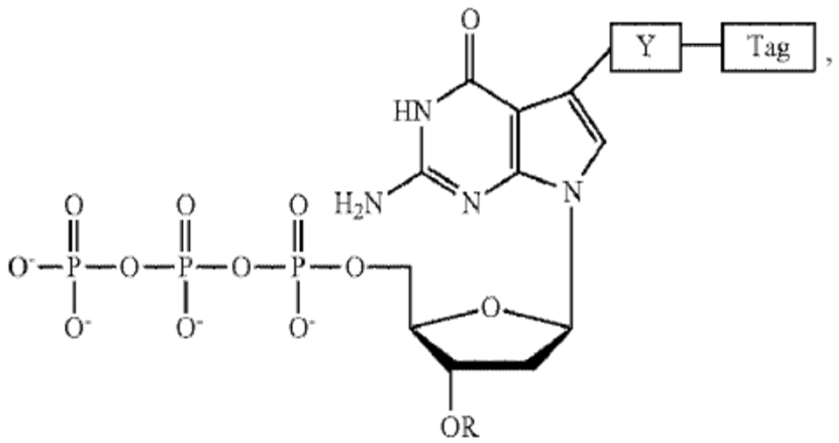


"A" or "an" is construed broadly when the open term "comprising" is present.

Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 977 (Fed. Cir. 1999).

Claim Language: Only One Linker

1. A guanine deoxyribonucleotide analogue having the structure:



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

- Columbia did not claim broadly using established conventions:

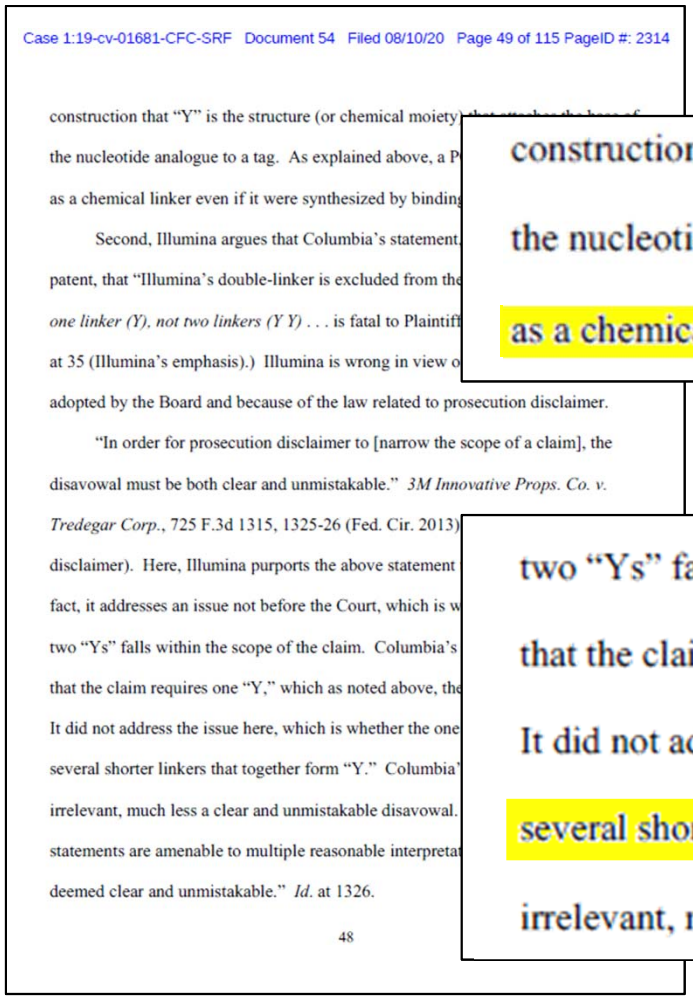
  "-Y-Y-"

  "-X-Y-"

  "–(Y)n– where n is 1 or greater"

  "–(X)m-(Y)n– where m and n are 1 or greater"

Plaintiffs' Position: Two Linkers Can Be Treated As One



construction that "Y" is the structure (or chemical moiety) that attaches the base of the nucleotide analogue to a tag. As explained above, a P as a chemical linker even if it were synthesized by binding

Second, Illumina argues that Columbia's statement patent, that "Illumina's double-linker is excluded from the *one linker (Y), not two linkers (Y Y)* . . . is fatal to Plaintiff at 35 (Illumina's emphasis).) Illumina is wrong in view o adopted by the Board and because of the law related to prosecution disclaimer.

"In order for prosecution disclaimer to [narrow the scope of a claim], the disavowal must be both clear and unmistakable." *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1325-26 (Fed. Cir. 2013) disclaimer). Here, Illumina purports the above statement fact, it addresses an issue not before the Court, which is w two "Ys" falls within the scope of the claim. Columbia's that the claim requires one "Y," which as noted above, the It did not address the issue here, which is whether the one several shorter linkers that together form "Y." Columbia' irrelevant, much less a clear and unmistakable disavowal. statements are amenable to multiple reasonable interpreta deemed clear and unmistakable." *Id.* at 1326.

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Plaintiffs' Brief

construction that "Y" is the structure (or chemical moiety) that attaches the base of the nucleotide analogue to a tag. As explained above, a POSA would refer to "Y" as a chemical linker even if it were synthesized by binding two or more linkers.

two "Ys" falls within the scope of the claim. Columbia's prior statement explained that the claim requires one "Y," which as noted above, the parties do not dispute. It did not address the issue here, which is whether the one "Y" can consist of several shorter linkers that together form "Y." Columbia's prior statement is irrelevant, much less a clear and unmistakable disavowal. "Where an applicant's

Law: Plaintiff Must Bear Cost Of Narrow Claiming

" [A]s between the patentee who had a clear opportunity to negotiate broader claims but did not do so, and the public at large, it is the patentee who must bear the cost of its failure to seek protection for this foreseeable alteration of its claimed structure."

SciMed Life Sys., Inc. v. Adv. Cardiovascular Sys., Inc., 242 F.3d 1337, 1346 (Fed. Cir. 2001)

Prosecution History: Dr. Ju Defined "Y"

Indefiniteness Rejection:

C. The term "Y"

The Examiner acknowledged that the claim recites some functional characteristics of Y but that these functional limitations do not set forth well-defined boundaries of the invention because they only state a problem solved or a result achieved.

Narrowing Definition:

C. The scope of Y

20. Y is defined as a chemically cleavable, chemical linker and as shown in the structure shown in the pending claim, Y is attached by covalent bonds at one end to the base of a nucleotide analogue at a specific position and at the other end to a detectable fluorescent moiety. 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. Therefore, a POSA would have readily understood the meaning of Y in the context of the pending claim as a whole read in light of the patent application.

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Dkt. 62239-BZA6AA/JPW/BI

NITED STATES PATENT AND TRADEMARK OFFICE

Trustees of Columbia University in the City New York

gyue Ju et al.

149,098 Examiner: Jezia Riley

ober 1, 2018 Art Unit: 1637

SIVE PARALLEL METHOD FOR DECODING DNA AND RNA

30 Rockefeller Plaza
20th Floor
New York, New York 10112
May 9, 2019

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL COMMUNICATION SUPPLEMENTING COMMUNICATION IN RESPONSE TO JANUARY 16, 2019 FIRST ACTION INTERVIEW PILOT PROGRAM PRE-INTERVIEW COMMUNICATION FILED FEBRUARY 12, 2019

emental Communication is submitted to supplement the on In Response To January 16, 2019 First Action Interview am Pre-Interview Communication filed February 12, 2019 in with the above-identified application.

JA0028

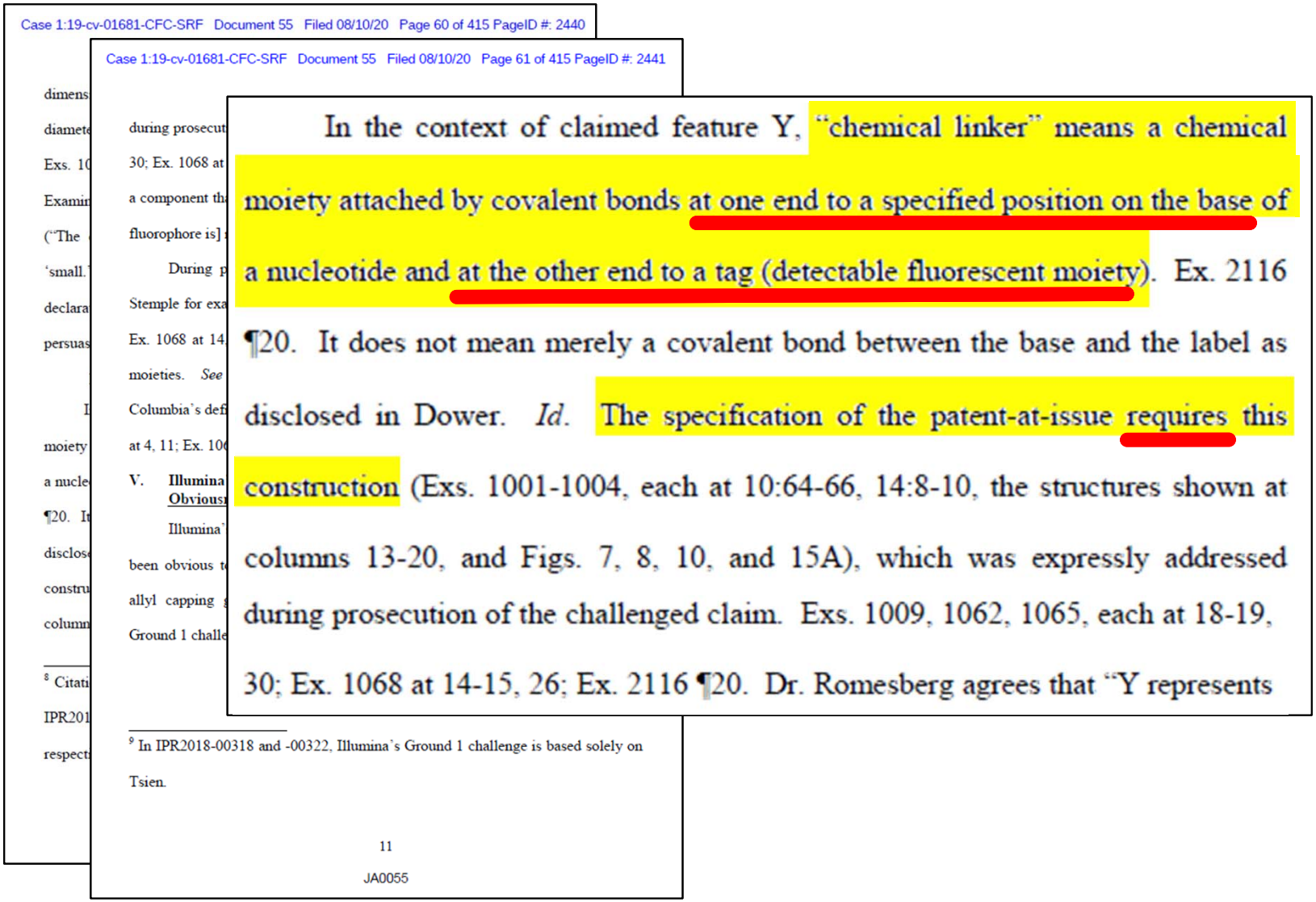
Supp. Submission (JA0033); Ju Declaration (JA0065).

Law: IPR Is Part Of Prosecution History

"Because an IPR proceeding involves reexamination of an earlier administrative grant of a patent, it follows that statements made by a patent owner during an IPR proceeding can be considered during claim construction and relied upon to support a finding of prosecution disclaimer."

Aylus Networks, Inc. v. Apple Inc., 856 F.3d 1353, 1361 (Fed. Cir. 2017).

Prosecution History: "Y" Is A Single Linker



Case 1:19-cv-01681-CFC-SRF Document 55 Filed 08/10/20 Page 60 of 415 PageID #: 2440

Case 1:19-cv-01681-CFC-SRF Document 55 Filed 08/10/20 Page 61 of 415 PageID #: 2441

In the context of claimed feature Y, "chemical linker" means a chemical moiety attached by covalent bonds at one end to a specified position on the base of a nucleotide and at the other end to a tag (detectable fluorescent moiety). Ex. 2116 ¶20. It does not mean merely a covalent bond between the base and the label as disclosed in Dower. *Id.* The specification of the patent-at-issue requires this construction (Exs. 1001-1004, each at 10:64-66, 14:8-10, the structures shown at columns 13-20, and Figs. 7, 8, 10, and 15A), which was expressly addressed during prosecution of the challenged claim. Exs. 1009, 1062, 1065, each at 18-19, 30; Ex. 1068 at 14-15, 26; Ex. 2116 ¶20. Dr. Romesberg agrees that "Y represents

[9] In IPR2018-00318 and -00322, Illumina's Ground 1 challenge is based solely on Tsien.

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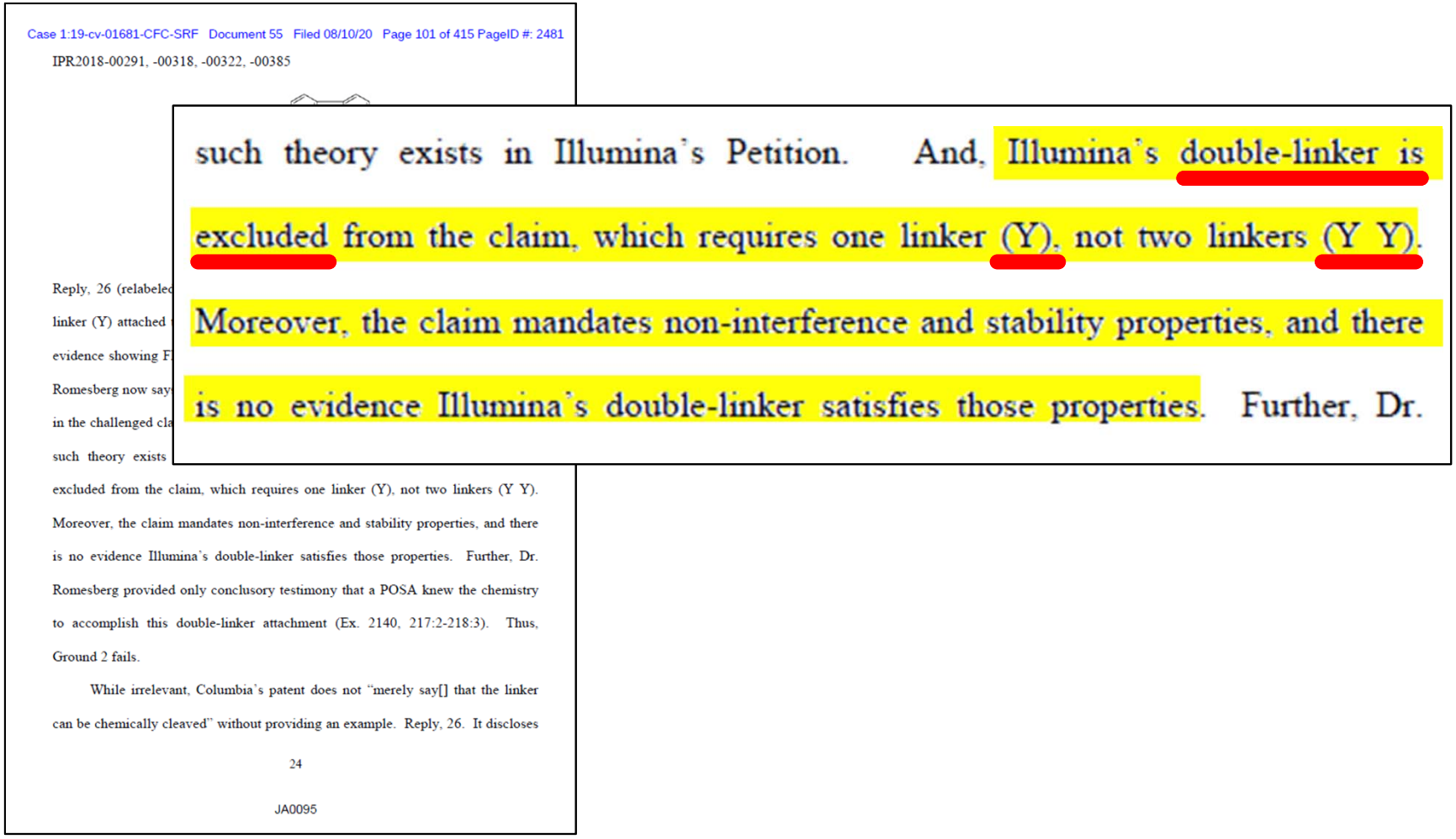
JA0055

Columbia's IPR Resp. (JA0054-0055)

Prosecution History: Double-Linker "Excluded"



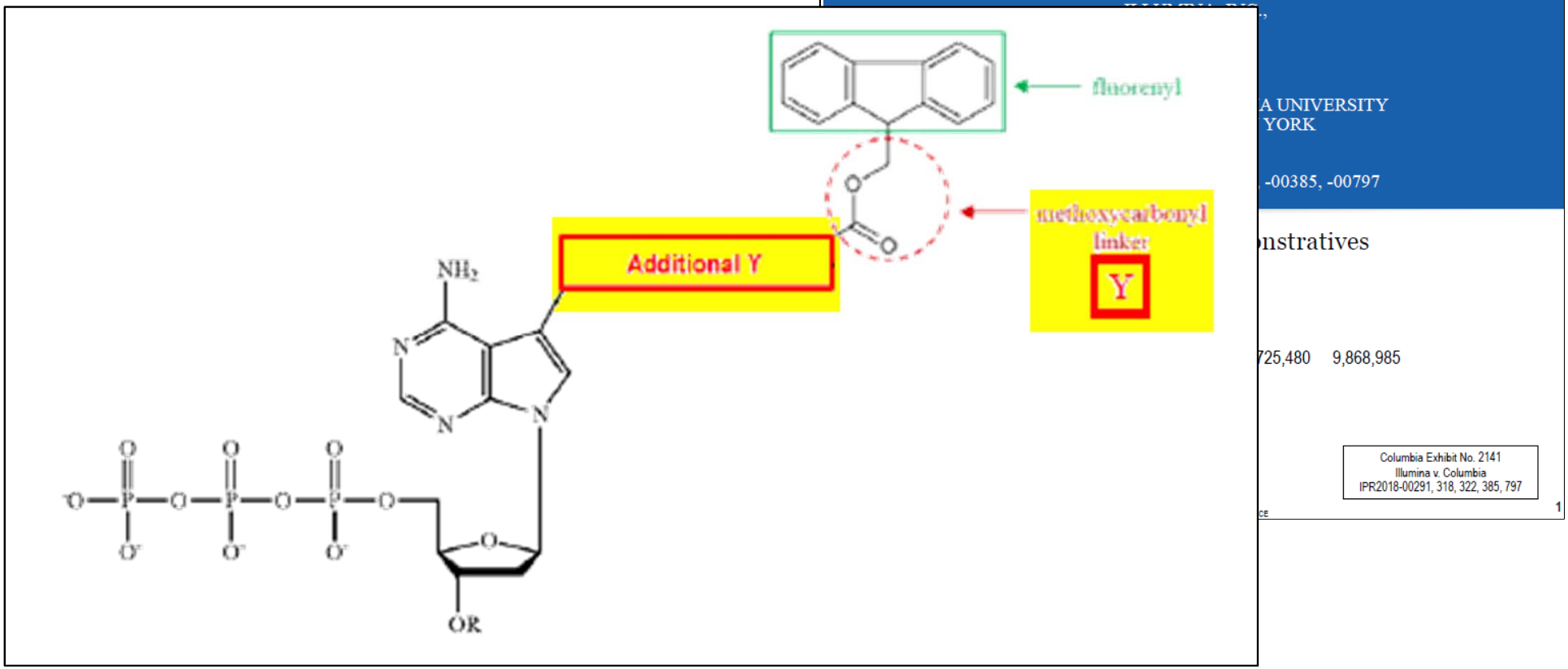
such theory exists in Illumina's Petition. And, Illumina's double-linker is excluded from the claim, which requires one linker (Y), not two linkers (Y Y). Moreover, the claim mandates non-interference and stability properties, and there is no evidence Illumina's double-linker satisfies those properties. Further, Dr.

Reply, 26 (relabeled
linker (Y) attached
evidence showing F
Romesberg now say
in the challenged cla
such theory exists
excluded from the claim, which requires one linker (Y), not two linkers (Y Y). Moreover, the claim mandates non-interference and stability properties, and there is no evidence Illumina's double-linker satisfies those properties. Further, Dr. Romesberg provided only conclusory testimony that a POSA knew the chemistry to accomplish this double-linker attachment (Ex. 2140, 217:2-218:3). Thus, Ground 2 fails.

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

Columbia's IPR Sur-Reply (JA0095)

Prosecution History: “Additional Y” Excluded



Columbia’s IPR Demonstrative (JA0133)

Plaintiffs' Argument: PTAB Rejected Construction

In any event, the PTAB expressly rejected any notion that "Y" was limited to one linker.

> Patent Owner argues that claim 1 excludes a
> attached to a propargyl amine because the cl
> one linker, not two linkers. Surreply 24. We
> a general rule, the words "a" or "an" in a pat
> carry the meaning of 'one or more.

