

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.

U.S. Serial No. : 15/167,917 Examiner: Jezia Riley

Filed : May 27, 2016 Group Art Unit: 1637

Conf. No. : 1260

For : MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA

30 Rockefeller Plaza
20th Floor
New York, NY 10112
November 4, 2016

BY EFS

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

**COMMUNICATION IN RESPONSE TO JULY 20, 2016 OFFICE ACTION
AND SUMMARY OF OCTOBER 27, 2016 INTERVIEW WITH EXAMINER RILEY**

This Communication is submitted in response to the Office Action issued July 20, 2016 in connection with the above-identified application. A response to the July 20, 2016 Office Action was due October 20, 2016 and applicant is concurrently filing a Petition for A One Month Extension of Time. Accordingly, a response is now due November 20, 2016 and this Communication is being timely filed.

Remarks begin on page 2 of this paper.

Illumina Ex. 1038 IPR Petition - USP 9,708,358
--

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 2 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

REMARKS

Claim 49 is the sole claim pending in the subject application and is not being amended in response to the July 20, 2016 Office Action.

As an initial matter, applicant wishes to express its gratitude to Examiner Riley for the in person interview held October 27, 2016 at the U.S. Patent and Trademark Office in Alexandria, Virginia. This interview was attended by the first named inventor, Dr. Jingyue Ju a professor at Columbia University in the City of New York, the assignee of the subject application, and the undersigned. Applicant thinks the interview was most helpful in terms of clarifying the scope of claim 49 and the content of the references cited in the July 20, 2016 Office Action. Applicant attaches as **Exhibit A** hereto a copy of the Claim Chart provided to Examiner Riley at the beginning of the interview. The remarks which follow were discussed with Examiner Riley during the interview.

I. Neither Tsien nor Seela discloses
multiple features required by claim 49.

As discussed during the October 27, 2016 interview and as shown in the attached Claim Chart, there are multiple features recited in claim 49 which are not disclosed in either Tsien or Seela. Among these features are the following:

- A. a fluorescent label (Tag) attached via a chemically cleavable, chemical linker (Y) to the 7-position of a deazaguanine deoxyribonucleotide analogue;
- B. a small, chemically cleavable group (R) capping the oxygen at the 3' position of the deoxyribose of the 7-deazaguanine nucleotide analogue and the resulting structure OR not being either a methoxy group or an ester group; and

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 3 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

- C. the ability of the claimed 7-deazaguanine deoxyribonucleotide analogue with features A and B to:
1. be recognized as a substrate by a DNA polymerase;
 2. be incorporated at the end of a growing DNA strand during a polymerase reaction;
 3. produce a 3'-OH group on the deoxyribose upon cleavage of R;
 4. no longer include a tag on the base upon cleavage of Y; and
 5. be capable of forming hydrogen bonds with cytosine or a cytosine nucleotide analogue.

In view of the absence of these features from both Tsien and Seela, no combination of these references can render obvious the 7-deazaguanine deoxyribonucleotide analogue recited in claim 49.

- A. A fluorescent label (Tag) attached via a chemically cleavable, chemical linker (Y) to the 7-position of a deazaguanine deoxyribonucleotide analogue.

In the July 20, 2016 Office Action at the top of page 3, the Examiner acknowledged that Tsien does not disclose "deazaguanine as a base". This is correct. Tsien also does not disclose a label attached via a cleavable linker to the 7-position of a guanine. Tsien discloses attachment of a label to a purine at the "ideal" 8-position (page 29, lines 3-4; structure on page 30). Substituting deazaguanine for guanine would result in a deazaguanine with a label attached at the 8-position, not the claimed 7-deazaguanine with a label attached at the 7-position via a cleavable linker.

Turning to Seela, the Examiner asserts on page 3 of the July 20, 2016 Office Action that Seela "discloses nucleotides comprising 7-deazapurine base having a label attached via a linker. And that said nucleotide can be used in nucleic acid sequencing (see col 15-16)." This is not correct. Seela discloses the addition of a label to an oligonucleotide, not applicant's claimed 7-deazaguanine

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 4 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

deoxyribonucleotide analogue molecule which includes a label on the 7-deazaguanine (see col 15, line 64; col 16 line 65 - col 17, line 4). Formula VI of Seela does not encompass a 7-deazaguanine deoxyribonucleotide analogue having the structure Y-Tag attached at the 7-position of the deazaguanine. Seela's substituent R₁₅ in Formula VI is not a Y-Tag structure, and there is no disclosure in Seela of such a structure attached to the 7-position of a 7-deazaguanine deoxyribonucleotide analogue.

Since neither Tsien nor Seela discloses a 7-deazaguanine deoxyribonucleotide analogue with a fluorescent label attached at the 7-position of the 7-deazaguanine, let alone attached via a chemically cleavable linker, no combination of the disclosures of these references can render obvious applicant's claimed compound.