(IPR2018-00291, Paper 67, 53-54 (JA0040–41, n.33) (cit
omitted).) As the Federal Circuit held in *Galderma Labs,*
806 F. App'x 1007, 1011 (Fed. Cir., 2020), when "the rec
skilled artisan that Patent Owner's arguments were reject
not impact claim scope." *See also Power Integrations, In*
Corp., 396 F. Supp. 3d 851, 855 (N.D. Cal. 2019) (findin
disclaimer arising from patent owner's statements in IPR
rejected the patent owner's arguments and that such reject
the public that the claim scope is different than what the p
the patentee's claim scope is wrong.").[15]

[15] The *Galderma* court noted that in *American Piledriving*
Inc., 637 F.3d 1324, 1336 (Fed. Cir. 2011), the Federal Ci
patentee's arguments during reexamination still can infor
term, regardless of whether the examiner agreed with the
distinguished the case, in part because "the statements we
inter partes review" and because the examiner had not "c
rejected the patentee's proposed construction." *Galderma*

Plaintiffs' Brief

In any event, the PTAB expressly rejected any notion that "Y" was limited to one linker.

> Patent Owner argues that claim 1 excludes a linker attached to a propargyl amine because the claim requires one linker, not two linkers. Surreply 24. We disagree. As a general rule, the words "a" or "an" in a patent claim carry the meaning of 'one or more.

(IPR2018-00291, Paper 67, 53-54 (JA0040–41, n.33) (citations and quotations omitted).) As the Federal Circuit held in *Galderma Labs, L.P. v. Amneal Pharms.* 806 F. App'x 1007, 1011 (Fed. Cir., 2020), when "the record makes clear to a skilled artisan that Patent Owner's arguments were rejected, those arguments do not impact claim scope." *See also Power Integrations, Inc. v. On Semiconductor*

Law: Columbia Cannot Escape Admissions

Patentee's IPR statements are relevant to claim construction regardless of whether they are accepted–or even disputed by PTAB

See Am. Piledriving, Inc. v. Geoquip, Inc., 637 F.3d 1324, 1336 (Fed. Cir. 2011).

Law: Columbia Cannot Escape Admissions

"We agree with the district court that arguments deliberately and repeatedly advanced by the patent applicant in regard to the scope of a claim term during prosecution may be used for purposes of claim construction even though the Patent Office rejected the arguments."

Lifestream Diagnostics, Inc. v. Polymer Tech. Inc., 109 F. App'x 411, 414-16 (Fed. Cir. 2004).

Law: Columbia Cannot Escape Admissions

"An applicant's argument made during prosecution may lead to a disavowal of claim scope even if the Examiner did not rely on the argument."

Seachange Int'l, Inc. v. C-COR Inc., 413 F.3d 1361, 1374 (Fed. Cir. 2005).

Law: Columbia Cannot Escape Admissions

"We have stated on numerous occasions that a patentee's statements during prosecution, whether relied on by the examiner or not, are relevant to claim interpretation."

Microsoft Corp. v. Multi-Tech Sys., 357 F.3d 1340, 1350 (Fed. Cir. 2004).

Law: Columbia Cannot Escape Admissions

Galderma Labs., L.P. v. Amneal Pharms. LLC, 806 Fed. App'x 1007 (Fed. Cir. 2020) (*non-precedential*).

- Pertains to doctrine of equivalents–not claim construction
- A "prosecution history statement may inform the proper construction of a term without rising to the level of a clear and unmistakable disclaimer."

Id. at 1011.

PTAB: Used Broadest Reasonable Interpretation

Broadest reasonable interpretation, so that "the patent examiner is able to 'reduce the possibility that, after the patent is granted, the claims may be interpreted as giving broader coverage than is justified.'"

PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC, 815 F.3d 734, 740 (Fed. Cir. 2016).

Phillips Standard Is Different

Under the *Phillips* standard, "district courts seek out the correct construction—the construction that most accurately delineates the scope of the claimed invention—under the framework laid out in" *Phillips*.

PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC, 815 F.3d 734, 740 (Fed. Cir. 2016).

Plaintiffs' Argument: Illumina Excludes Embodiments

the final linker)).) As shown above, the structure that equates to Y in the claimed structures shown in Figures 8 and 16 are not limited to a "single linker."

Accordingly, Illumina's construction is n

construction taught by *01 Communique L*

rejected on the ground that it would exclu

16 of the specification. *See, e.g., Verizon*

503 F.3d 1295, 1305 (Fed. Cir. 2007) ("W

in a way that excludes disclosed example

b. Illumina Admi
More Than a S

In Illumina's IPR of a related Colu

("the '852 Patent")[7], Illumina argued that

make Y from two linkers that nonetheless

with the Patents-in-Suit. Specifically, in

allegedly invalid over the combination of

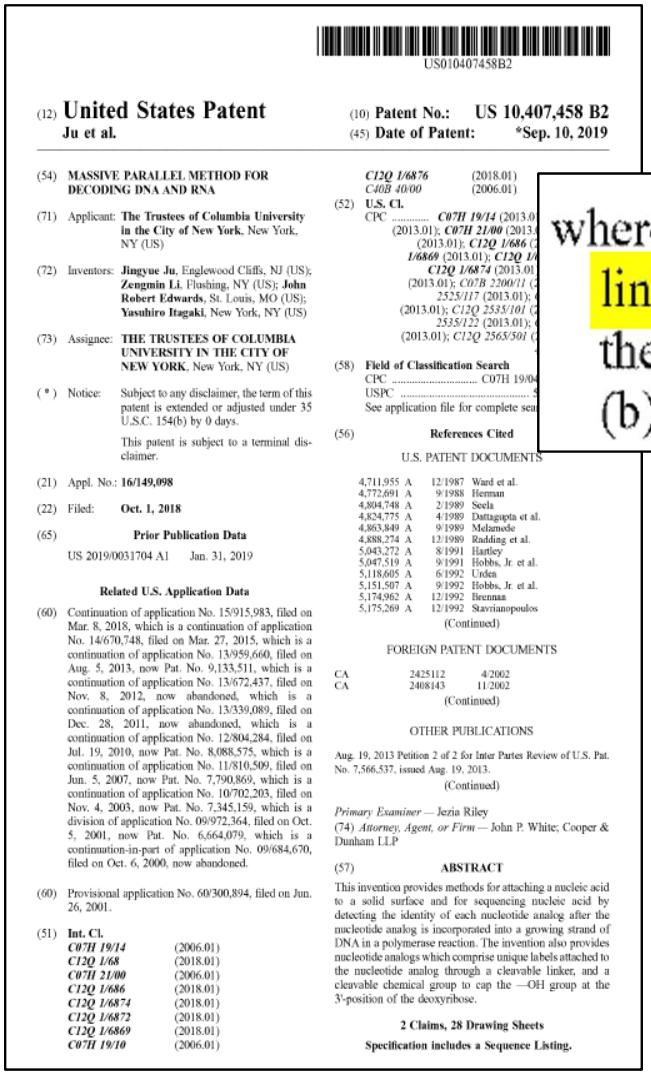
[7] The Patents-in-Suit and the '852 Patent
the same specification and claim languag
1001 (JA0043–44 at claim 1).) Thus, the
intrinsic evidence that the Court may con
du Pont de Nemours & Co. v. Unifrax I LLC, 921 F.3d 1060, 1070 (Fed. Cir. 2019) (noting that "familial patents" with common subject matter "inform the construction of a claim term and are appropriately treated as intrinsic evidence"); *See Galderma Labs., L.P. v. Amneal Pharms. LLC*, 2020 U.S. App. LEXIS 9341, **6, 7 (Fed. Cir. March 25, 2020), (assessing the patent owner's and PTAB's statements in affirming claim construction).

Plaintiffs' Brief

the final linker)).) As shown above, the structure that equates to Y in the claimed structures shown in Figures 8 and 16 are not limited to a "single linker."

Accordingly, Illumina's construction is not just contrary to the canons of construction taught by *01 Communique Lab* and *Baldwin*, but also should be rejected on the ground that it would exclude embodiments shown in Figures 8 and 16 of the specification. *See, e.g., Verizon Servs. Corp. v. Vonage Holdings Corp.*,

Claim Language: “Chemically Cleavable” Linkers



US010407458B2

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

(10) **Patent No.: US 10,407,458 B2**
(45) **Date of Patent: *Sep. 10, 2019**

(54) **MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA**

(71) Applicant: **The Trustees of Columbia University in the City of New York**, New York, NY (US)

(72) Inventors: **Jingyue Ju**, Englewood Cliffs, NJ (US); **Zengmin Li**, Flushing, NY (US); **John Robert Edwards**, St. Louis, MO (US); **Yasuhiro Itagaki**, New York, NY (US)

(73) Assignee: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK**, New York, NY (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.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/149,098**

(22) Filed: **Oct. 1, 2018**

(65) **Prior Publication Data**

US 2019/0031704 A1 Jan. 31, 2019

Related U.S. Application Data

(60) Continuation of application No. 15/915,983, filed on Mar. 8, 2018, which is a continuation of application No. 14/670,748, filed on Mar. 27, 2015, which is a continuation of application No. 13/959,660, filed on Aug. 5, 2013, now Pat. No. 9,133,511, which is a continuation of application No. 13/672,437, filed on Nov. 8, 2012, now abandoned, which is a continuation of application No. 13/339,089, filed on Dec. 28, 2011, now abandoned, which is a continuation of application No. 12/804,284, filed on Jul. 19, 2010, now Pat. No. 8,088,575, which is a continuation of application No. 11/810,509, filed on Jun. 5, 2007, now Pat. No. 7,790,869, which is a continuation of application No. 10/702,203, filed on Nov. 4, 2003, now Pat. No. 7,345,159, which is a division of application No. 09/972,364, filed on Oct. 5, 2001, now Pat. No. 6,664,079, which is a continuation-in-part of application No. 09/684,670, filed on Oct. 6, 2000, now abandoned.

(60) Provisional application No. 60/300,894, filed on Jun. 26, 2001.

(51) **Int. Cl.**

C07H 19/14	(2006.01)
C12Q 1/68	(2018.01)
C07H 21/00	(2006.01)
C12Q 1/686	(2018.01)
C12Q 1/6874	(2018.01)
C12Q 1/6872	(2018.01)
C12Q 1/6869	(2018.01)
C07H 19/10	(2006.01)
C12Q 1/6876	(2018.01)
C40B 40/00	(2006.01)

(52) **U.S. Cl.**
CPC ***C07H 19/14*** (2013.0
(2013.01); ***C07H 21/00*** (2013.
(2013.01); ***C12Q 1/686*** (2
1/6869 (2013.01); ***C12Q 1/***
C12Q 1/6874 (2013.01
(2013.01); *C07B 2200/11* (2
2525/117 (2013.01);
(2013.01); *C12Q 2535/101* (2
2535/122 (2013.01);
(2013.01); *C12Q 2565/501* (2

(58) **Field of Classification Search**
CPC C07H 19/04
USPC .....
See application file for complete sea

(56) **References Cited**

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4,772,691	A	9/1988	Herman
4,804,748	A	2/1989	Seela
4,824,775	A	4/1989	Dattagupta et al.
4,863,849	A	9/1989	Melamede
4,888,274	A	12/1989	Radding et al.
5,043,272	A	8/1991	Hartley
5,047,519	A	9/1991	Hobbs, Jr. et al.
5,118,605	A	6/1992	Urden
5,151,507	A	9/1992	Hobbs, Jr. et al.
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(Continued)

Primary Examiner — Jezia Riley
(74) *Attorney, Agent, or Firm* — John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

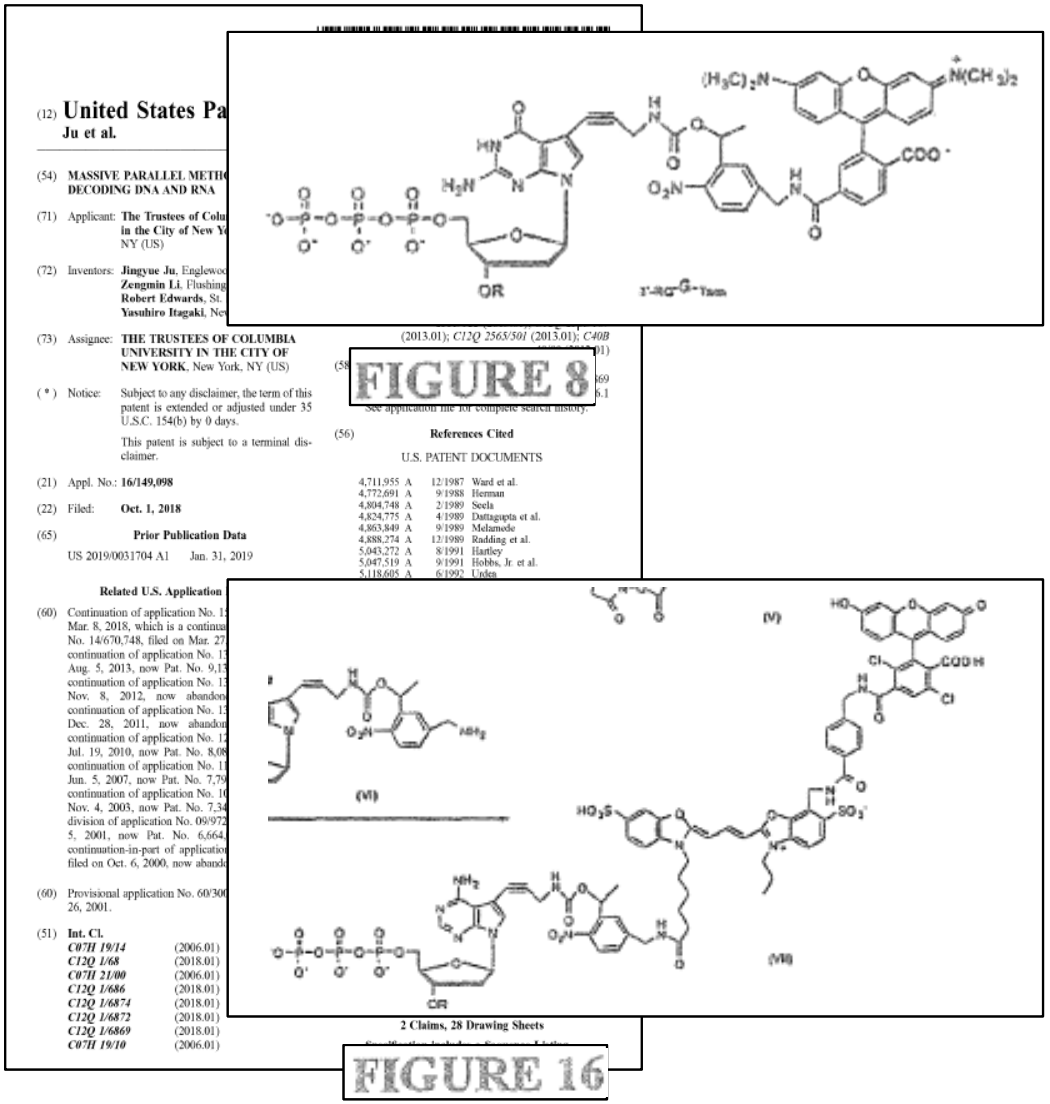
This invention provides methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3′-position of the deoxyribose.

2 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

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

Specification: Figs. 8 & 16 Are Photocleavable Linkers



(12) **United States Pa**
Ju et al.

(54) **MASSIVE PARALLEL METH**
DECODING DNA AND RNA

(71) Applicant: **The Trustees of Colu**
in the City of New Y
NY (US)

(72) Inventors: **Jingyue Ju**, Englewoo
Zengmin Li, Flushing
Robert Edwards, St.
Yasuhiro Itagaki, Ne

(73) Assignee: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK**, New York, NY (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.

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(21) Appl. No.: **16/149,098**

(22) Filed: **Oct. 1, 2018**

(65) **Prior Publication Data**

US 2019/0031704 A1 Jan. 31, 2019

Related U.S. Application

(60) Continuation of application No. 1
Mar. 8, 2018, which is a continua
No. 14/670,748, filed on Mar. 27
continuation of application No. 1
Aug. 5, 2013, now Pat. No. 9,1
continuation of application No. 1
Nov. 8, 2012, now abandon
continuation of application No. 1
Dec. 28, 2011, now abandon
continuation of application No. 1
Jul. 19, 2010, now Pat. No. 8,0
continuation of application No. 1
Jun. 5, 2007, now Pat. No. 7,7
continuation of application No. 1
Nov. 4, 2003, now Pat. No. 7,3
division of application No. 09/97
5, 2001, now Pat. No. 6,664,
continuation-in-part of applicatio
filed on Oct. 6, 2000, now aband

(60) Provisional application No. 60/30
26, 2001.

(51) **Int. Cl.**

C07H 19/14	(2006.01)
C12Q 1/68	(2018.01)
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C12Q 1/686	(2018.01)
C12Q 1/6874	(2018.01)
C12Q 1/6872	(2018.01)
C12Q 1/6869	(2018.01)
C07H 19/10	(2006.01)

(2013.01); *C12Q 2563/501* (2013.01); *C40B*

FIGURE 8

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

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4,772,691	A	9/1988	Herman
4,804,748	A	2/1989	Seela
4,824,775	A	4/1989	Dattagupta et al.
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5,047,519	A	9/1991	Hobbs, Jr. et al.
5,118,605	A	6/1992	Urden

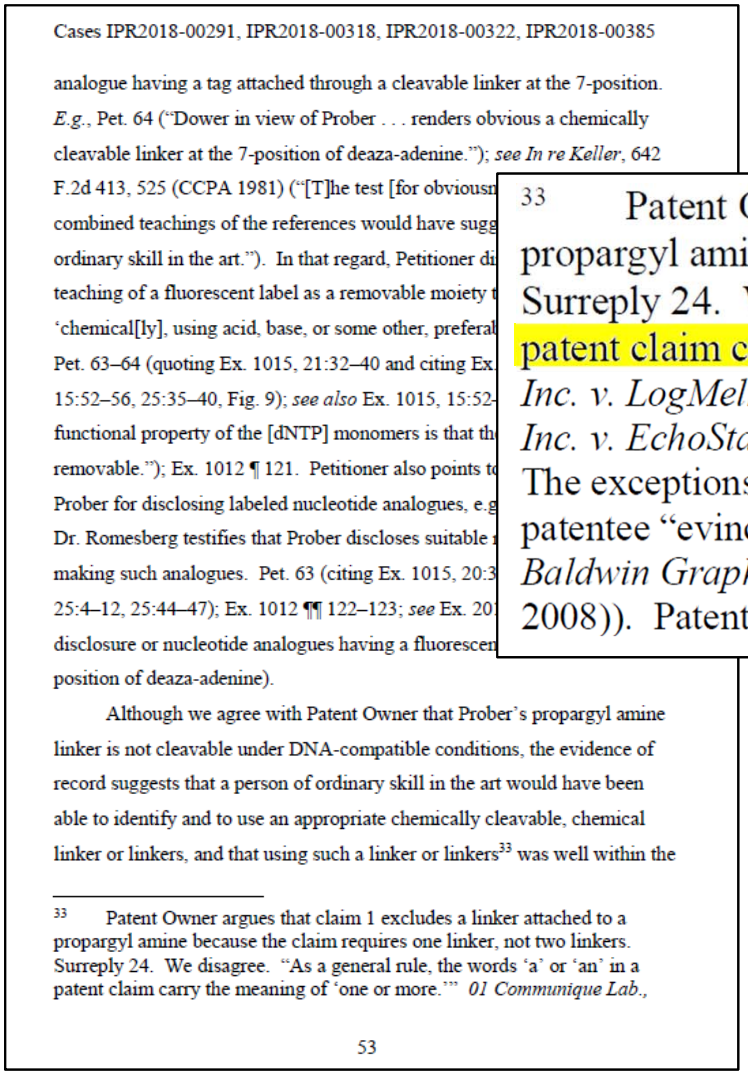
2 Claims, 28 Drawing Sheets

FIGURE 16

As a representative example, the synthesis of $_{3'\text{-}HO}$-G-$_{Dye3}$ (Dye3=Tam) is shown in FIG. **8**. 7-deaza-alkynylamino-dGTP is prepared using well-established procedures (Prober et al. 1987; Lee et al. 1992 and Hobbs et al. 1991). Linker-Tam is synthesized by coupling the Photocleavable Linker (Rollaf 1982) with NHS-Tam. 7-deaza-alky-

a donor (Hung et al. 1996). FIG. **16** shows a synthetic scheme for an ET dye labeled nucleotide analogue with Cy2 as a donor and Cl_2FAM as an acceptor using similar coupling chemistry as for the synthesis of an energy transfer system using FAM as a donor (Lee et al. 1997). Coupling of Cl_2FAM (I) with spacer 4-aminomethylbenzoic acid (II) produces III, which is then converted to NHS ester IV. Coupling of IV with amino-Cy2, and then converting the resulting compound to a NHS ester produces V, which subsequently couples with amino-photolinker nucleotide VI yields the ET dye labeled nucleotide VII.

PTAB Construction Leads To Multiple Cleavable Linkers



Cases IPR2018-00291, IPR2018-00318, IPR2018-00322, IPR2018-00385

analogue having a tag attached through a cleavable linker at the 7-position. *E.g.*, Pet. 64 ("Dower in view of Prober . . . renders obvious a chemically cleavable linker at the 7-position of deaza-adenine."); *see In re Keller*, 642 F.2d 413, 525 (CCPA 1981) ("[T]he test [for obviousn combined teachings of the references would have sugg ordinary skill in the art."). In that regard, Petitioner di teaching of a fluorescent label as a removable moiety t 'chemical[ly], using acid, base, or some other, preferal Pet. 63–64 (quoting Ex. 1015, 21:32–40 and citing Ex. 15:52–56, 25:35–40, Fig. 9); *see also* Ex. 1015, 15:52- functional property of the [dNTP] monomers is that th removable."); Ex. 1012 ¶ 121. Petitioner also points t Prober for disclosing labeled nucleotide analogues, e.g Dr. Romesberg testifies that Prober discloses suitable making such analogues. Pet. 63 (citing Ex. 1015, 20:3 25:4–12, 25:44–47); Ex. 1012 ¶¶ 122–123; *see* Ex. 20 disclosure or nucleotide analogues having a fluorescen position of deaza-adenine).

Although we agree with Patent Owner that Prober's propargyl amine linker is not cleavable under DNA-compatible conditions, the evidence of record suggests that a person of ordinary skill in the art would have been able to identify and to use an appropriate chemically cleavable, chemical linker or linkers, and that using such a linker or linkers[33] was well within the

[33] Patent Owner argues that claim 1 excludes a linker attached to a propargyl amine because the claim requires one linker, not two linkers. Surreply 24. We disagree. "As a general rule, the words 'a' or 'an' in a patent claim carry the meaning of 'one or more.'" *01 Communique Lab.,*

53

PTAB Final Written Decision

[33] Patent Owner argues that claim 1 excludes a linker attached to a propargyl amine because the claim requires one linker, not two linkers. Surreply 24. We disagree. "As a general rule, the words 'a' or 'an' in a patent claim carry the meaning of 'one or more.'" *01 Communique Lab., Inc. v. LogMeln, Inc.*, 687 F.3d 1292, 1297 (Fed. Cir. 2012) (quoting *TiVo, Inc. v. EchoStar Commc'ns Corp.*, 516 F.3d 1290, 1303 (Fed. Cir. 2008)). The exceptions to the rule are "extremely limited" and require that a patentee "evince a clear intent to limit 'a' or 'an' to 'one.'" *Id.* (quoting *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008)). Patent Owner's bare argument does not establish such a clear intent.

- Linkers should be chemically cleavable

“Small”

Disputed Claim Term

Claim Term	Illumina's Construction	Plaintiffs' Construction
"small" '458 Patent: Claims 1, 2 '459 Patent: Claims 1, 2 '742 Patent: Claims 1, 2 '984 Patent: Claims 1, 2 '380 Patent: Claims 1, 3	"A chemical group that fits within the rat DNA polymerase active site shown in Fig. 1 of the patent, i.e. has a longest dimension less than 3.7Å, including the 3' oxygen"	"A chemical group that has a diameter, i.e., width, that is less than 3.7Å"

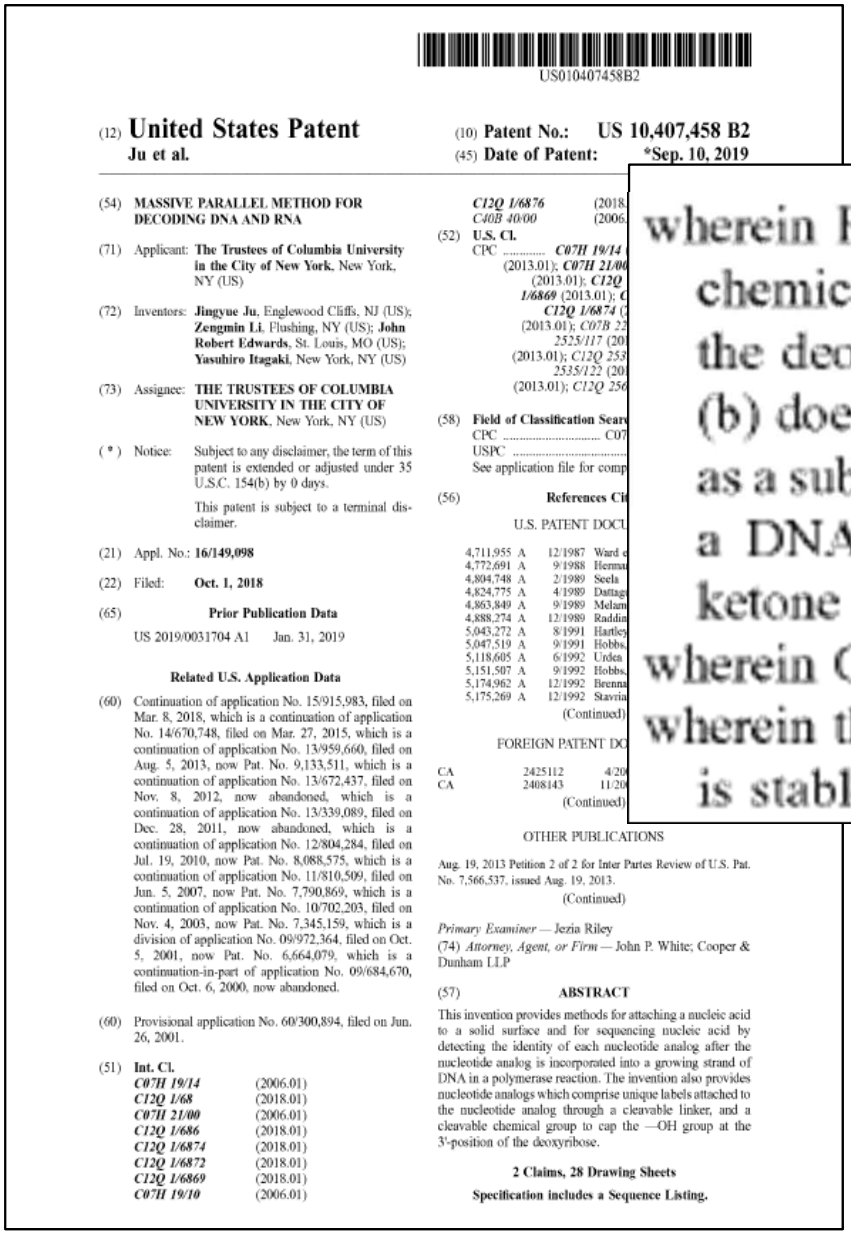
Key Disputes

- Whether “small” should be defined in terms of rat polymerase?
- Whether “diameter” should be replaced with “width”?

Key Disputes

- Whether “small” should be defined in terms of rat polymerase?
- Whether “diameter” should be replaced with “width”?

Claim Language: Does Not Clarify "Small"



US010407458B2

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

(10) **Patent No.: US 10,407,458 B2**
(45) **Date of Patent: *Sep. 10, 2019**

(54) **MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA**

(71) Applicant: **The Trustees of Columbia University in the City of New York**, New York, NY (US)

(72) Inventors: **Jingyue Ju**, Englewood Cliffs, NJ (US); **Zengmin Li**, Flushing, NY (US); **John Robert Edwards**, St. Louis, MO (US); **Yasuhiro Itagaki**, New York, NY (US)

(73) Assignee: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK**, New York, NY (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.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/149,098**

(22) Filed: **Oct. 1, 2018**

(65) **Prior Publication Data**

US 2019/0031704 A1 Jan. 31, 2019

Related U.S. Application Data

(60) Continuation of application No. 15/915,983, filed on Mar. 8, 2018, which is a continuation of application No. 14/670,748, filed on Mar. 27, 2015, which is a continuation of application No. 13/959,660, filed on Aug. 5, 2013, now Pat. No. 9,133,511, which is a continuation of application No. 13/672,437, filed on Nov. 8, 2012, now abandoned, which is a continuation of application No. 13/339,089, filed on Dec. 28, 2011, now abandoned, which is a continuation of application No. 12/804,284, filed on Jul. 19, 2010, now Pat. No. 8,088,575, which is a continuation of application No. 11/810,509, filed on Jun. 5, 2007, now Pat. No. 7,790,869, which is a continuation of application No. 10/702,203, filed on Nov. 4, 2003, now Pat. No. 7,345,159, which is a division of application No. 09/972,364, filed on Oct. 5, 2001, now Pat. No. 6,664,079, which is a continuation-in-part of application No. 09/684,670, filed on Oct. 6, 2000, now abandoned.

(60) Provisional application No. 60/300,894, filed on Jun. 26, 2001.

(51) **Int. Cl.**

C07H 19/14	(2006.01)
C12Q 1/68	(2018.01)
C07H 21/00	(2006.01)
C12Q 1/686	(2018.01)
C12Q 1/6874	(2018.01)
C12Q 1/6872	(2018.01)
C12Q 1/6869	(2018.01)
C07H 19/10	(2006.01)

C12Q 1/6876 (2018.
C40B 40/00 (2006.

(52) **U.S. Cl.**
CPC ***C07H 19/14*** (2013.01); ***C07H 21/00*** (2013.01); ***C12Q 1/6869*** (2013.01); ***C12Q 1/6874*** (2013.01); *C07B 2525/117* (2013.01); *C12Q 2535/122* (2013.01); *C12Q 256*

(58) **Field of Classification Sear**
CPC C07
USPC .....
See application file for comp

(56) **References Cit**

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(Continued)

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(Continued)

Primary Examiner — Jezia Riley
(74) *Attorney, Agent, or Firm* — John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

This invention provides methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

2 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

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, (d) does not contain a ketone group, and (e) is not a $—CH_2CH═CH_2$ 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;

Prosecution History: No Ordinary Meaning For "Small"

researchers developing nucleotides for SBS between 1994 and the Priority Date who cited Pelletier. Ex. 2116 ¶87. Illumina's reliance on Pelletier represents hindsight, driven by Columbia's citation to that reference in the speci prosecution history to explain that a POSA *reading the specification of at-issue* would be able to determine whether a capping group was suit Contrary to Illumina's assertions, Columbia did not concede that a PO the benefit of the patent-at-issue's specification would have consulte Moreover, "[t]he inventor's own path itself never leads to a co obviousness; that is hindsight." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 1296 (Fed. Cir. 2012).

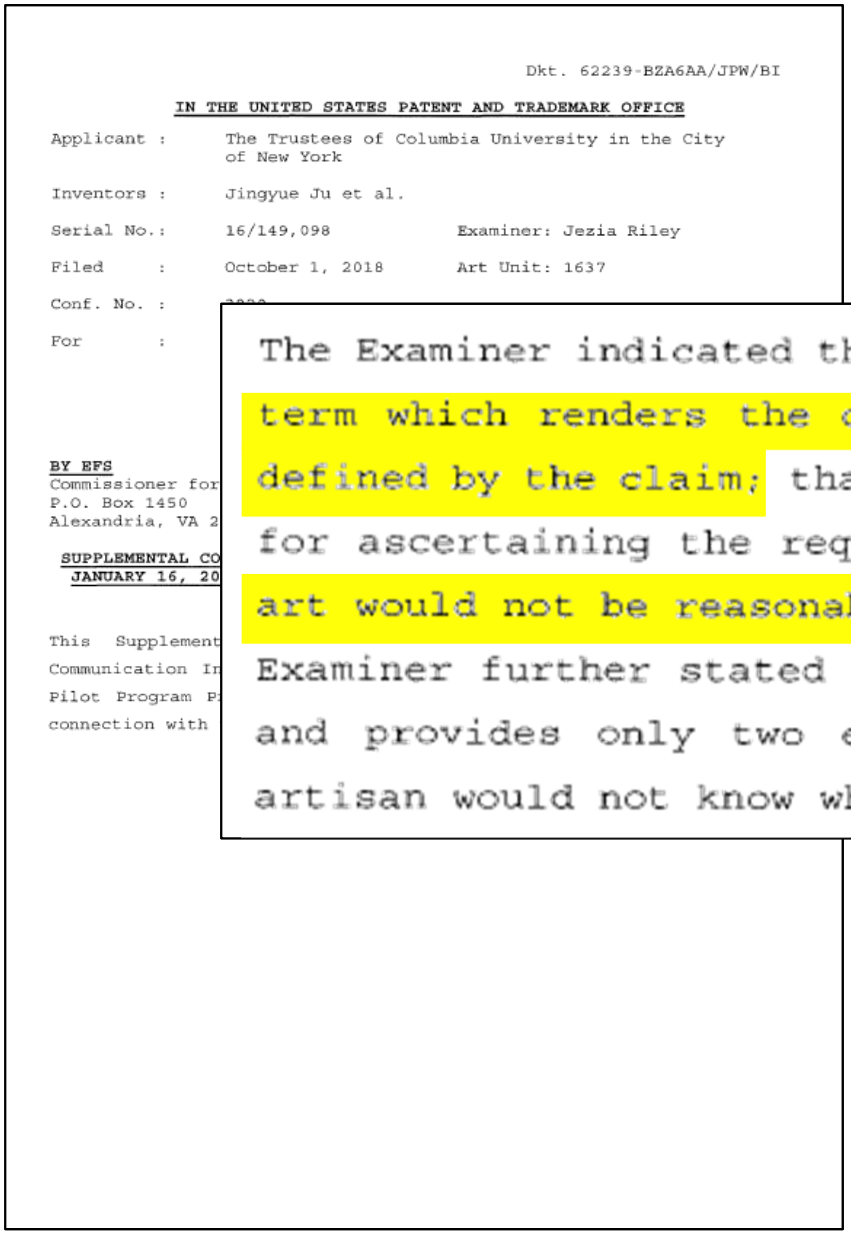
Third, Drs. Romesberg and Menchen agree that a POSA woul expected a capping group to possess the characteristics necessary for efficient incorporation of the capped nucleotide) simply because it was 2007 ¶58; Ex. 2126 at 81-84; Ex. 2116 ¶88.

Fourth, contrary to Illumina's assertions that "Dower dis desirability of nucleotides having 'small blocking groups' on the 3' IPR2018-00291, Petition at 11 (Dec. 8, 2017), Dower's use of the term describe several capping groups (Ex. 1015 at 25:48-51) does not conclusion that Dower teaches that "small" capping groups are "desirable." Ex. 2116 ¶89. Dower does not state that the four capping groups it characterizes as

Columbia's IPR Prelimary Response

Fourth, contrary to Illumina's assertions that "Dower disclosed the desirability of nucleotides having 'small blocking groups' on the 3'-OH," *e.g.*, IPR2018-00291, Petition at 11 (Dec. 8, 2017), Dower's use of the term "small" to describe several capping groups (Ex. 1015 at 25:48-51) does not support a conclusion that Dower teaches that "small" capping groups are "desirable." Ex. 2116 ¶89. Dower does not state that the four capping groups it characterizes as small are desirable because of their size. *Id.* Regardless, Dower's use of "small" when referring to capping groups does not equate to "small" as defined by the patent-at-issue (*i.e.*, smaller than 3.7Å in diameter). For example, the NBOC

Prosecution History: "Small" Rejected as Indefinite



Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

Serial No.: 16/149,098 Examiner: Jezia Riley

Filed : October 1, 2018 Art Unit: 1637

Conf. No. :

For :

BY EFS
Commissioner for
P.O. Box 1450
Alexandria, VA 2

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JANUARY 16, 20

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Communication In
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connection with

The Examiner indicated that the term "small" in the claims is a relative term which renders the claim indefinite; that the term "small" is not defined by the claim; that the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner further stated that the specification does not define "small" and provides only two examples, MOM ether and allyl, and a skilled artisan would not know which other groups meet the limitation "small".

Prosecution History: Rat Polymerase Definition

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors :

Serial No.:

Filed :

Conf. No. :

For :

BY EFS

Commissioner f

P.O. Box 1450

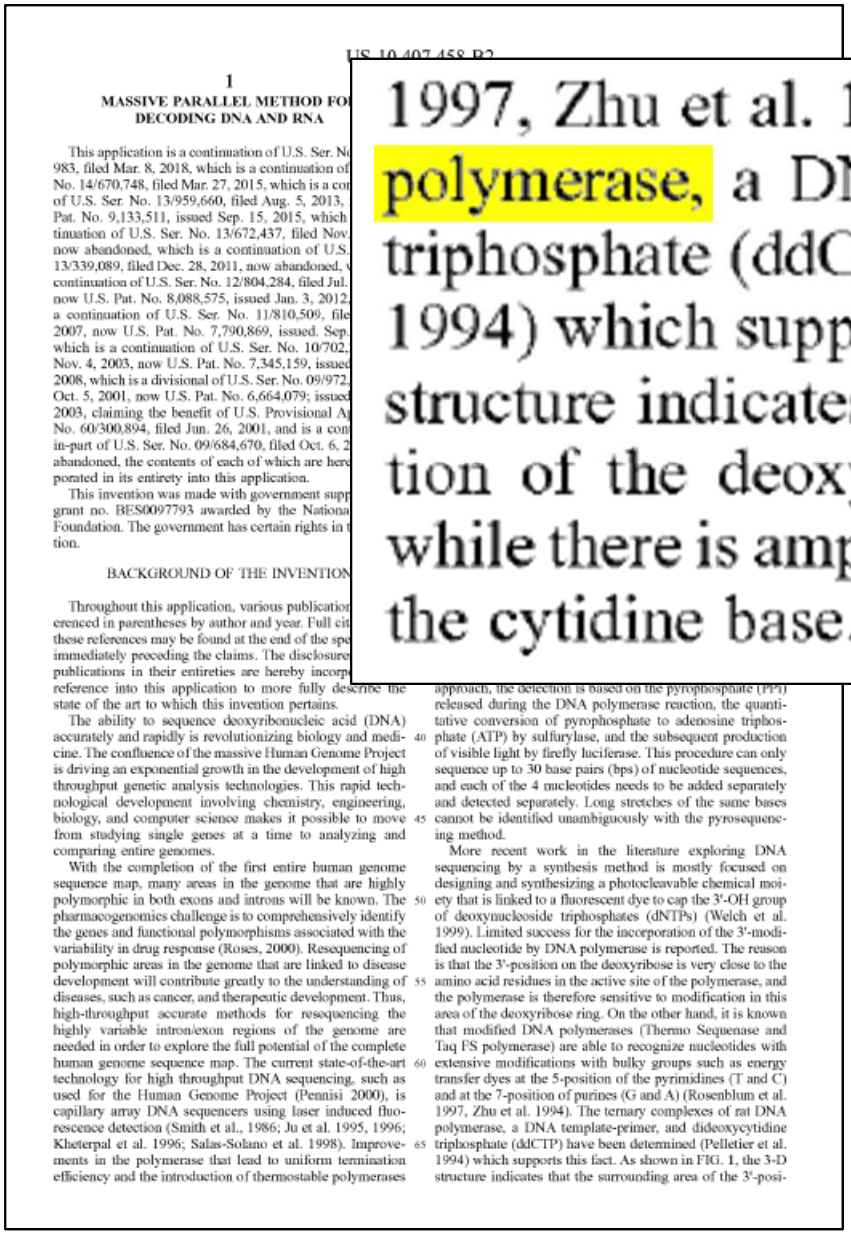
Alexandria, VA 22313-1450

SUPPLEMENTAL COMMUNICATION SUPPLEMENTING COMMUNICATION IN RESPONSE TO JANUARY 16, 2019 FIRST ACTION INTERVIEW PILOT PROGRAM PRE-INTERVIEW COMMUNICATION FILED FEBRUARY 12, 2019

This Supplemental Communication is submitted to supplement the Communication In Response To January 16, 2019 First Action Interview Pilot Program Pre-Interview Communication filed February 12, 2019 in connection with the above-identified application.

on its ability to fit into the active site of a polymerase. As of October 6, 2000, the person of ordinary skill in the art ("POSA") reading the specification would have understood that "small" referred to the ability to fit into the active site of the polymerase defined by reference to the three-dimensional structure shown in FIG. 1. The POSA would have

Specification: Fig. 1 Is Rat Polymerase



US 10,407,458 B2

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MASSIVE PARALLEL METHOD FO
DECODING DNA AND RNA

This application is a continuation of U.S. Ser. N
983, filed Mar. 8, 2018, which is a continuation of
No. 14/670,748, filed Mar. 27, 2015, which is a co
of U.S. Ser. No. 13/959,660, filed Aug. 5, 2013,
Pat. No. 9,133,511, issued Sep. 15, 2015, which
tinuation of U.S. Ser. No. 13/672,437, filed Nov.
now abandoned, which is a continuation of U.S.
13/339,089, filed Dec. 28, 2011, now abandoned,
continuation of U.S. Ser. No. 12/804,284, filed Jul.
now U.S. Pat. No. 8,088,575, issued Jan. 3, 2012,
a continuation of U.S. Ser. No. 11/810,509, file
2007, now U.S. Pat. No. 7,790,869, issued Sep.
which is a continuation of U.S. Ser. No. 10/702,
Nov. 4, 2003, now U.S. Pat. No. 7,345,159, issued
2008, which is a divisional of U.S. Ser. No. 09/972,
Oct. 5, 2001, now U.S. Pat. No. 6,664,079; issued
2003, claiming the benefit of U.S. Provisional Ap
No. 60/300,894, filed Jun. 26, 2001, and is a con
in-part of U.S. Ser. No. 09/684,670, filed Oct. 6, 2
abandoned, the contents of each of which are here
porated in its entirety into this application.

This invention was made with government supp
grant no. BES0097793 awarded by the Nationa
Foundation. The government has certain rights in t
tion.

BACKGROUND OF THE INVENTION

Throughout this application, various publicatio
erenced in parentheses by author and year. Full cit
these references may be found at the end of the spe
immediately preceding the claims. The disclosure
publications in their entireties are hereby incorp
reference into this application to more fully describe the
state of the art to which this invention pertains.