B. A small, chemically cleavable group (R) capping the oxygen at the 3' position of the deoxyribose of a 7-deazaguanine deoxyribonucleotide wherein the resulting structure OR is not a methoxy group or an ester group.

At the bottom of page 2 of the July 20, 2016 Office Action the Examiner stated that "Tsien disclose 3'-blocked DNTP compounds comprising fluorescent label and a blocking group that can be different than methoxy or ester (see pages 20-21, 24-25)." Although this statement is correct, Tsien does not disclose the species of blocking group recited in claim 49. Tsien does not disclose the requirement that the blocking group be small and in fact discloses that it can be large, including, for example, a fluorescent label or an enzyme. Moreover, Tsien does not require that the structure OR not be a methoxy group or an ester group. To the contrary, Tsien discloses that such groups may be used, disclosing methoxy on page 21, line 15 and esters as preferred blocking groups on page 21, lines 12-14 and 20-24. As discussed during the interview it is the inventors' insight and conception that R must be small and OR must not be either a methoxy group or an ester group that has resulted in a compound useful in sequencing by synthesis, namely, the compound

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 5 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

recited in claim 49. As further discussed during the interview, applicant discloses in the subject application small, cleavable ethers other than methoxy as examples of the OR structure needed to successfully accomplish sequencing by synthesis.

Turning to Seela, applicant notes that the R_{13} of Formula VI may be large such as C_{18} -alkoxy and can be a methoxy group (a C_1 -alkoxy - col 15, line 37). There is no disclosure in Seela that the capping group be small or that the structure OR not be a methoxy group or an ester group.

Importantly, and contrary to the Examiner's assertion in the July 20, 2016 Office Action that the compounds of Formula VI may be used in sequencing, Seela explicitly states that for sequencing R_{13} must be either H or OH (col 16, lines 45-46). Thus, Seela does not disclose a chemically cleavable group capping the 3'-O of the deoxyribose of a 7-deazaguanine deoxyribonucleotide analogue for use in sequencing as required by claim 49.

Since neither Tsien nor Seela disclose the species of R and of OR recited in claim 49, no combination of Tsien and Seela can render claim 49 obvious.

- C. The ability of a 7-deazaguanine deoxyribonucleotide with the features discussed in preceding sections A and B to:
1. be recognized as a substrate by a DNA polymerase;
 2. be incorporated at the end of a growing DNA strand during a polymerase reaction;
 3. produce a 3'-OH group on the deoxyribose upon cleavage of R;
 4. no longer include a tag on the base upon cleavage of Y; and
 5. be capable of forming hydrogen bonds with cytosine or a cytosine nucleotide analogue.

As discussed during the interview the provision of a nucleotide

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 6 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

having the five properties enumerated above is critical to enable sequencing by synthesis. Neither Tsien nor Seela disclose features required by claim 49 that result in a 7-deazaguanine deoxyribonucleotide analogue having the five properties recited in claim 49.

Tsien suggests the goal of sequencing by synthesis but fails to disclose features required to achieve the goal. Tsien also fails to disclose a chemical synthesis to make a nucleotide having the recited features.

Seela discusses sequencing only in two contexts: (a) Sanger sequencing using dideoxyribonucleotides as irreversible terminator or uncapped deoxyribonucleotides, neither of which are compatible with sequencing by synthesis or (b) sequencing using labeled oligonucleotide probes which are not useful for sequencing by synthesis. In contrast, applicant defines essential features of a nucleotide analogue required to achieve sequencing by synthesis and provides synthetic schemes to make such nucleotide analogues.

The lack of relevance of Seela is underscored by the fact that Formula VI relates only to nucleotides produced by adding triphosphates to previously known nucleosides (see col 17, lines 15-22). No nucleosides having the features of claim 49 are disclosed in the prior art. Furthermore, the lack of relevance of Seela is shown by the inclusion of alkynyl groups as possible R₁₅ groups. Such groups could only be cleaved by harsh conditions which would damage DNA and destroy the ability of the nucleotide compound to form hydrogen bonds with a cytosine or cytosine analogue (required property 5 of claim 49 discussed above).

Solely based on the lack of recited features in either Tsien or Seela the Examiner has not made out a prima facie showing of obviousness. Nevertheless, applicant comments on other shortcomings of the Examiner's prima facie case of obviousness.

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 7 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

II. Lack of Motivation.

On pages 3 and 4 of the July 20, 2016 Office Action the Examiner asserts that a motivation to combine the references and make the claimed compound is to avoid "band compression" associated with Sanger sequencing. However, the claimed compound is a reversible terminator, not an irreversible terminator, and a person skilled in the art would not have made the claimed compound to address "band compression", a phenomenon not relevant to sequencing by synthesis which does not involve the use of gel electrophoresis. Therefore, the motivation to avoid "band compression" would have led a skilled person to make an irreversible terminator, not the reversible terminator of claim 49.