The ability to sequence deoxyribonucleic acid (DNA) accurately and rapidly is revolutionizing biology and medicine. The confluence of the massive Human Genome Project is driving an exponential growth in the development of high throughput genetic analysis technologies. This rapid technological development involving chemistry, engineering, biology, and computer science makes it possible to move from studying single genes at a time to analyzing and comparing entire genomes.

With the completion of the first entire human genome sequence map, many areas in the genome that are highly polymorphic in both exons and introns will be known. The pharmacogenomics challenge is to comprehensively identify the genes and functional polymorphisms associated with the variability in drug response (Roses, 2000). Resequencing of polymorphic areas in the genome that are linked to disease development will contribute greatly to the understanding of diseases, such as cancer, and therapeutic development. Thus, high-throughput accurate methods for resequencing the highly variable intron/exon regions of the genome are needed in order to explore the full potential of the complete human genome sequence map. The current state-of-the-art technology for high throughput DNA sequencing, such as used for the Human Genome Project (Pennisi 2000), is capillary array DNA sequencers using laser induced fluorescence detection (Smith et al., 1986; Ju et al. 1995, 1996; Kheterpal et al. 1996; Salas-Solano et al. 1998). Improvements in the polymerase that lead to uniform termination efficiency and the introduction of thermostable polymerases

approach, the detection is based on the pyrophosphate (PPi) released during the DNA polymerase reaction, the quantitative conversion of pyrophosphate to adenosine triphosphate (ATP) by sulfurylase, and the subsequent production of visible light by firefly luciferase. This procedure can only sequence up to 30 base pairs (bps) of nucleotide sequences, and each of the 4 nucleotides needs to be added separately and detected separately. Long stretches of the same bases cannot be identified unambiguously with the pyrosequencing method.

More recent work in the literature exploring DNA sequencing by a synthesis method is mostly focused on designing and synthesizing a photocleavable chemical moiety that is linked to a fluorescent dye to cap the 3'-OH group of deoxynucleoside triphosphates (dNTPs) (Welch et al. 1999). Limited success for the incorporation of the 3'-modified nucleotide by DNA polymerase is reported. The reason is that the 3'-position on the deoxyribose is very close to the amino acid residues in the active site of the polymerase, and the polymerase is therefore sensitive to modification in this area of the deoxyribose ring. On the other hand, 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) and at the 7-position of purines (G and A) (Rosenblum et al. 1997, Zhu et al. 1994). The ternary complexes of rat DNA polymerase, a DNA template-primer, and dideoxycytidine triphosphate (ddCTP) have been determined (Pelletier et al. 1994) which supports this fact. As shown in FIG. 1, the 3-D structure indicates that the surrounding area of the 3'-posi-

1997, Zhu et al. 1994). The ternary complexes of rat DNA polymerase, a DNA template-primer, and dideoxycytidine triphosphate (ddCTP) have been determined (Pelletier et al. 1994) which supports this fact. As shown in FIG. 1, the 3-D structure indicates that the surrounding area of the 3'-position of the deoxyribose ring in ddCTP is very crowded, while there is ample space for modification on the 5-position the cytidine base.

Specification: Fig. 1 Is Rat Polymerase

1

MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA

This application is a continuation of U.S. Ser. No. 15/915,983, filed Mar. 8, 2018, which is a continuation of U.S. Ser. No. 14/670,748, filed Mar. 27, 2015, which is a continuation of U.S. Ser. No. 13/959,660, filed Aug. 5, 2013, now U.S. Pat. No. 9,133,511, issued Sep. 15, 2015, which is a continuation of U.S. Ser. No. 13/672,437, filed Nov. 8, 2012, now abandoned, which is a continuation of U.S. Ser. No. 13/339,089, filed Dec. 28, 2011, now abandoned, which is a continuation of U.S. Ser. No. 12/804,284, filed Jul. 19, 2010, now U.S. Pat. No. 8,088,575, issued Jan. 3, 2012, which is a continuation of U.S. Ser. No. 11/810,509, filed Jun. 5, 2007, now U.S. Pat. No. 7,790,869, issued Sep. 7, 2010, which is a continuation of U.S. Ser. No. 10/702,203, filed Nov. 4, 2003, now U.S. Pat. No. 7,345,159, issued Mar. 18, 2008, which is a divisional of U.S. Ser. No. 09/972,364, filed Oct. 5, 2001, now U.S. Pat. No. 6,664,079; issued Dec. 16, 2003, claiming the benefit of U.S. Provisional Application No. 60/300,894, filed Jun. 26, 2001, and is a continuation-in-part of U.S. Ser. No. 09/684,670, filed Oct. 6, 2000, now abandoned, the contents of each of which are hereby incorporated in its entirety into this application.

This invention was made with government support under grant no. BES0097793 awarded by the National Science Foundation. The government has certain rights in the invention.

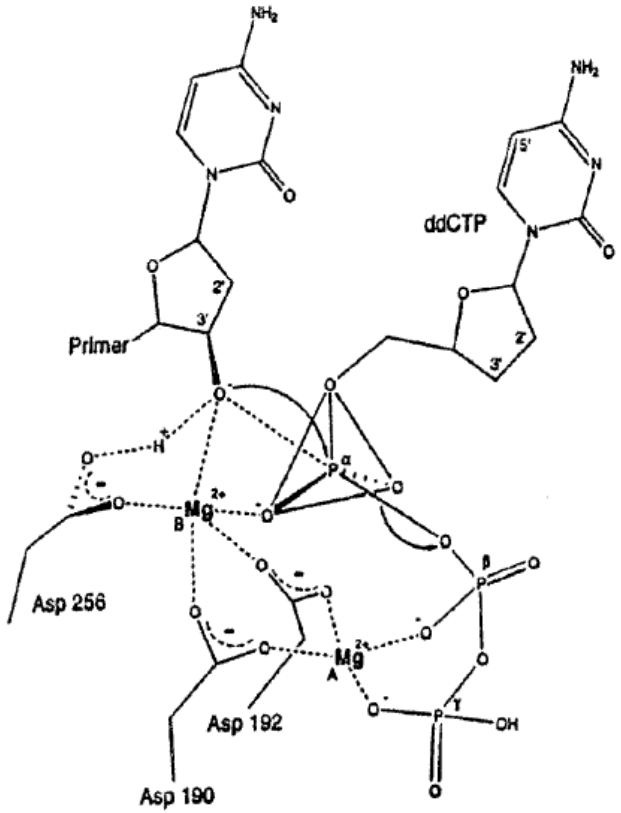
BACKGROUND OF THE INVENTION

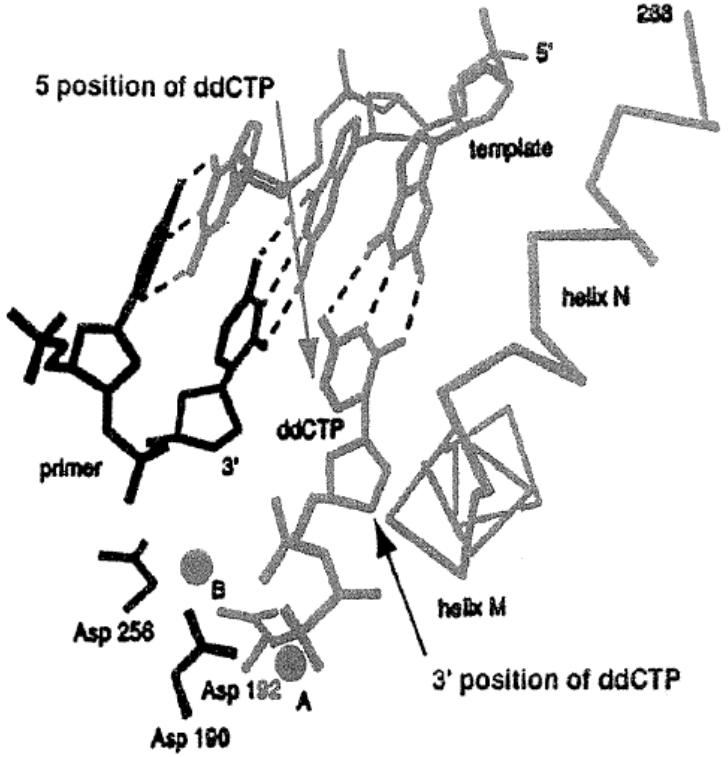
Throughout this application, various publications are referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

The ability to sequence deoxyribonucleic acid (DNA) accurately and rapidly is revolutionizing biology and medicine. The confluence of the massive Human Genome Project is driving an exponential growth in the development of high throughput genetic analysis technologies. This rapid technological development involving chemistry, engineering, biology, and computer science makes it possible to move from studying single genes at a time to analyzing and comparing entire genomes.

With the completion of the first entire human genome sequence map, many areas in the genome that are highly polymorphic in both exons and introns will be known. The pharmacogenomics challenge is to comprehensively identify the genes and functional polymorphisms associated with the variability in drug response (Roses, 2000). Resequencing of polymorphic areas in the genome that are linked to disease development will contribute greatly to the understanding of diseases, such as cancer, and therapeutic development. Thus, high-throughput accurate methods for resequencing the highly variable intron/exon regions of the genome are needed in order to explore the full potential of the complete human genome sequence map. The current state-of-the-art technology for high throughput DNA sequencing, such as used for the Human Genome Project (Pennisi 2000), is capillary array DNA sequencers using laser induced fluorescence detection (Smith et al., 1986; Ju et al. 1995, 1996; Kheterpal et al. 1996; Salas-Solano et al. 1998). Improvements in the polymerase that lead to uniform termination efficiency and the introduction of thermostable polymerases

FIGURE 1





Asp = Aspartic Acid

FIG. 1: The 3D structure of the ternary complexes of rat DNA polymerase, a DNA template-primer, and dideoxycy-

Prosecution History: Rat Polymerase Definition

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors :

Serial No.:

Filed :

Conf. No. :

For :

BY EFS

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P.O. Box 1450

Alexandria, VA

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[MPEP 2175.05(b)]. More importantly, applicant maintains that the specification of the subject application at page 4, lines 10-32; page 5, lines 1-32; page 6, lines 1-27; and page 13, lines 3-11, taken together with FIG. 1 referred to at page 4, line 31 of the application, set forth a standard for assessing whether a 3'-O capping group is "small" based on its ability to fit into the active site of a polymerase. As of October 6, 2000, the person of ordinary skill in the art ("POSA") reading the specification would have understood that "small" referred to the ability to fit into the active site of the polymerase defined by reference to the three-dimensional structure shown in FIG. 1. The POSA would have further understood that FIG. 1 corresponds to FIG. 6 of previously published Pelletier et al. (*Science*, Vol. 264, June 24, 1994, 1891-1903) cited at page 4, line 30 of the application. The POSA would also have

Prosecution History: Rat Polymerase Definition

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

Serial No.: 16/149,098 Examiner: Jezia Riley

Filed : October 1, 2018 Art Unit: 1637

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Based on the 3-dimensional structure of the ternary complex (*polymerase, DNA template/primer, nucleotide*) determined by Pelletier et al. (Pelletier et al. "*Structures of ternary complexes of rat DNA polymerase beta, a DNA template-primer, and ddCTP.*" *Science* 1994, 264, 1891-1903), which is cited in U.S. Serial No. 15/167,917 (Ju et al. *Massive parallel method for decoding DNA and RNA*), an analysis was performed to determine the space available for a 3'-O capping group on the 3' carbon of the deoxyribose of the nucleotide. The results indicate that there is only a small space available between amino acids in the active site of the polymerase and the 3' carbon of the deoxyribose of the nucleotide, as shown in the Figure below (corresponding to Fig. 1 of U.S. Serial No. 15/167,917 and to Fig. 6 of Pelletier et al.; color and labels added for clarity). This space can only accommodate a capping group of limited diameter on the 3' position of the deoxyribose of the nucleotide. Pelletier et al. (1994) determined that three amino acids of the polymerase, Tyr 271, Phe272, and Gly274, are in close proximity to the 3' carbon of the deoxyribose of the nucleotide. (Pelletier et al. 1994, Table 3). In Table 3 Pelletier et al. highlight the distances from the nucleotide to these amino acids in the polymerase ternary complex as follows: 3.2 Å between the 3' carbon of the deoxyribose ring and Phe272; 3.2 Å between the 2' carbon of the deoxyribose ring and Gly274; and 3.5 Å between the 2' carbon and Tyr271.

The distances given in Pelletier et al. were used to calculate the available space around the 3' carbon of the deoxyribose ring of the nucleotide. It was determined that the diameter of the available space in the active site of the polymerase ternary complex is approximately 3.7 Å.

Prosecution History: Rat Polymerase Definition

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PATENT OWNER'S RESPONSE

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

A. "Small"

The term "small" refers to the ability of the capping group to fit into the active site of the polymerase whose three-dimensional structure is shown in Figure 1 of the patent-at-issue. More specifically, "small" means the group has a diameter less than 3.7Å. This construction is based on the specification of the patent-at-issue. Exs. 1001-1004, each at 2:63-3:54, 5:52-59, Fig. 1, 7:51-8:28. As explained

Plaintiffs' Position: Rat Polymerase Is "Benchmark"

Plaintiffs' Brief

> 16 It is unclear why Illumina recites "rat DNA polymerase" in its definition. The inventors used the rat DNA polymerase as a benchmark for determining the space around the 3′ position. Even Illumina's expert agrees that a POSA would

Dr. Kuriyan: Does Not Rebut Rat Polymerase

John Kuriyan, Ph.D.
Plaintiffs' Expert

> Based on your work in this case, you don't have any reason to contest defendant's proposed construction of small that includes the requirement that the chemical group fit within the rat DNA polymerase active site shown in figure 1?
>
> A. I did not reach an opinion on this matter.

Dr. Kuriyan: 3 Feet Long Is "Small"

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. (BY MR. REINES) Now the way you were analyzing diameter, a protecting group could be 3 feet long and still fall within the definition of being less than 3.7 angstroms in length?

A. That is correct. It's an exaggerated characterization of my testimony, but I will not object to it.

- 3 foot long molecule will not fit within rat polymerase

Key Disputes

- Whether “small” should be defined in terms of rat polymerase?
- Whether “diameter” should be replaced with “width”?

Dr. Kuriyan: Construction Not Based In Specification

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. (BY MR. REINES) Dr. Kuriyan, is there anything in the patents-in-suit that supports any use of width as the diameter?

A. Are you referring to the patent specifications or are you including --

Q. (BY MR. REINES) Yes.

A. Oh, okay.

In the patent specifications, I had been asked earlier if the term width occurs and whether I have noticed it. And my answer at that time had been I had not noticed it, and so I assumed that the term width doesn't occur. And I am fairly certain the term diameter also doesn't occur. So I do not believe, based on that, that the patent specifications speak to this matter.

Prosecution History: Columbia Uses "Diameter"

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

Serial No.: 16/149,098 Examiner: Jezia Riley

Filed : October 1, 2018 Art Unit: 1637

Conf. No. :

For :

BY EFS
Commissioner for
P.O. Box 1450
Alexandria, VA 2

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JANUARY 16, 20

This Supplement
Communication In
Pilot Program P
connection with

With the benefit of applicant's specification, a POSA in October 2000 could have readily determined 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. More specifically, using this approach the POSA would have known that the space available around the 3' position of a deoxyribose in the active site of the polymerase was approximately 3.7Å in diameter. By this standard, R when present as OR would need to be less than 3.7Å in diameter. Consistently, the POSA would have known that the two examples in the application, MOM and Allyl with diameters of 2.1Å and 3.0Å, respectively, would fit in the active site of the polymerase and would be "small". [See also

Prosecution History: Dr. Ju Uses "Diameter"

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

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Based on the 3-dimensional structure of the ternary complex (*polymerase, DNA template/primer, nucleotide*) determined by Pelletier et al. (Pelletier et al. "*Structures of ternary complexes of rat DNA polymerase beta, a DNA template-primer, and ddCTP.*" *Science* 1994, 264, 1891-1903), which is cited in U.S. Serial No. 15/167,917 (Ju et al. *Massive parallel method for decoding DNA and RNA*), an analysis was performed to determine the space available for a 3'-O capping group on the 3' carbon of the deoxyribose of the nucleotide. The results indicate that there is only a small space available between amino acids in the active site of the polymerase and the 3' carbon of the deoxyribose of the nucleotide, as shown in the Figure below (corresponding to Fig. 1 of U.S. Serial No. 15/167,917 and to Fig. 6 of Pelletier et al.; color and labels added for clarity). This space can only accommodate a capping group of limited diameter on the 3' position of the deoxyribose of the nucleotide. Pelletier et al. (1994) determined that three amino acids of the polymerase, Tyr 271, Phe272, and Gly274, are in close proximity to the 3' carbon of the deoxyribose of the nucleotide. (Pelletier et al. 1994, Table 3). In Table 3 Pelletier et al. highlight the distances from the nucleotide to these amino acids in the polymerase ternary complex as follows: 3.2 Å between the 3' carbon of the deoxyribose ring and Phe272; 3.2 Å between the 2' carbon of the deoxyribose ring and Gly274; and 3.5 Å between the 2' carbon and Tyr271.

The distances given in Pelletier et al. were used to calculate the available space around the 3' carbon of the deoxyribose ring of the nucleotide. It was determined that the diameter of the available space in the active site of the polymerase ternary complex is approximately 3.7 Å.

Prosecution History: Columbia Uses "Diameter"

Paper No. _
Filed: October 26, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFOR

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small are desirable because of their size. *Id.* Regardless, Dower's use of "small" when referring to capping groups does not equate to "small" as defined by the patent-at-issue (*i.e.*, smaller than 3.7Å in diameter). For example, the NBOC

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

PATENT OWNER'S RESPONSE

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

Prosecution History: “Space Around” 3’ Carbon

Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

Inventors : Jingyue Ju et al.

Serial No.: 16/149,098 Examiner: Jezia Riley

Filed : October 1, 2018 Art Unit: 1637

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The distances given in Pelletier et al. were used to calculate the available space around the 3’ carbon of the deoxyribose ring of the nucleotide. It was determined that the diameter of the available space in the active site of the polymerase ternary complex is approximately 3.7 Å.

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Alexandria, VA 22313-1450

SUPPLEMENTAL COMMUNICATION SUPPLEMENTING COMMUNICATION IN RESPONSE TO JANUARY 16, 2019 FIRST ACTION INTERVIEW PILOT PROGRAM PRE-INTERVIEW COMMUNICATION FILED FEBRUARY 12, 2019

This Supplemental Communication is submitted to supplement the Communication In Response To January 16, 2019 First Action Interview Pilot Program Pre-Interview Communication filed February 12, 2019 in connection with the above-identified application.

Dr. Kuriyan: 3 Feet Long Is "Small"

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. (BY MR. REINES) Now the way you were analyzing diameter, a protecting group could be 3 feet long and still fall within the definition of being less than 3.7 angstroms in length?

A. That is correct. It's an exaggerated characterization of my testimony, but I will not object to it.

- 3 foot long molecule will not fit within rat polymerase

Columbia's IPR Expert: 3 Foot Long Not "Small"

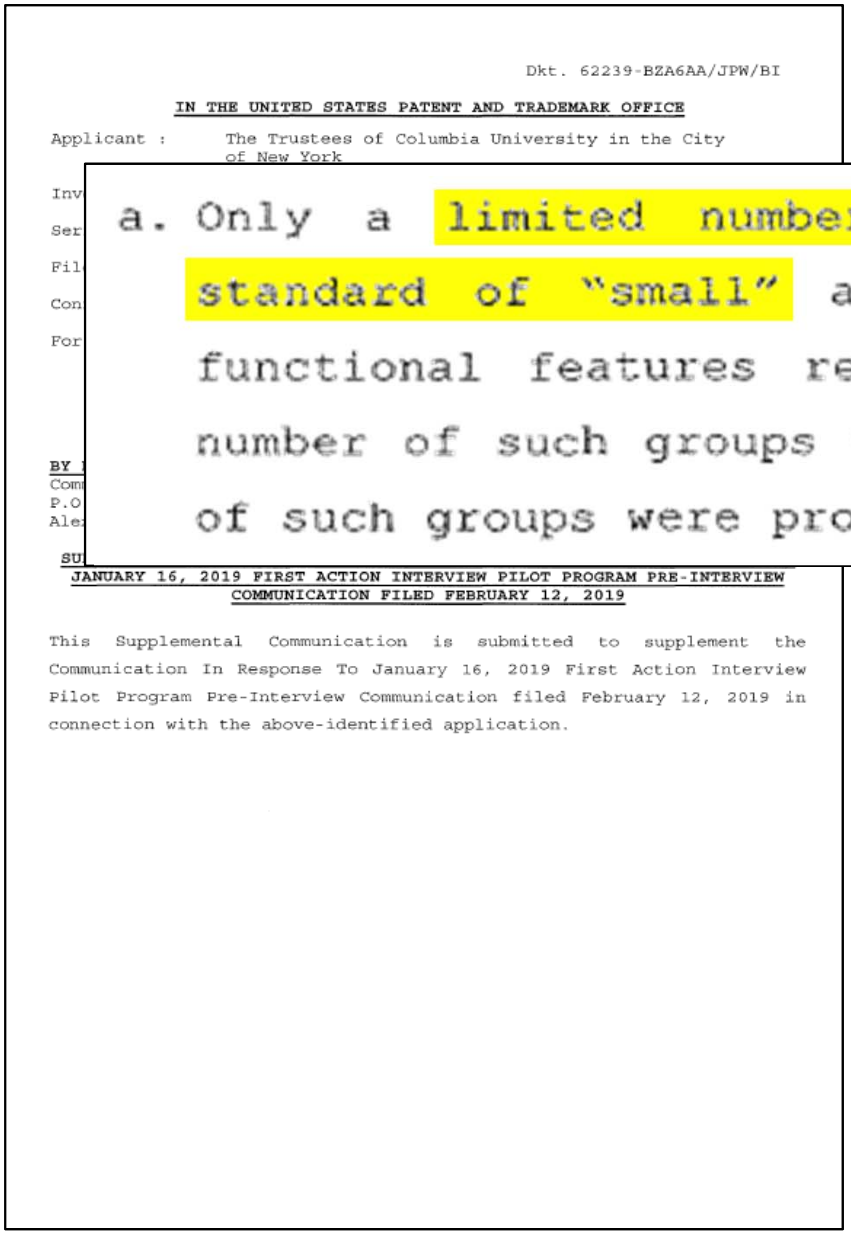
DR. GEORGE L. TRAINOR
Columbia's IPR Expert

Q. So as long as it works, it -- it's going to be small, in the context of the Ju invention?

A. I think it's -- I can't give you a precise cutoff, I imagine if you give me something with a molecular weight of 1,000 and that was accepted, I would say that wouldn't be small, but I think most chemists would say I would never call that small but it was accepted and perhaps surprising. But I think the

JA0289-90

Prosecution History: Undermines Unlimited Length



Dkt. 62239-BZA6AA/JPW/BI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : The Trustees of Columbia University in the City of New York

JANUARY 16, 2019 FIRST ACTION INTERVIEW PILOT PROGRAM PRE-INTERVIEW COMMUNICATION FILED FEBRUARY 12, 2019

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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.