A further reason given for combining the references is a quotation from Seela (col 16-17 bridging paragraph) which concerns adding a fluorescent label to an oligonucleotide synthesized using nucleotide analogues of Formula VI. This disclosure of the use of a labeled oligonucleotide would not provide a reason to place a fluorescent label on a 7-deazaguanine deoxyribonucleotide analogue at all, let alone via a cleavable linker.

Thus, the reasons given by the Examiner for combining Tsien and Seela to obtain the invention of claim 49 do not support doing so, a further flaw in the Examiner's prima facie case of obviousness.

III. Lack of Expectation of Success of Obtaining A Compound Having Claimed Properties (i) to (v).

The Examiner asserts simply that combining the cited references in the manner of the claims would achieve the expected benefits, optimizations and/or expanded applications as this is well known practice in the art. The question of reasonable expectation of success needs to be addressed by reference to the claimed invention

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

U.S. Serial No.: 15/167,917

Filed : May 27, 2016

Page 8 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

including particularly the five properties of the 7-deazadeoxyribonucleotide analogue recited in claim 49. There is no evidence that a person skilled in the art would, or could, have had a reasonable expectation that a compound having the features recited in claim 49 would have had each of the five properties recited in claim 49. Thus, once again there is a flaw in the Examiner's prima facie case of obviousness.

IV. Objective Indicia of Non-Obviousness.

Further support for the non-obviousness of the invention recited in claim 49 is provided by objective indicia of non-obviousness including long felt need, commercial success, praise, and unexpected results. By way of example, the 10-year gap between (1) the publication of Tsien suggesting the goal of sequencing by synthesis and a myriad of possible approaches to achieving this goal and (2) the filing of the subject application disclosing the first viable approach to actually performing sequencing by synthesis is clear evidence of long felt need and non-obviousness.


In summary, the Examiner has not made out a prima facie case of the obviousness of claim 49 and applicant respectfully requests that the Examiner reconsider and withdraw this rejection, the sole ground of rejection raised against claim 49.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

Applicant : The Trustees of Columbia University in the City
of New York
U.S. Serial No.: 15/167,917
Filed : May 27, 2016
Page 9 of 9 of Communication in Response to July 20, 2016 Office
Action and Summary of October 27, 2016 Interview with Examiner Riley

No fee is deemed necessary in connection with the filing of this
Communication. However, if any fee is required, authorization is
hereby given to charge the amount of any such fee to Deposit Account
No. 03-3125.

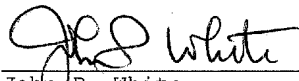
Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicant
Cooper & Dunham LLP
30 Rockefeller Plaza
20th Floor
New York, New York 10112
(212) 278-0400

Certificate of Transmission

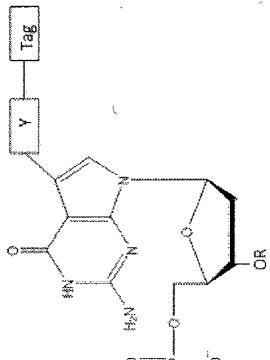

I hereby certify that this
correspondence is being
transmitted via the Electronic
Filing System (EFS) to the U.S.
Patent and Trademark Office on
November 4, 2016.



John P. White
Reg. No. 28,678

CLAIM CHART

October 26, 2016

62239-BZA7 Claim	Tsien	Seela
<p>A guanine deoxyribonucleotide analogue having the structure:</p> 	<p>No</p> <p>Does not disclose:</p> <ol style="list-style-type: none"> 1) a deazaguanine nucleotide 2) a 7-deazaguanine nucleotide 3) a purine labeled at the 7 position 4) a 7-deazaguanine labeled at the 7 position 	<p>No</p> <p>Discloses 7-deazaguanine and 8-deazaguanine nucleotide analogues.</p> <p>Contrary to the Examiner's assertion on page 3 of the Office Action, does not disclose a 7-deazaguanine nucleotide analogue containing the structure .</p>
<p>wherein R</p> <p>(a) represents a <u>small</u>, chemically cleavable chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide</p>	<p>No</p> <p>Does not mention, let alone require, a small R cap on the 3'-O.</p> <p>Discloses that R can be large, e.g., a fluorophore. (P. 26, L. 28-32).</p>	<p>No</p> <p>Does not require a small R cap on the 3'-O.</p> <p>Formula VI (referred to by the Examiner on page 3 of the Office Action) discloses large R caps on the 3'-O, e.g., C₁-C₁₈-alkoxy. (Col. 15, L. 37).</p> <p>For sequencing, discloses that there is no 3'-O cap R, stating there is a 3' H or OH (Col. 16, L. 45-46) which is in the passage cited by the Examiner.</p>
<p>(b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase</p>	<p>Yes¹</p> <p>Explicitly disclosed on P. 24, L. 1.</p>	<p>No</p> <p>Does not disclose use of a 3'-O cap R in sequencing; only 3'H or OH. (Col 16, L. 45-46).</p>
<p>(c) is stable during a DNA polymerase reaction</p>	<p>Yes¹</p> <p>Impliedly discloses this feature by disclosing that R (the 3'-O cap) is removed after incorporation of the nucleotide analogue. (P. 23, L. 28-32).</p>	<p>No</p> <p>Does not disclose use of a 3'-O cap R in sequencing; therefore does not disclose cap R must be stable during polymerase reaction.</p>