- "Limited number" of "small" groups irreconcilable with unlimited length

Plaintiffs' Tunnel Theory

Plaintiffs' Brief

the space. (*Supra* at 73.) The dimension "diameter," however, is not limited to spheres (*see* Romesberg Dep., (JA0333–34 at 74:19-75:1, JA0344–47 at 134:14-137:8)), and Illumina ignores the common sense explanation that Dr. Ju did not identify other dimensions because such dimensions would not be critical in determining whether a capping group fits within the active site (*see* Romesberg Dep., (JA0336–37 at 79:17-80:7)), just as a train's length is not critical for determining whether it will fit through a given tunnel. Moreover, Dr. Romesberg

Dr. Romesberg: "Tunnel" Theory Is Wrong

Floyd Romesberg, Ph.D.
Illumina's Expert

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33. This is further evidenced by the fact that a POSITA would be most concerned with the accommodation of the longest dimension of the object. As can be seen in Figure A, the space around the 3' carbon is constricted in every direction. A POSITA would understand that occasionally, a crystal structure reveals a "tunnel-like" structure through which an object can extend in an unrestricted fashion, and which thus removes concerns about the accommodation of the length of the object, leaving only restrictions on the object's width and height. However, in most scenarios, such as the crystal structure disclosed in Figure 1 of the Patents-in-Suit, a POSITA would understand that the space available around the 3' position forms a pocket that blocks infinite extension in any direction. In these cases, the length, width, and height of the object (protecting group) are all restricted. When this is the case, the POSITA would be most concerned with whether the longest dimension of the protecting group would be too great to be accommodated within the available space, since the longest dimension is most likely to interfere (the greater the distance in any direction, the greater the likelihood of encountering a restriction).

Dr. Romesberg: “Tunnel” Theory Is Wrong

Floyd Romesberg, Ph.D.
Illumina’s Expert

Q. You agree that polymerases can have tunnel-like structures through which an object can extend in an unrestricted fashion?

A. I believe that it would be rare. In general there have been polymerase structures solved, including rat polymerase beta, and there are no such tunnels. It is possible. But there's not one in rat pol beta, and it's certainly possible there could be.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

> Q. Did you evaluate what the available space was in the rat polymerase as part of your work in this case?
>
> A. No.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Do you have any idea at all whether any of the protecting groups referenced in your declaration would actually fit so -- such that they could successfully serve as protecting groups in a sequencing by synthesis process?

A. I made no analysis of whether a protecting group of any kind would fit within the polymerase, and so I did not form an opinion about the ability of a protecting group to function, if that's what you're asking me, in sequencing by synthesis.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Okay. In terms of what the benchmark polymerase is that you refer to there, you understand that to be the rat DNA polymerase shown in figure 1. Correct?

A. Yes, I do.

Q. Whether allyl, MOM or azidomethyl fits within the active site of the benchmark polymerase, that's not something that you've opined on at all, correct, or considered?

A. That's correct.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. (BY MR. REINES) Which parts of the Pelletier article did you consider to be relevant?

A. Relevant to the opinion I gave in my declaration, I did not consider the -- any aspect of the Pelletier article to be relevant to the specific items that I opined on in my declaration.

Plaintiffs' Position: "Width" Matches Dr. Ju

Plaintiffs' Brief

(JA0083–84).) Plaintiffs' expert, following Dr. Ju's guidance, reproduced Dr. Ju's results and confirmed that Dr. Ju's diameter measurements corresponded to the *width* of the capping groups. (Kuriyan Decl. (JA00167–173 at ¶¶ 29-37).)

JA0056, JA0060

Prosecution History: Dr. Ju's "Diameters"

The calculated diameter (D) for each group is as follows:

1. Allyl ($-CH_2-CH=CH_2$): D = 3.0 Å

2. Methoxymethyl (MOM; $-CH_2-OCH_3$): D= 2.1 Å

3. Methylthiomethyl ($-CH_2-SCH_3$): D= 2.4 Å

4. Azidomethyl ($-CH_2-N_3$): D= 2.1 Å

5. 2-Nitrobenzyl ($-C_7H_6O_2N$): D = 5.0 Å

- Dr. Ju never referred to "width"
- Dr. Ju does not show how he calculated "diameters"

Dr. Romesberg: No Explanation For Dr. Ju's Results

Floyd Romesberg, Ph.D.
Illumina's Expert

> And I was actually kind of interested in that. I was curious. So I did sort of keep an eye on those numbers and I was looking at measurements, but nothing ever came out that was chemically sensible and -- and satisfied these numbers.
>
> So in the end I didn't come up with an obvious explanation. But I -- I don't think it would be accurate to say that I didn't keep this in my mind, keep his values in my mind as I was looking, because if there would have been numbers that started to look consistent that I understood, then I would have understood what he did, and I was unable to do that.

“Small” Definition Here is Unique to the Patents

Paper No. _
Filed: October 26, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFOR

small are desirable because of their size. *Id.* Regardless, Dower's use of "small" when referring to capping groups does not equate to "small" as defined by the patent-at-issue (*i.e.*, smaller than 3.7Å in diameter). For example, the NBOC

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IPR2018-00291 (Patent 9,718,852)
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IPR2018-00322 (Patent 9,708,358)
IPR2018-00385 (Patent 9,725,480)[1]

PATENT OWNER'S RESPONSE

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

Dr. Kuriyan: No Opinion On “Diameter”

John Kuriyan, Ph.D.
Plaintiffs’ Expert

Q. And let me ask again. Do you have any explanation at all or even a working hypothesis as to why Dr. Ju used the term diameter, whereas you're saying the word width is more precise?

A. I would say that both diameter and width require context, and as to the question of why Dr. Ju used the term diameter, I have no opinion.

Dr. Kuriyan: Does Not Know How 3.7 Å Determined

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. In terms of how Ju calculated the available space around this 3' carbon in Pelletier, do you know what he did based on what's here?

A. I didn't verify or check what he meant by the measurements that he records here on this page.

Q. (BY MR. REINES) In forming your opinions in this case, did you take into account for those opinions how Ju calculated the 3.7 angstrom number based on Pelletier?

A. No.

Dr. Kuriyan: Does Not Know How 3.7 Å Determined

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. So in the Exhibit 3 to the Ju declaration that we're looking at in the second paragraph where it states the distances given in Pelletier et al. were used to calculate the available space around the 3' carbon of the deoxyribose ring of the nucleotide. It was determined that the diameter of the available space in the active site of the polymerase ternary complex is approximately 3.7 angstrom. Do you see that?

A. Yes.

Q. Did you do anything to -- did you consider at all in this case about how Dr. Ju came to the 3.7 angstrom calculation?

A. No.

Dr. Kuriyan: Does Not Know How 3.7 Å Determined

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Do you have any idea how Dr. Ju reached the 3.7 angstrom calculation for the available space as described in Pelletier?

A. I did not go beyond the statements made at the documents we see before me and associated text.

Q. (BY MR. REINES) In the bottom of the first paragraph, it states that Pelletier shows 3.2 angstroms between the 3' carbon of the deoxyribose ring and Phe272. Do you see that?

A. Yes.

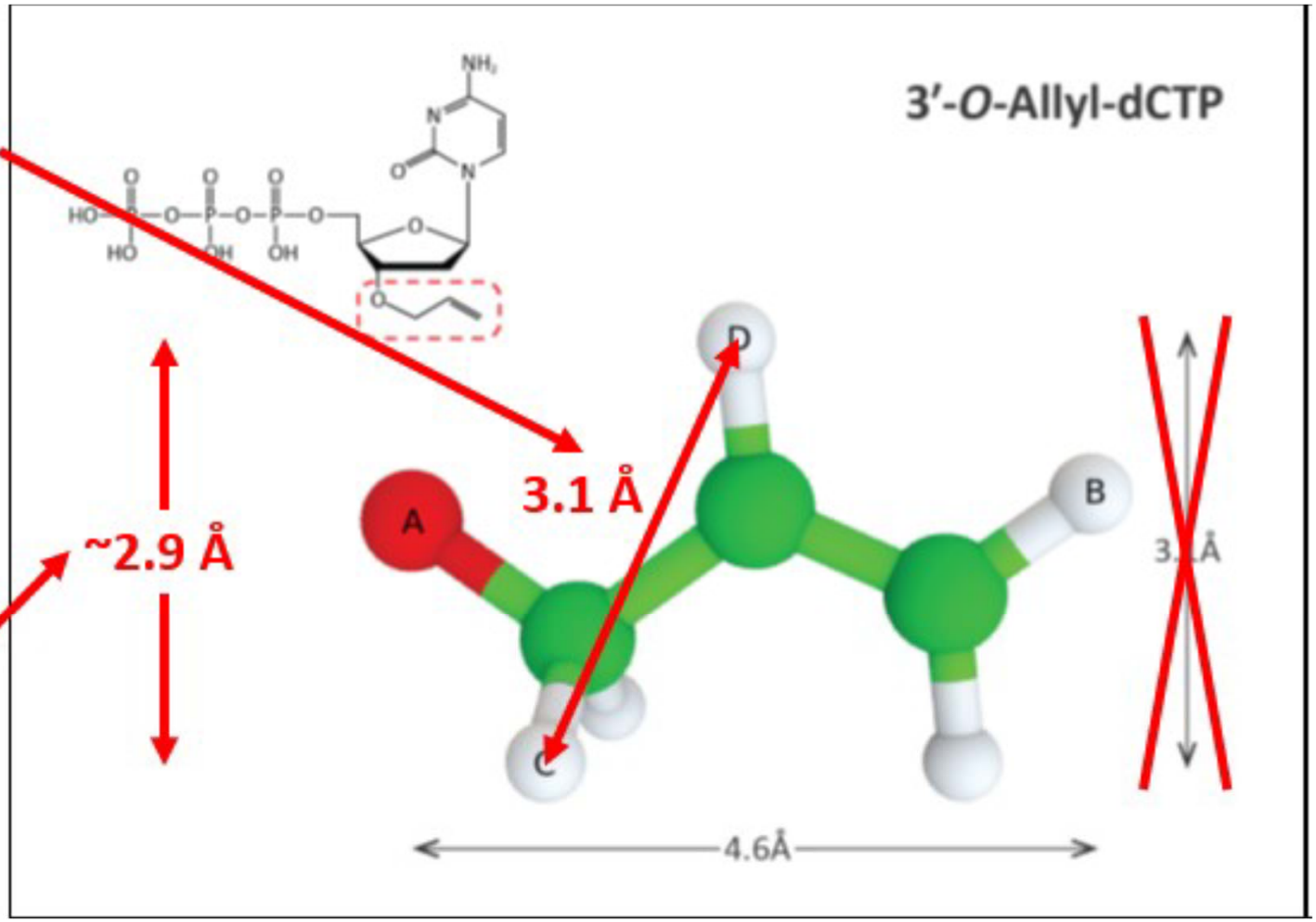
Q. Did you attempt to understand how that calculation was performed?

A. No.

Dr. Kuriyan's Judge By Eye Approach

Dr. Kuriyan's measured "diameter, i.e., width"

Plaintiffs' dictionary "diameter, i.e., width"



Dr. Kuriyan's Method: Imprecise and Indefinite

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Did you -- in using something perpendicular, largely or roughly, was there any particular tolerance you used?

A. I restricted myself to internuclear distances or interatomic distances, and there are a very small number of interatomic distances in this molecule. So it was a judgment by eye that I made.

Q. Was there any numerical tolerance you used to determine what would be orthogonal from the longest dimension?

A. No. I used visual inspection by eye using the computer program that I used.

Dr. Kuriyan's Method: Imprecise and Indefinite

John Kuriyan, Ph.D.
Plaintiffs' Expert

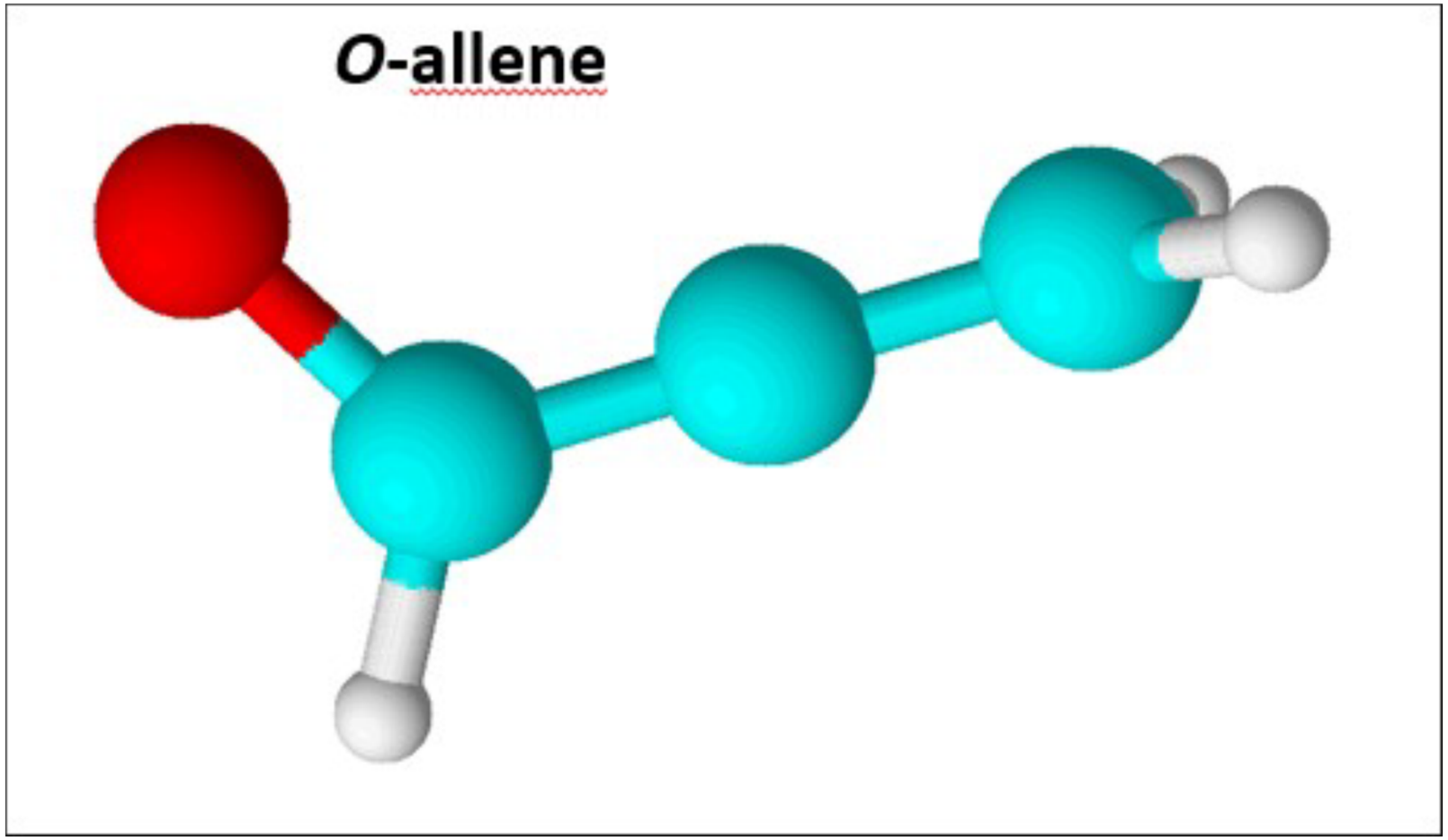
> Q. When you went, for example, in the allyl in paragraph 32 from C to D, I mean, that dimension is not perpendicular or orthogonal to the longest dimension, is it?
>
> A. No. I used the word roughly perpendicular or largely -- I think in the abstract I used the word -- I am not able to find it immediately, but I think I used the word largely perpendicular, roughly perpendicular.

Law: Claims Must Inform with "Reasonably Certainty"

"We hold that claim 1 is invalid for indefiniteness by clear and convincing evidence because read in light of the specification and the prosecution history, the patentee has failed to inform with ***reasonable certainty*** those skilled in the art about the scope of the invention."

Teva Pharm. USA, Inc. v. Sandoz, Inc., 789 F.3d 1335, 1345 (Fed. Cir. 2015) (emphasis in original)

Finding Distances That Match Dr. Ju Is Irrelevant



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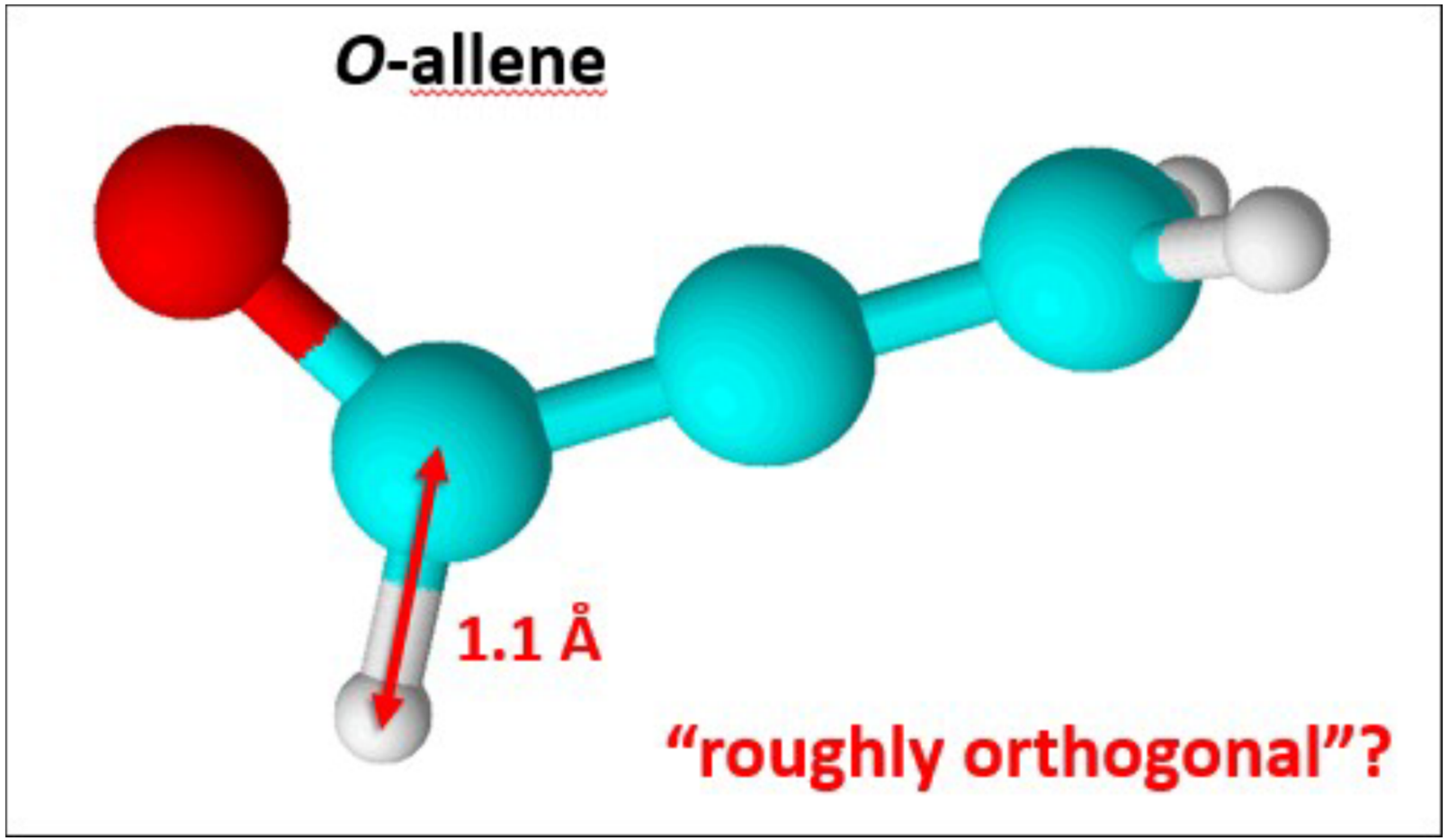

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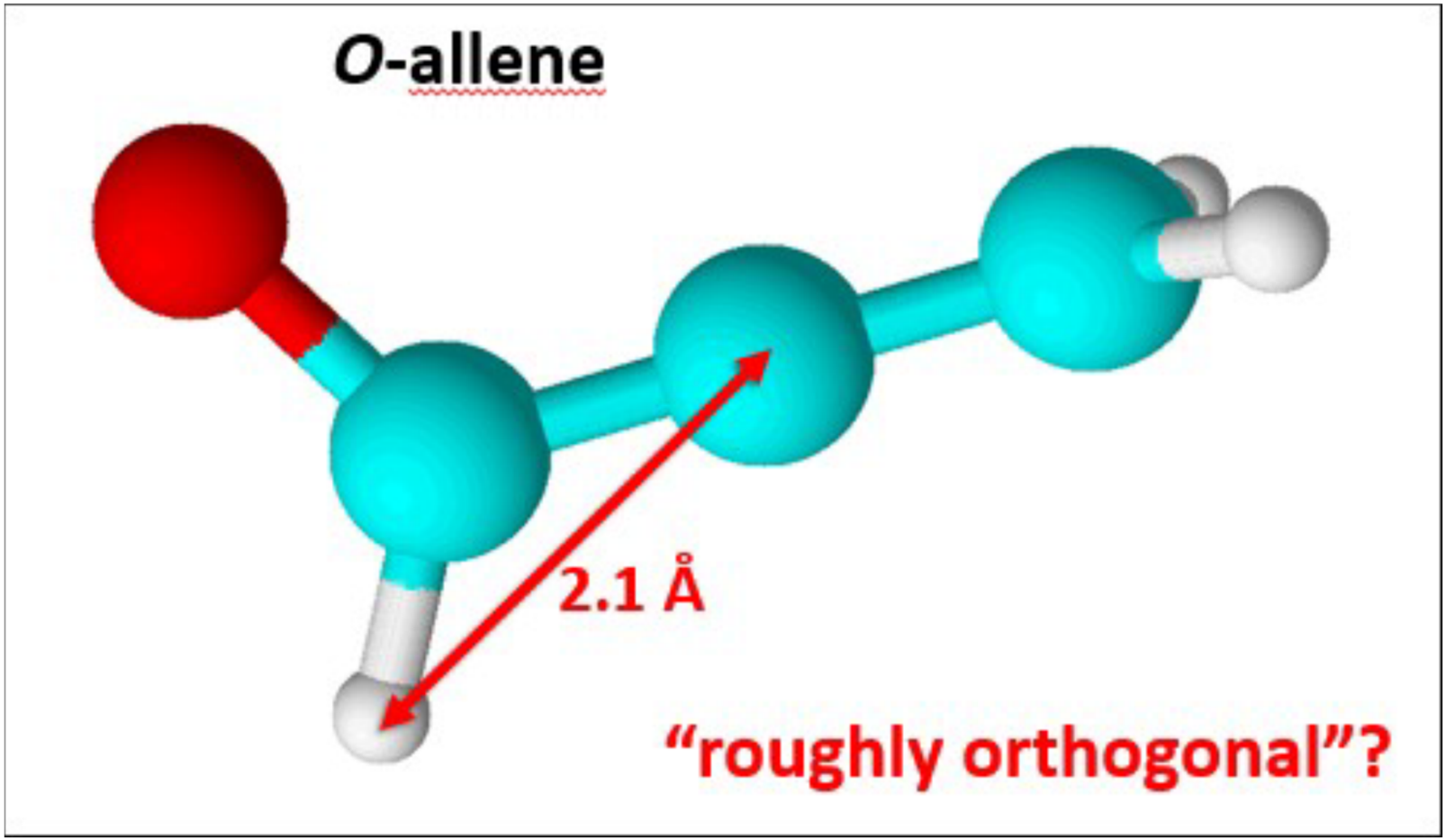

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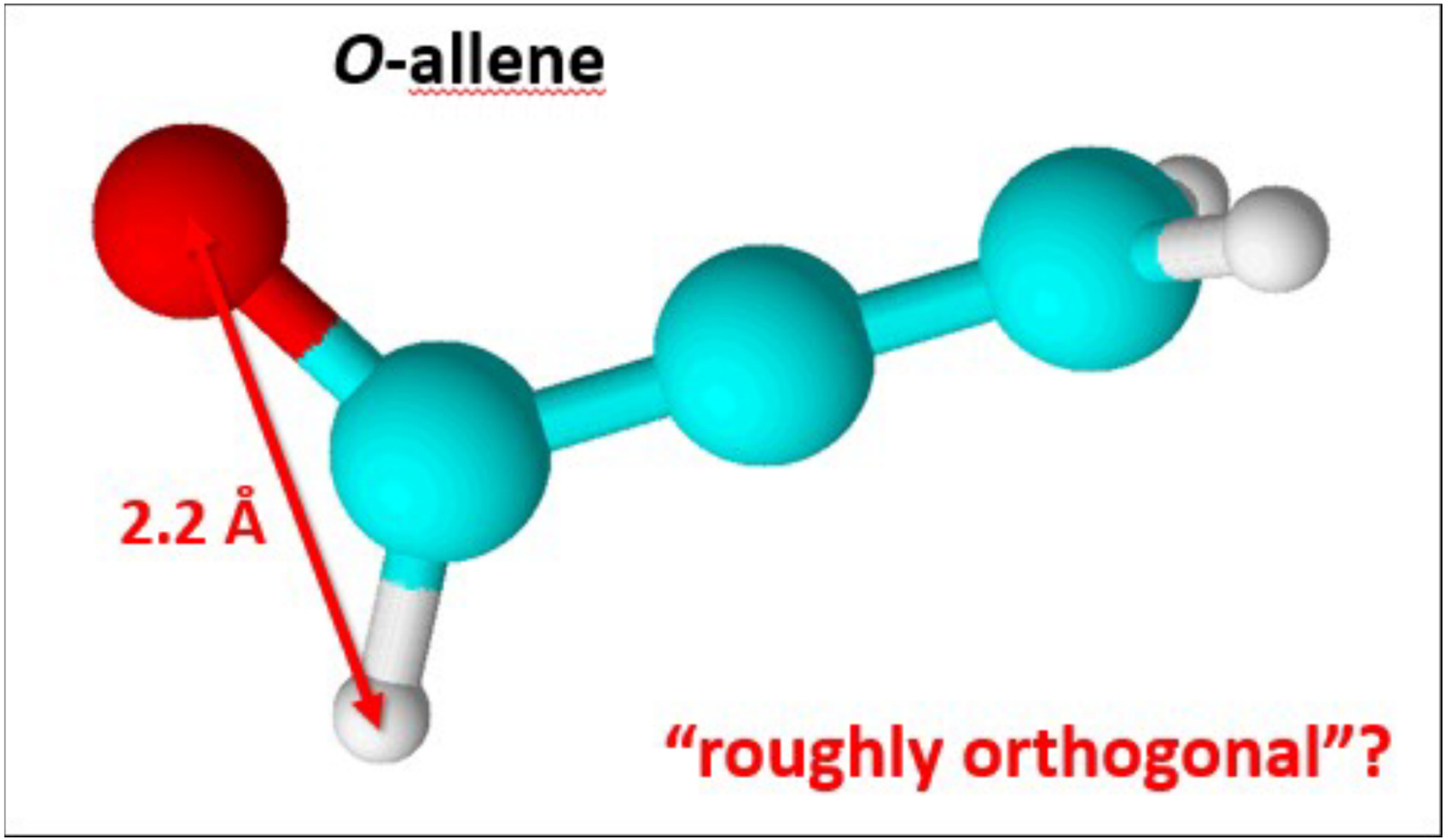

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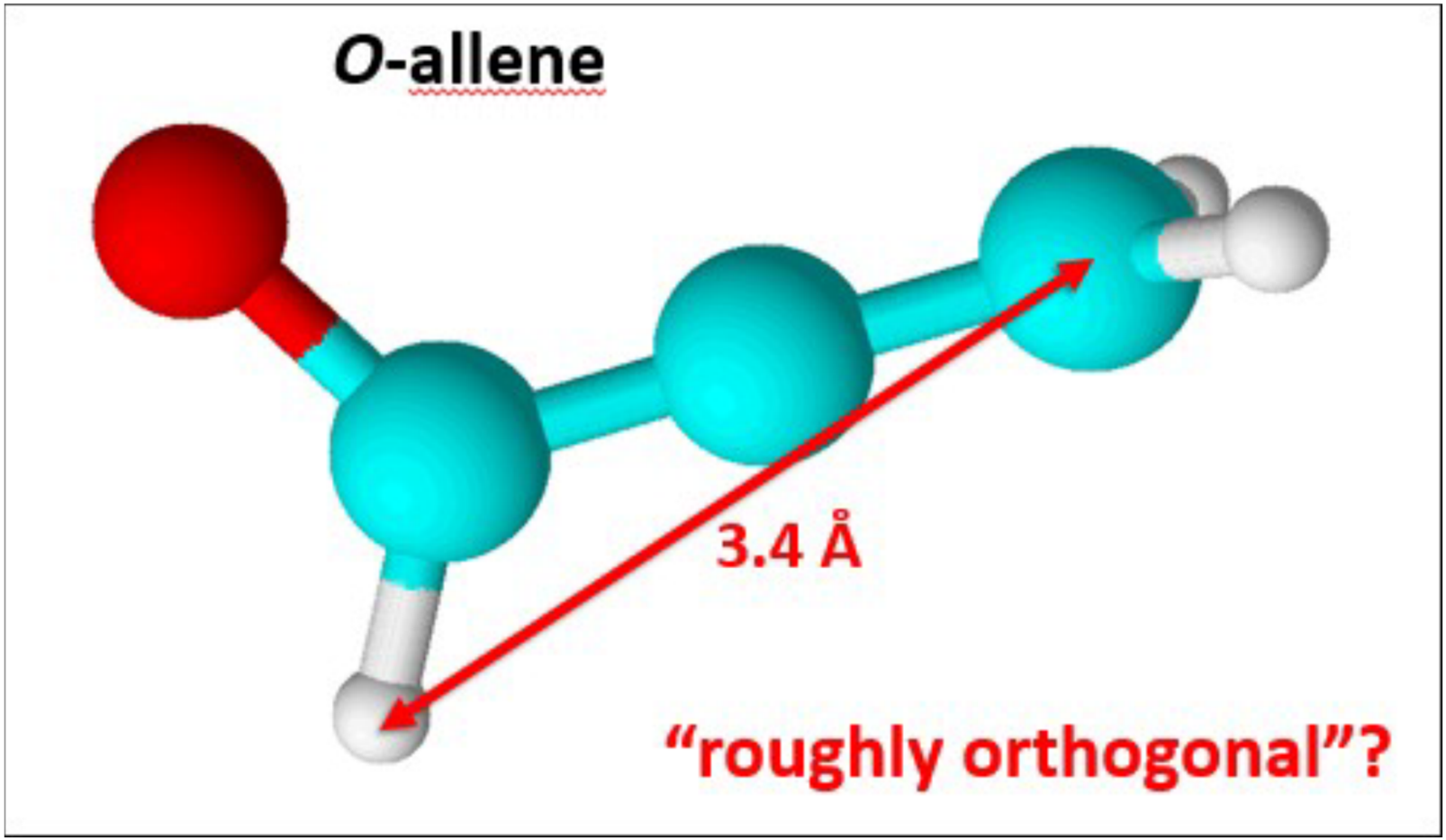

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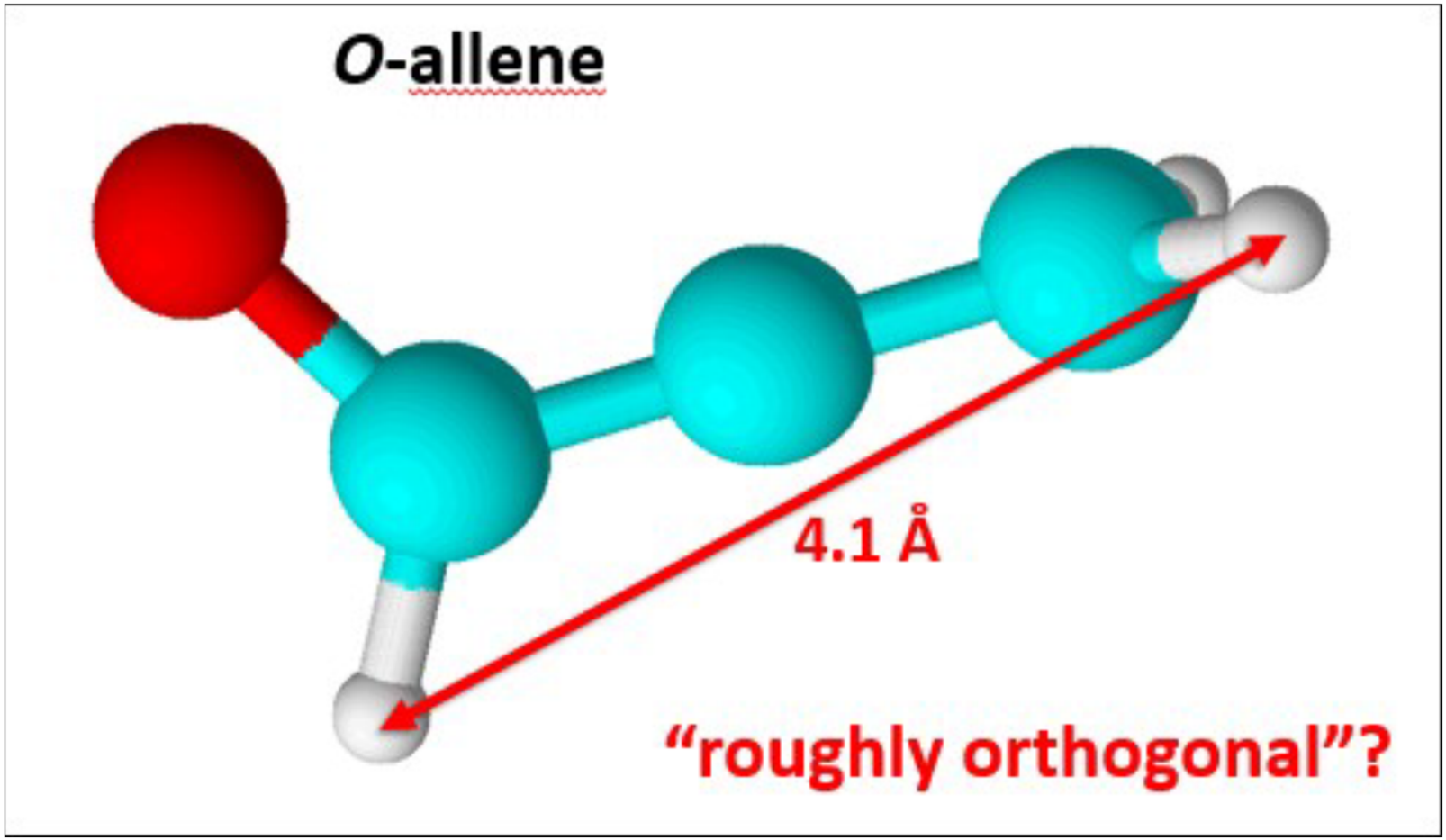

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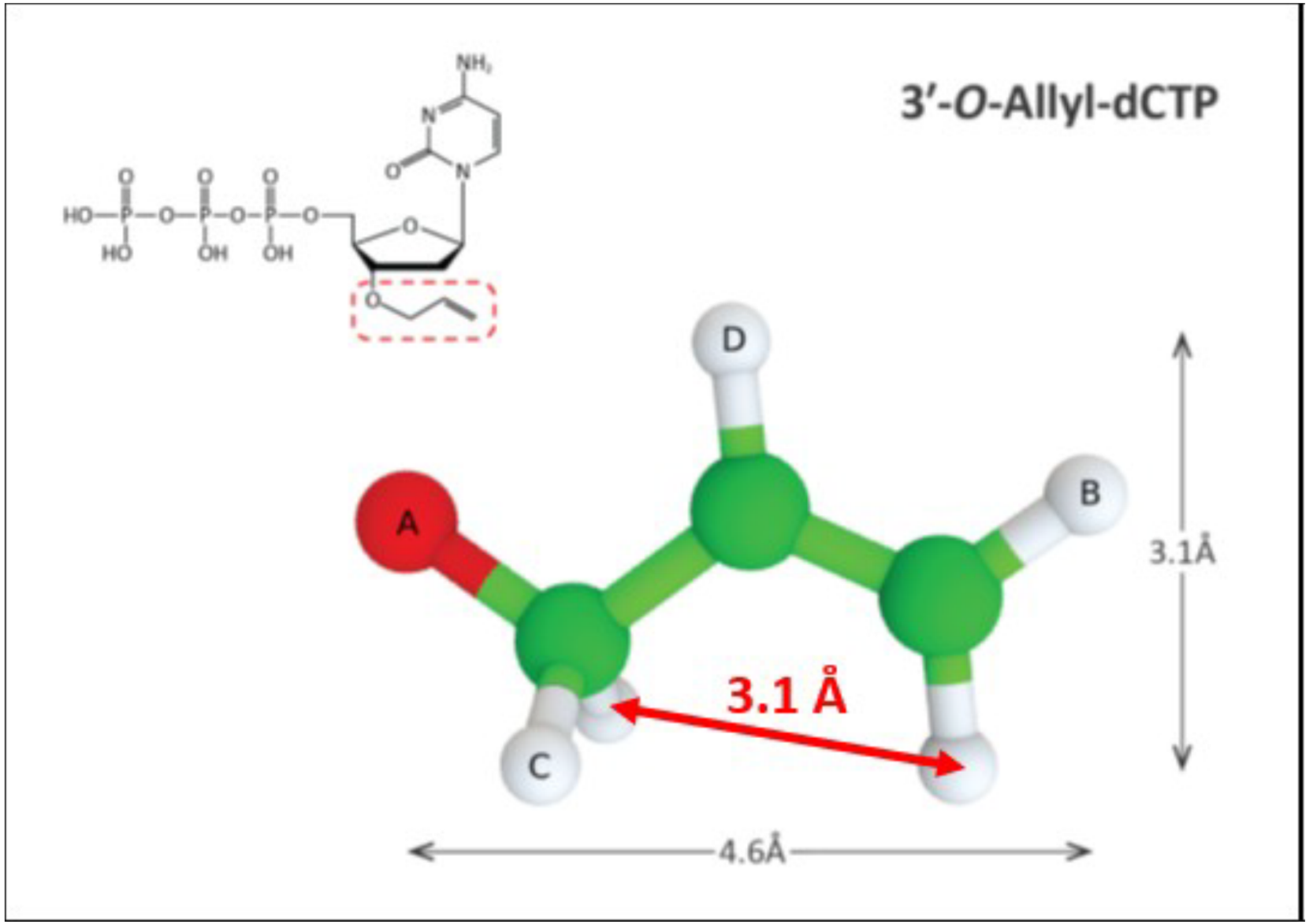

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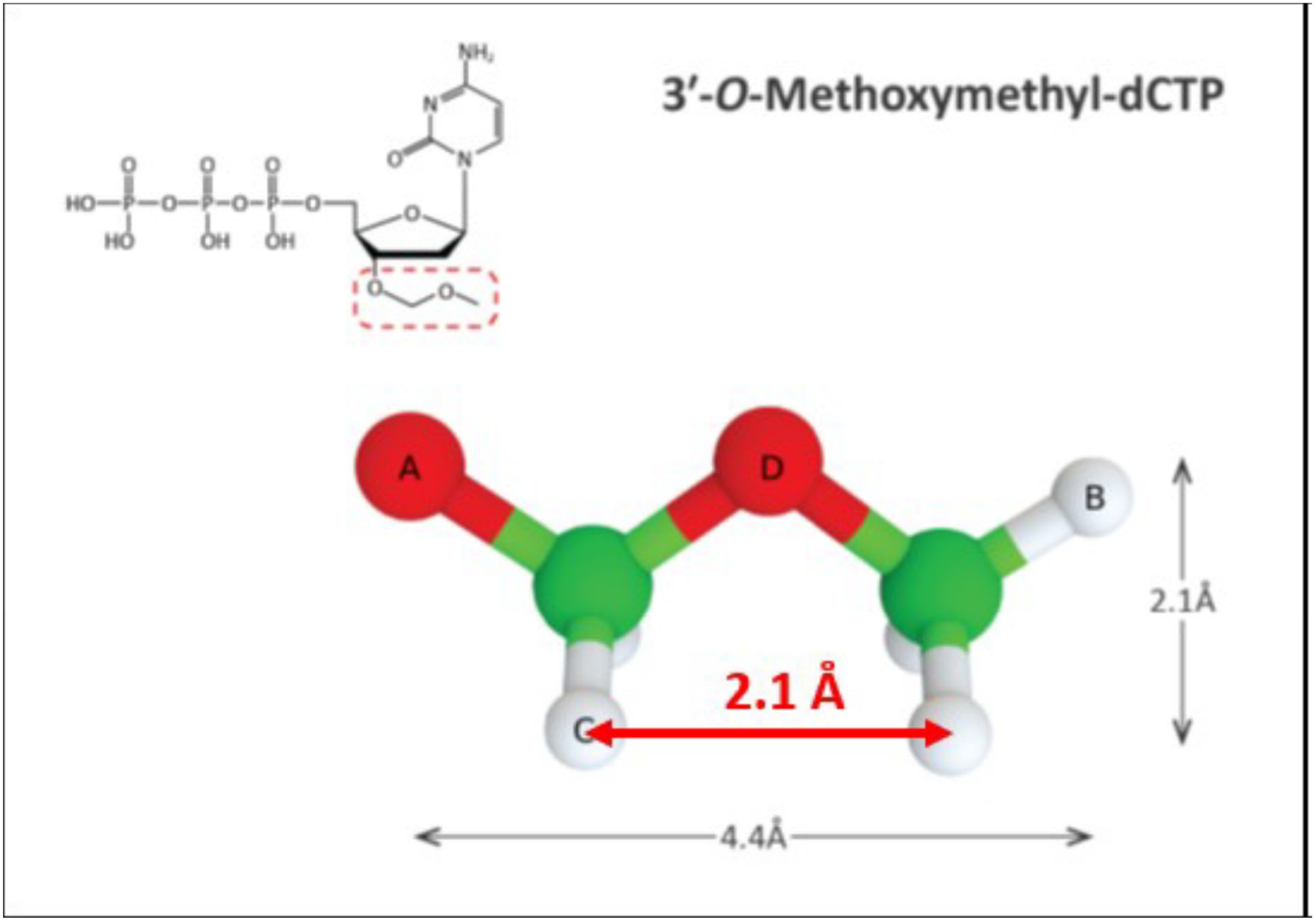

Plaintiffs' Position: Illumina Excludes Embodiments

Plaintiffs' Brief

> Defendant's construction that the "longest dimension," or length,—rather than the diameter or width[17]—must be less than 3.7Å would exclude chemical groups designated as small in the specification and prosecution history. In the

Specification: Only Two Embodiments

MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA

This application is a continuation of U.S. Ser. No. 15/915,983, filed Mar. 8, 2018, which is a continuation of U.S. Ser. No. 14/670,748, filed Mar. 27, 2015, which is a continuation of U.S. Ser. No. 13/959,660, filed Aug. 5, 2013, now U.S. Pat. No. 9,133,511, issued Sep. 15, 2015, which is a continuation of U.S. Ser. No. 13/672,437, filed Nov. 8, 2012, now abandoned, which is a continuation of U.S. Ser. No. 13/339,089, filed Dec. 28, 2011, now abandoned, which is a continuation of U.S. Ser. No. 12/804,284, filed Jul. 19, 2010, now U.S. Pat. No. 8,088,575, issued Jan. 3, 2012, which is a continuation of U.S. Ser. No. 11/810,509, filed Jun. 5, 2007, now U.S. Pat. No. 7,790,869, issued Sep. 7, 2010, which is a continuation of U.S. Ser. No. Nov. 4, 2003, now U.S. Pat. No. 7,345,15 2008, which is a divisional of U.S. Ser. No. Oct. 5, 2001, now U.S. Pat. No. 6,664,07 2003, claiming the benefit of U.S. Provis No. 60/300,894, filed Jun. 26, 2001, and in-part of U.S. Ser. No. 09/684,670, filed abandoned, the contents of each of which porated in its entirety into this applicatio

This invention was made with governm grant no. BES0097793 awarded by the Foundation. The government has certain r tion.

BACKGROUND OF THE INV

Throughout this application, various pu erenced in parentheses by author and year these references may be found at the end o immediately preceding the claims. The di publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

The ability to sequence deoxyribonucleic acid (DNA) accurately and rapidly is revolutionizing biology and medicine. The confluence of the massive Human Genome Project is driving an exponential growth in the development of high throughput genetic analysis technologies. This rapid technological development involving chemistry, engineering, biology, and computer science makes it possible to move from studying single genes at a time to analyzing and comparing entire genomes.

With the completion of the first entire human genome sequence map, many areas in the genome that are highly polymorphic in both exons and introns will be known. The pharmacogenomics challenge is to comprehensively identify the genes and functional polymorphisms associated with the variability in drug response (Roses, 2000). Resequencing of polymorphic areas in the genome that are linked to disease development will contribute greatly to the understanding of diseases, such as cancer, and therapeutic development. Thus, high-throughput accurate methods for resequencing the highly variable intron/exon regions of the genome are needed in order to explore the full potential of the complete human genome sequence map. The current state-of-the-art technology for high throughput DNA sequencing, such as used for the Human Genome Project (Pennisi 2000), is capillary array DNA sequencers using laser induced fluorescence detection (Smith et al., 1986; Ju et al. 1995, 1996; Kheterpal et al. 1996; Salas-Solano et al. 1998). Improvements in the polymerase that lead to uniform termination efficiency and the introduction of thermostable polymerases

have also significantly improved the quality of sequencing data (Tabor and Richardson, 1987, 1995). Although capillary array DNA sequencing technology to some extent addresses the throughput and read length requirements of large scale DNA sequencing projects, the throughput and accuracy required for mutation studies needs to be improved for a wide variety of applications ranging from disease gene discovery to forensic identification. For example, electrophoresis based DNA sequencing methods have difficulty detecting heterozygotes unambiguously and are not 100% accurate in regions rich in nucleotides comprising guanine or cytosine due to compressions (Bowling et al. 1991; Yamakawa et al. 1997). In addition, the first few bases after the priming site are often masked by the high fluorescence signal from excess dye-labeled primers or dye-labeled ter-

used for mutation detection (Ronaghi 1998). In this approach, the detection is based on the pyrophosphate (PPi) released during the DNA polymerase reaction, the quantitative conversion of pyrophosphate to adenosine triphosphate (ATP) by sulfurylase, and the subsequent production of visible light by firefly luciferase. This procedure can only sequence up to 30 base pairs (bps) of nucleotide sequences, and each of the 4 nucleotides needs to be added separately and detected separately. Long stretches of the same bases cannot be identified unambiguously with the pyrosequencing method.

More recent work in the literature exploring DNA sequencing by a synthesis method is mostly focused on designing and synthesizing a photocleavable chemical moiety that is linked to a fluorescent dye to cap the 3'-OH group of deoxynucleoside triphosphates (dNTPs) (Welch et al. 1999). Limited success for the incorporation of the 3'-modified nucleotide by DNA polymerase is reported. The reason is that the 3'-position on the deoxyribose is very close to the amino acid residues in the active site of the polymerase, and the polymerase is therefore sensitive to modification in this area of the deoxyribose ring. On the other hand, 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) and at the 7-position of purines (G and A) (Rosenblum et al. 1997, Zhu et al. 1994). The ternary complexes of rat DNA polymerase, a DNA template-primer, and dideoxycytidine triphosphate (ddCTP) have been determined (Pelletier et al. 1994) which supports this fact. As shown in FIG. 1, the 3-D structure indicates that the surrounding area of the 3'-posi-

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). The approach

Dr. Romesberg: MOM And Allyl Fit, Azido Does Not

Floyd Romesberg, Ph.D.
Illumina's Expert

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45. As can be seen in Figure E, the MOM and allyl groups fit within a sphere with diameter 3.7 Å, but the azido does not, regardless of orientation. This is because, as explained above, the MOM and allyl groups bonds are generally more free to rotate than are the bonds in the azidomethyl group. This allows the MOM and allyl groups to bend and twist into conformations that fit into the sphere (and the polymerase active site, as previously demonstrated in Figure B). In contrast, the rigidity of the azido group force it to remain linear and thus preclude its accommodation within the sphere. This confirms the accuracy of the model to reflect the actual space available in the polymerase.

Dr. Romesberg: Azidomethyl Not “Small”

Floyd Romesberg, Ph.D.
Illumina’s Expert

Q. And in your declaration you conclude that the azidomethyl is not small; is that right?

A. Using the definition provided by -- by Ju in this -- Professor Ju in this declaration, yes, I concluded that azidomethyl was not small.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Did you evaluate what the available space was in the rat polymerase as part of your work in this case?

A. No.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Do you have any idea at all whether any of the protecting groups referenced in your declaration would actually fit so -- such that they could successfully serve as protecting groups in a sequencing by synthesis process?

A. I made no analysis of whether a protecting group of any kind would fit within the polymerase, and so I did not form an opinion about the ability of a protecting group to function, if that's what you're asking me, in sequencing by synthesis.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. Okay. In terms of what the benchmark polymerase is that you refer to there, you understand that to be the rat DNA polymerase shown in figure 1. Correct?

A. Yes, I do.

Q. Whether allyl, MOM or azidomethyl fits within the active site of the benchmark polymerase, that's not something that you've opined on at all, correct, or considered?

A. That's correct.

Dr. Kuriyan: Does Not Rebut Romesberg

John Kuriyan, Ph.D.
Plaintiffs' Expert

Q. (BY MR. REINES) Which parts of the Pelletier article did you consider to be relevant?

A. Relevant to the opinion I gave in my declaration, I did not consider the -- any aspect of the Pelletier article to be relevant to the specific items that I opined on in my declaration.

Plaintiffs' Construction: Layers Of Spin

- "small" is indefinite

- Space inside rat polymerase is 3.7 Å "diameter"
- Does not provide calculations
- Does not refer to "width"

- Devises scheme to "match" Dr. Ju's "diameters"

Law: Prosecution History Cannot Enlarge Claims

"Multiform's dictionary definitions added during patent prosecution, although stating a broad definition of 'degradable,' could not serve to enlarge the scope of the claims in order to cover the Medzam device."

Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1478 (Fed. Cir. 1988)

"The district court did not accept Multiform's position that the dictionary definitions provided during the prosecution simply clarified the inventor's original usage of 'degradable.'"

Id.

Law: Prosecution History Cannot Enlarge Claims

"When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.

We conclude that the meaning of "degradable" in claims 1 and 6 (and the claims dependent thereon) is limited to the dissolution/degradation of the envelope as described in the specification."

Multiform Desiccants, Inc. v. Medzam, Ltd.,

133 F.3d 1473, 1478 (Fed. Cir. 1988)

“R...is stable during a DNA polymerase reaction”

Disputed Claim Term

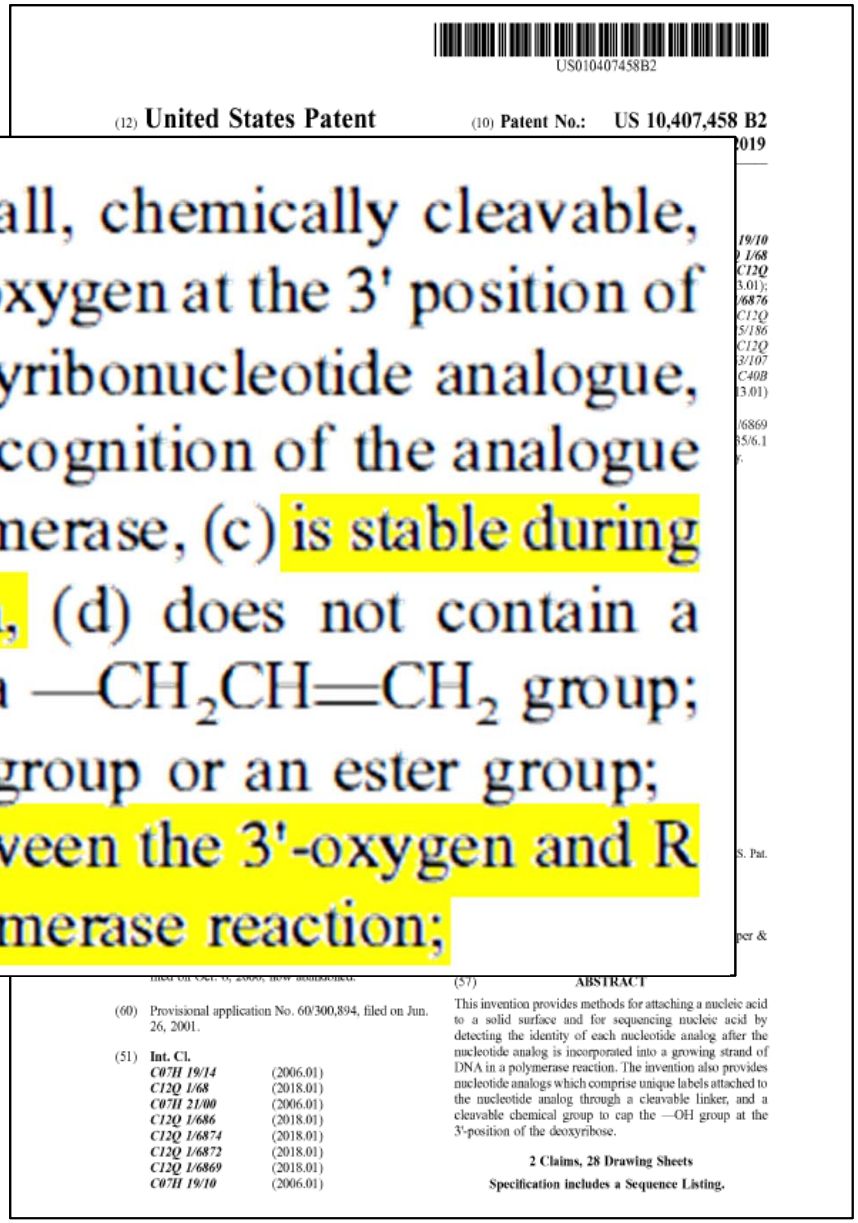
Claim Term	Illumina's Construction	Plaintiffs' Construction
"R . . . is stable during a DNA polymerase reaction" '458 Patent: Claims 1, 2 '459 Patent: Claims 1, 2 '742 Patent: Claims 1, 2 '984 Patent: Claims 1, 2 '380 Patent: Claims 1, 3	"R has at least the stability of a MOM ether (-CH2OCH3) or allyl (-CH2CH=CH2) group"	"R remains bonded to 3´ oxygen during a DNA polymerase reaction"

Key Dispute

- Can two separate limitations be redundant?
  - Illumina's position: No
  - Plaintiffs' position: Yes

Claim Language: Requires Two Forms Of Stability

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, (d) does not contain a ketone group, and (e) is not a $—CH_2CH═CH_2$ 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;



US010407458B2

(12) United States Patent (10) Patent No.: US 10,407,458 B2

(60) Provisional application No. 60/300,894, filed on Jun. 26, 2001.

(51) Int. Cl.

C07H 19/14	(2006.01)
C12Q 1/68	(2018.01)
C07H 21/00	(2006.01)
C12Q 1/686	(2018.01)
C12Q 1/6874	(2018.01)
C12Q 1/6872	(2018.01)
C12Q 1/6869	(2018.01)
C07H 19/10	(2006.01)

(57) ABSTRACT

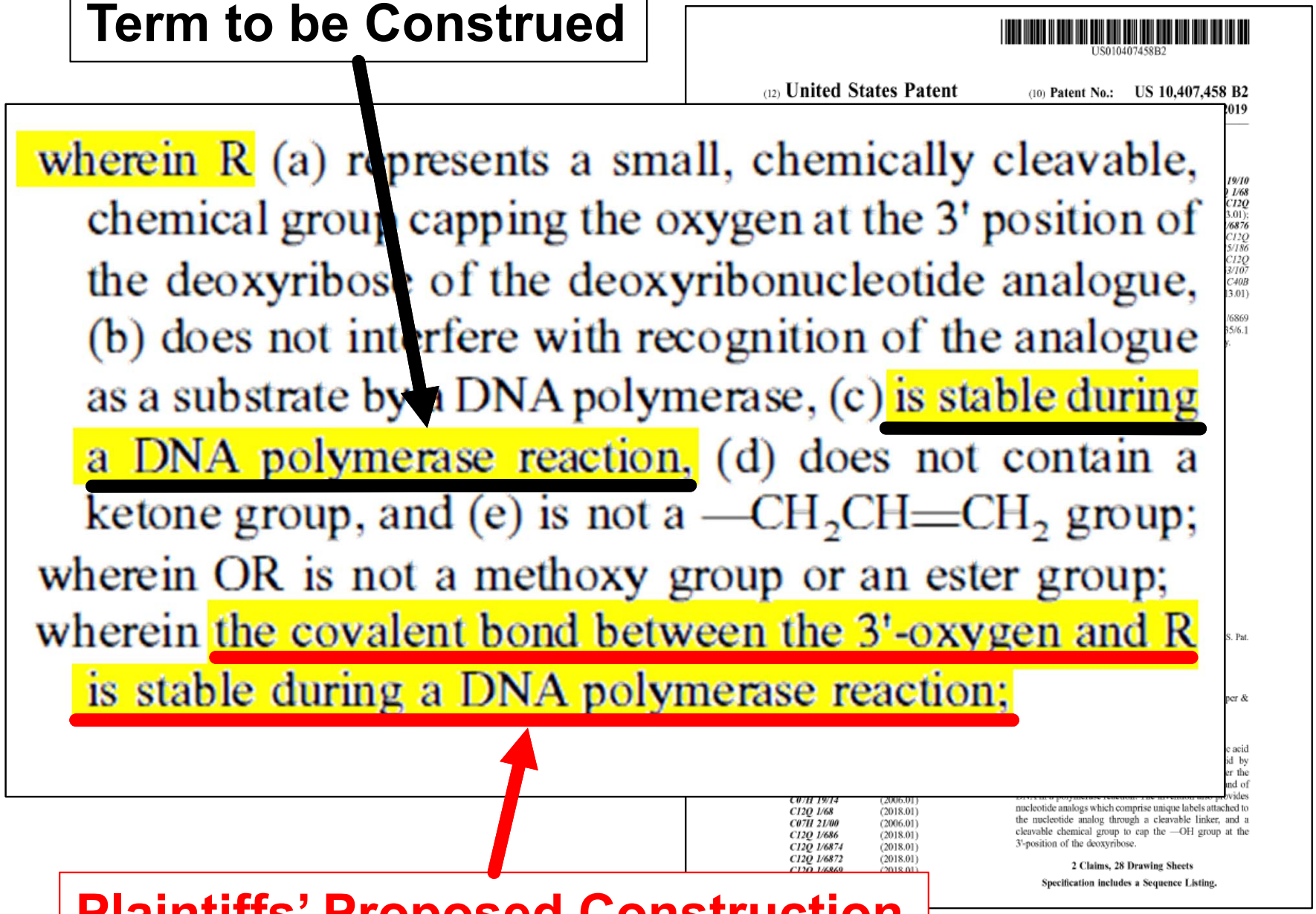
This invention provides methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

2 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

Claim Language: Requires Two Forms Of Stability

Term to be Construed



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, (d) does not contain a ketone group, and (e) is not a $—CH_2CH═CH_2$ 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;

US010407458B2

(12) United States Patent (10) Patent No.: US 10,407,458 B2

nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

2 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

Plaintiffs' Proposed Construction

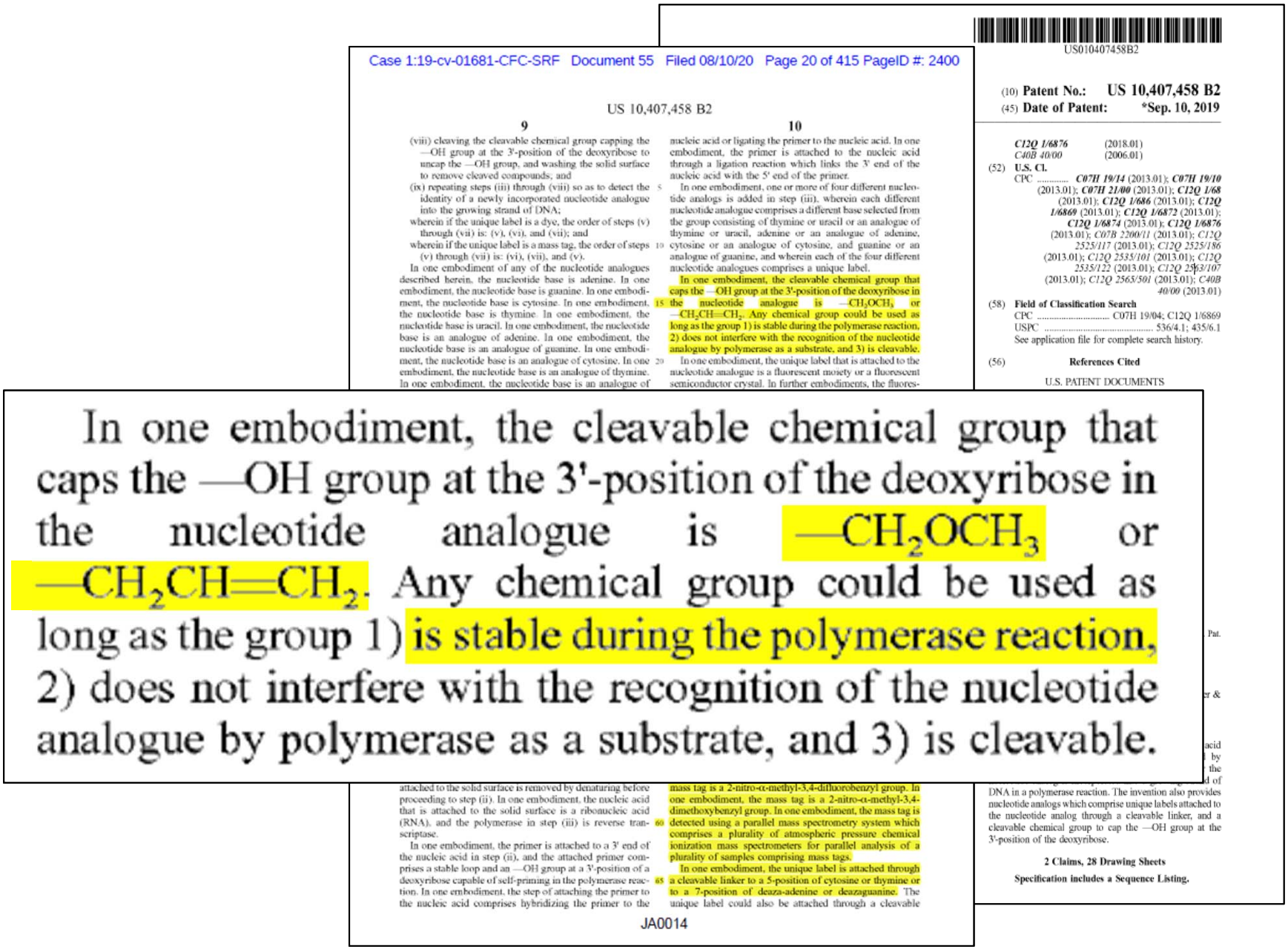
Law: All Claims Terms Must Be Given Effect

"Claims must be interpreted with an eye toward giving effect to all terms in the claim."

Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP,

616 F.3d 1249, 1257 (Fed. Cir. 2010).

Specification: Provides Stability Standard



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US 10,407,458 B2

9 10

(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).

In one embodiment of any of the nucleotide analogues described herein, the nucleotide base is adenine. In one embodiment, the nucleotide base is guanine. In one embodiment, the nucleotide base is cytosine. In one embodiment, the nucleotide base is thymine. In one embodiment, the nucleotide base is uracil. In one embodiment, the nucleotide base is an analogue of adenine. In one embodiment, the nucleotide base is an analogue of guanine. In one embodiment, the nucleotide base is an analogue of cytosine. In one embodiment, the nucleotide base is an analogue of thymine. In one embodiment, the nucleotide base is an analogue of

nucleic acid or ligating the primer to the nucleic acid. In one embodiment, the primer is attached to the nucleic acid through a ligation reaction which links the 3' end of the nucleic acid with the 5' end of the primer.

In one embodiment, one or more of four different nucleotide analogs is added in step (iii), wherein each different nucleotide analogue comprises a different base selected from the group consisting of thymine or uracil or an analogue of thymine or uracil, adenine or an analogue of adenine, cytosine or an analogue of cytosine, and guanine or an analogue of guanine, and wherein each of the four different nucleotide analogues comprises a unique label.

In one embodiment, the cleavable chemical group that caps the —OH group at the 3'-position of the deoxyribose in the nucleotide analogue is $—CH_2OCH_3$ or $—CH_2CH═CH_2$. Any chemical group could be used as long as the group 1) is stable during the polymerase reaction, 2) does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate, and 3) is cleavable.

In one embodiment, the unique label that is attached to the nucleotide analogue is a fluorescent moiety or a fluorescent semiconductor crystal. In further embodiments, the fluores-

attached to the solid surface is removed by denaturing before proceeding to step (ii). In one embodiment, the nucleic acid that is attached to the solid surface is a ribonucleic acid (RNA), and the polymerase in step (iii) is reverse transcriptase.

In one embodiment, the primer is attached to a 3' end of the nucleic acid in step (ii), and the attached primer comprises a stable loop and an —OH group at a 3'-position of a deoxyribose capable of self-priming in the polymerase reaction. In one embodiment, the step of attaching the primer to the nucleic acid comprises hybridizing the primer to the

mass tag is a 2-nitro-α-methyl-3,4-difluorobenzyl group. In one embodiment, the mass tag is a 2-nitro-α-methyl-3,4-dimethoxybenzyl group. In one embodiment, the mass tag is detected using a parallel mass spectrometry system which comprises a plurality of atmospheric pressure chemical ionization mass spectrometers for parallel analysis of a plurality of samples comprising mass tags.

In one embodiment, the unique label is attached through a cleavable linker to a 5-position of cytosine or thymine or to a 7-position of deaza-adenine or deazaguanine. The unique label could also be attached through a cleavable

JA0014

US010407458B2

(10) **Patent No.: US 10,407,458 B2**
(45) **Date of Patent: *Sep. 10, 2019**

C12Q 1/6876 (2018.01)
C40B 40/00 (2006.01)

(52) **U.S. Cl.**
CPC ***C07H 19/14*** (2013.01); ***C07H 19/10*** (2013.01); ***C07H 21/00*** (2013.01); ***C12Q 1/68*** (2013.01); ***C12Q 1/686*** (2013.01); ***C12Q 1/6869*** (2013.01); ***C12Q 1/6872*** (2013.01); ***C12Q 1/6874*** (2013.01); ***C12Q 1/6876*** (2013.01); *C07B 2200/11* (2013.01); *C12Q 2525/117* (2013.01); *C12Q 2525/186* (2013.01); *C12Q 2535/101* (2013.01); *C12Q 2535/122* (2013.01); *C12Q 2563/107* (2013.01); *C12Q 2563/501* (2013.01); *C40B 40/00* (2013.01)

(58) **Field of Classification Search**
CPC C07H 19/04; C12Q 1/6869
USPC 536/4.1; 435/6.1
See application file for complete search history.

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DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

2 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

In one embodiment, the cleavable chemical group that caps the —OH group at the 3'-position of the deoxyribose in the nucleotide analogue is $—CH_2OCH_3$ or $—CH_2CH═CH_2$. Any chemical group could be used as long as the group 1) is stable during the polymerase reaction, 2) does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate, and 3) is cleavable.

“A method for sequencing a nucleic acid”

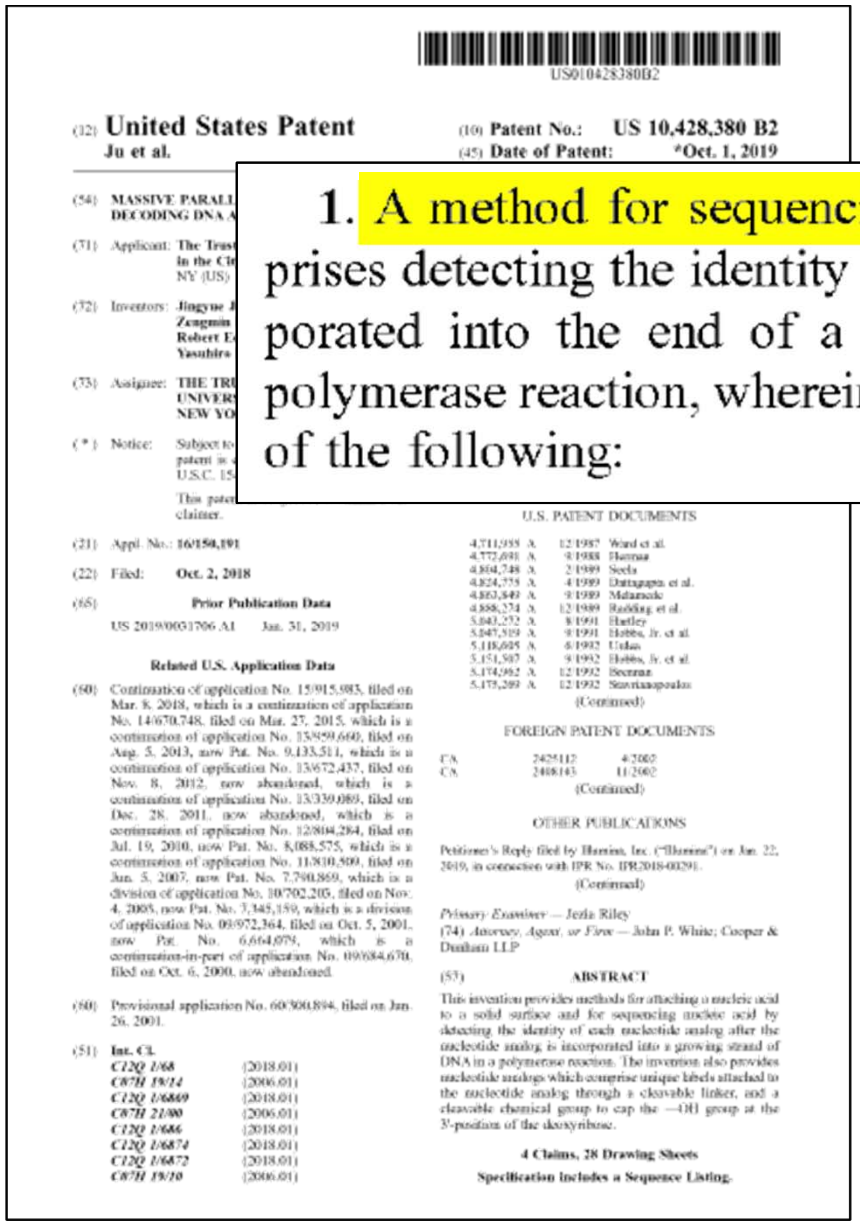
Disputed Claim Term

Claim Term	Illumina's Construction	Plaintiffs' Construction
"A method for sequencing a nucleic acid" '380 Patent: Claims 1, 3	Preamble is not limiting	"A method for detecting the identity and sequence of a strand of nucleotides"

Key Dispute

- Whether preamble is limiting?
  - Illumina's position: Non-limiting
  - Plaintiffs' position: Limiting.

’380 Patent: Preamble



US010428380B2

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

(10) **Patent No.: US 10,428,380 B2**
(45) **Date of Patent: *Oct. 1, 2019**

(54) MASSIVE PARALL… DECODING DNA A…

(71) Applicant: The Trust… in the Ci… NY (US)

(72) Inventors: Jingyue J… Zengmin… Robert L… Yasuhiro…

(73) Assignee: THE TR… UNIVERS… NEW YO…

(*) Notice: Subject to… patent is … U.S.C. 15…
This pate… claimer.

(21) Appl. No.: **16/150,191**

(22) Filed: **Oct. 2, 2018**

(65) **Prior Publication Data**

US 2019/0031706 A1 Jan. 31, 2019

Related U.S. Application Data

(60) Continuation of application No. 15/915,983, filed on Mar. 8, 2018, which is a continuation of application No. 14/670,748, filed on Mar. 27, 2015, which is a continuation of application No. 13/959,660, filed on Aug. 5, 2013, now Pat. No. 9,133,511, which is a continuation of application No. 13/672,437, filed on Nov. 8, 2012, now abandoned, which is a continuation of application No. 13/339,089, filed on Dec. 28, 2011, now abandoned, which is a continuation of application No. 12/804,284, filed on Jul. 19, 2010, now Pat. No. 8,088,575, which is a continuation of application No. 11/810,509, filed on Jun. 5, 2007, now Pat. No. 7,790,869, which is a division of application No. 10/702,205, filed on Nov. 4, 2003, now Pat. No. 7,345,159, which is a division of application No. 09/972,364, filed on Oct. 5, 2001, now Pat. No. 6,664,079, which is a continuation-in-part of application No. 09/684,670, filed on Oct. 6, 2000, now abandoned.

(60) Provisional application No. 60/300,894, filed on Jun. 26, 2001.

(51) **Int. Cl.**

C12Q 1/68	(2018.01)
C07H 19/14	(2006.01)
C12Q 1/6869	(2018.01)
C07H 21/00	(2006.01)
C12Q 1/686	(2018.01)
C12Q 1/6874	(2018.01)
C12Q 1/6872	(2018.01)
C07H 19/10	(2006.01)

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(Continued)

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(Continued)

Primary Examiner — Jezia Riley
(74) *Attorney, Agent, or Firm* — John P. White; Cooper & Dunham LLP

(57) **ABSTRACT**

This invention provides methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

4 Claims, 28 Drawing Sheets

Specification includes a Sequence Listing.

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:

’380 Patent, cl. 1

Law: Preamble Is Not Limiting By Default

- The default rule is that preamble language is not limiting.

Aspex Eyewear, Inc. v. Marchon Eyewear, Inc., 672 F.3d 1335, 1347 (Fed. Cir. 2012).

Law: Merely Stating Purpose Does Not Limit Claims

- Where "a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation."

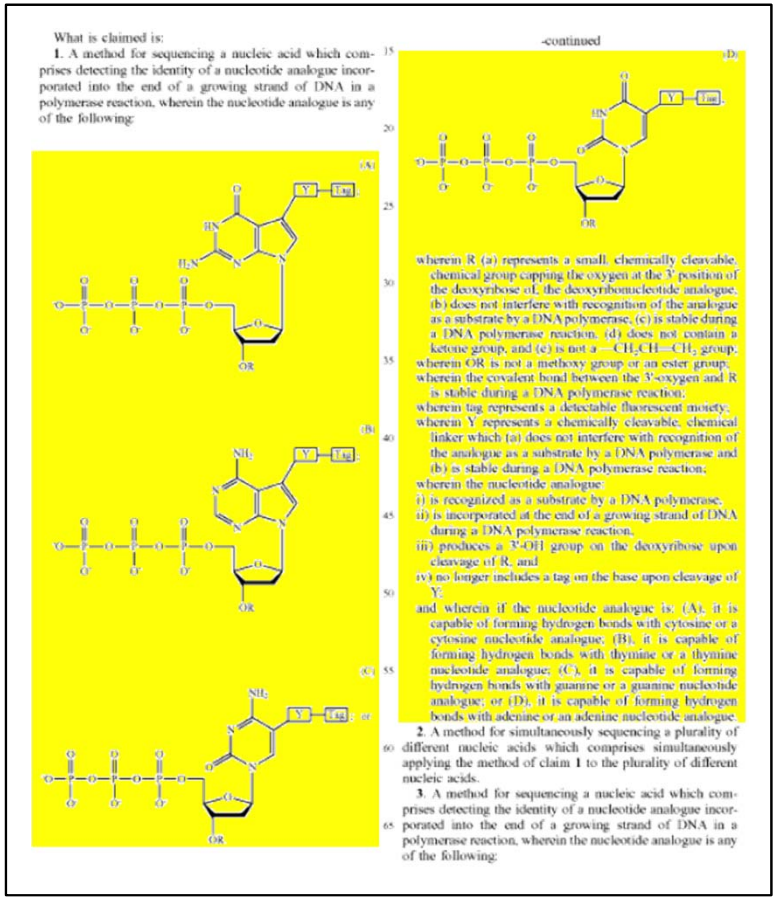
See Rowe v. Dror, 112 F. 3d 473, 478 (Fed. Cir. 1997).

Preamble Merely States Purpose Or Intended Use

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:

Claim Discloses Structurally Complete Invention

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:



What is claimed is:

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:

-continued

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, (d) does not contain a ketone group, and (e) is not a $—CH_2CH—CH_2$ 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; wherein the nucleotide 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, and

iv) no longer includes a tag on the base upon cleavage of Y;

and wherein if the nucleotide analogue is: (A), it is capable of forming hydrogen bonds with cytosine or a cytosine nucleotide analogue; (B), it is capable of forming hydrogen bonds with thymine or a thymine nucleotide analogue; (C), it is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue; or (D), it is capable of forming hydrogen bonds with adenine or an adenine nucleotide analogue.

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.

3. 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:

Conditions For A Limiting Preamble Not Present

- A preamble is only limiting "if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim."

  Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002).

- The preamble may also be limiting to the extent it is "necessary to provide antecedent basis for the body of the claim."

  Symantec Corp. v. Computer Assoc. Int'l, Inc., 522 F.3d 1279, 1288 (Fed. Cir. 2008).

Plaintiffs' Proffered Construction Is Duplicative

- "A method for detecting the identity and sequence of a strand of nucleotides which comprises *detecting the identity of a nucleotide analogue incorporated into the end of a growing strand of DNA in a polymerase reaction*...."

- "If the preamble 'is reasonably susceptible to being construed to be merely duplicative of the limitations in the body of the claim (and was not clearly added to overcome a [prior art] rejection), we do not construe it to be a separate limitation.'"

TomTom, Inc. v. Adolph, 790 F.3d 1315, 1324 (Fed. Cir. 2015).

Plaintiffs' Law Is Inapposite

"'Growing' and 'isolating' are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself. Divorced from the process of growing and isolating virus, the claimed method reduces to nothing more than a process for producing cytopathic effects in sheets of cultured MA-104 cells-a process whose absence of fathomable utility rather suggests the academic exercise. Gauging the effect of preamble language based on the claim as a whole…it becomes apparent that claim 2 is in fact directed to a process for growing or isolating viruses."

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,

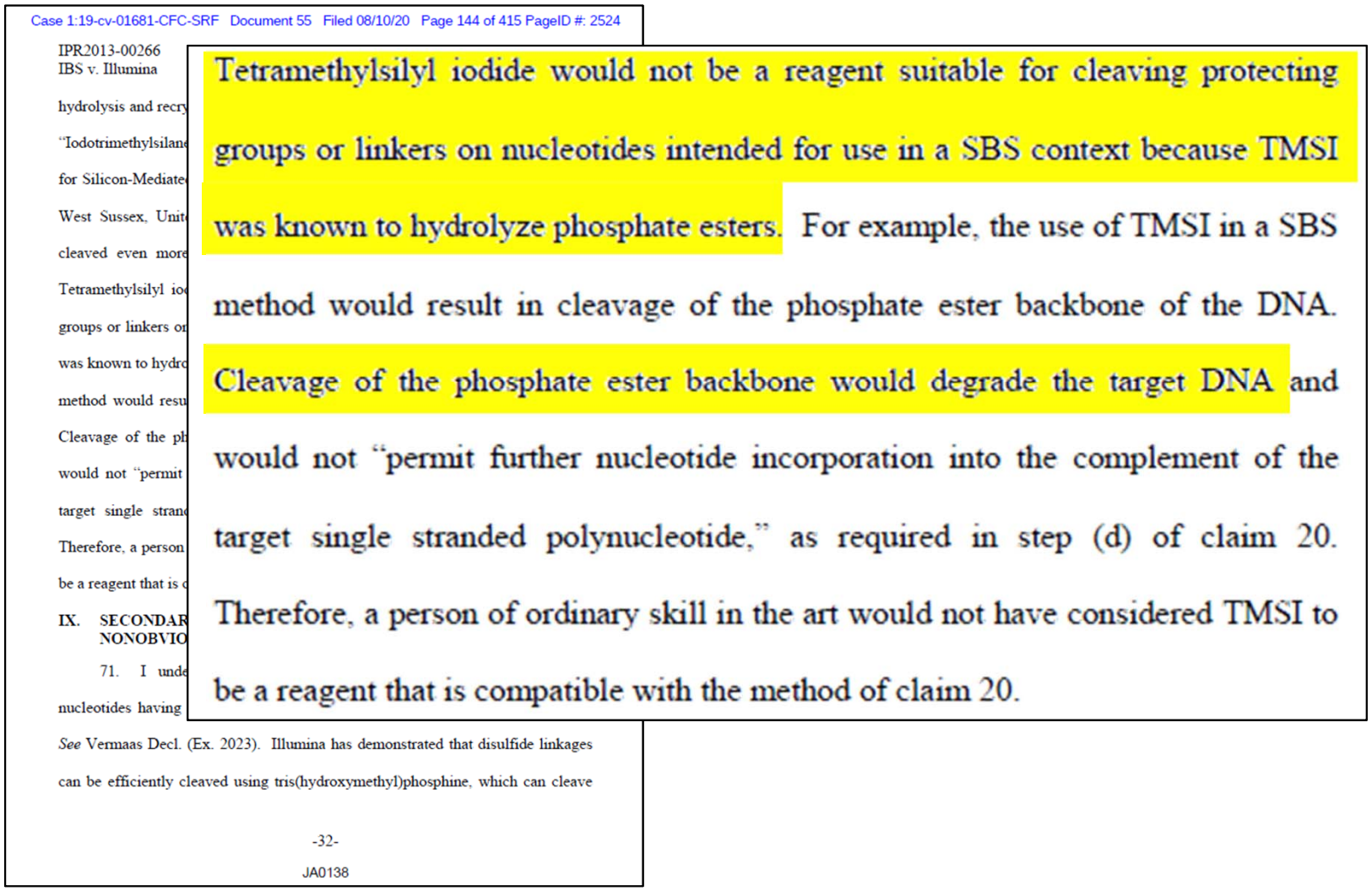
320 F.3d 1339 (Fed. Cir. 2003).

Plaintiffs' Case Law Examples Are Inapposite

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:

End

TMSI Destroys DNA



Case 1:19-cv-01681-CFC-SRF Document 55 Filed 08/10/20 Page 144 of 415 PageID #: 2524

IPR2013-00266
IBS v. Illumina

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for Silicon-Mediate

West Sussex, Unit

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Tetramethylsilyl io

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IX. SECONDAR
NONOBVIO

71. I unde

nucleotides having

See Vermaas Decl. (Ex. 2023). Illumina has demonstrated that disulfide linkages can be efficiently cleaved using tris(hydroxymethyl)phosphine, which can cleave

-32-

JA0138

Tetramethylsilyl iodide would not be a reagent suitable for cleaving protecting groups or linkers on nucleotides intended for use in a SBS context because TMSI was known to hydrolyze phosphate esters. For example, the use of TMSI in a SBS method would result in cleavage of the phosphate ester backbone of the DNA. Cleavage of the phosphate ester backbone would degrade the target DNA and would not "permit further nucleotide incorporation into the complement of the target single stranded polynucleotide," as required in step (d) of claim 20. Therefore, a person of ordinary skill in the art would not have considered TMSI to be a reagent that is compatible with the method of claim 20.

Romesberg IPR Decl. (JA0137-0138)