¹ Qualified by fact that reference doesn't disclose a compound having other features of the claimed structure or a rationale to use or achieve the specific feature in question

October 26, 2016

(d) does not contain a ketone group	No	Discloses an R containing a ketone -NHC(=O)CH ₃ . (P. 21, L. 15) ²	No	Does not disclose that R should not contain a ketone. (However, formula VI does not encompass any R containing a ketone.)
wherein OR is <u>not</u> a methoxy group	No	Discloses that OR may be methoxy. (P. 21, L. 15)	No	In formula VI, R may be methoxy. (Col. 15, L. 37, wherein R ¹³ of "formula VI" is a C ₁ -alkoxy).
or an ester group	No	Discloses that esters are among the most common R caps on 3'-Os (P. 21, L. 12-14) and that "preferred embodiments focus on ester blocking groups", suggesting several specific esters. (P. 21, L. 20-24).	No	Does not disclose that OR should not be an ester. (However, formula VI does not encompass an OR which is an ester.)
wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction	Yes ¹	Impliedly discloses this feature by disclosing removal of R (the 3'-O cap) after incorporating the nucleotide analogue into a growing strand. (P. 23, L. 28-32).	No	Does not disclose use of a 3'-O cap R in sequencing, only 3'H or OH. Therefore, does not disclose R must be stable during polymerase reaction.
wherein tag represents a detectable fluorescent moiety [as part of structure $\text{Y}-\text{Tag}$ attached to the 7-position of a deazaguanine nucleotide analogue]	No	Only discloses attaching fluorescent labels via linkers to the 8-position of non-deaza purine bases, referring to the 8-position as the "ideal position for attachment of a label." (P. 29, L. 3-4).	No	Does not disclose a label attached via a linker to the 7-position of a 7-deazaguanine nucleotide analogue; rather discloses a label can be attached to a substituent on the 7-position of a deazaguanine <u>after</u> <u>incorporation</u> of the nucleotide analogue into an oligonucleotide. (Col 16, L. 65 – Col. 17, L. 4).

¹ Qualified by fact that reference doesn't disclose a compound having other features of the claimed structure or a rationale to use or achieve the specific feature in question

² Assuming definition of a ketone is a carbonyl group present in a compound

October 26, 2016

wherein Y represents a chemically cleavable, chemical linker	No	Does not require that a linker Y be a chemically cleavable, chemical linker; only discloses that such a linker "can be cleavable if desired." (P. 28, L. 22)	No	Does not disclose a chemically cleavable, chemical linker at the 7-position of a deazaguanine as part of a $\boxed{Y}-\boxed{\text{Tag}}$ structure.
which (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase	Yes ¹	Discloses only that non-deaza nucleotide analogue labeled via a linker will not interfere with the action of a polymerase. (P. 28; L. 31-35).	No	Does not disclose a $\boxed{Y}-\boxed{\text{Tag}}$ structure on a 7-deazaguanine nucleotide analogue.
and (b) is stable during a DNA polymerase reaction	Yes ¹	Impliedly discloses that the linker attached to non-deaza base be stable during a polymerase reaction in that the linker survives a polymerase reaction and is removed prior to subsequent incorporations. (P. 28, L. 23-25).	No	Does not disclose a $\boxed{Y}-\boxed{\text{Tag}}$ structure on a 7-deazaguanine nucleotide analogue.
; and				
wherein the [7-deaza]guanine deoxyribonucleotide analogue:	No		No	
i) is recognized as a substrate by a DNA polymerase,	Does not disclose a 7-deazaguanine deoxyribonucleotide at all (let alone one containing the structure $\boxed{Y}-\boxed{\text{Tag}}$).	Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.	No	Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.
ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,	Does not disclose that DNA polymerase would recognize such an analogue.	Does not disclose that DNA polymerase would recognize such an analogue.	No	Does not disclose that DNA polymerase would recognize such an analogue.
	No	Does not disclose a 7-deazaguanine deoxyribonucleotide at all (let alone one containing the structure $\boxed{Y}-\boxed{\text{Tag}}$).	No	Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.
	Does not disclose incorporating such a nucleotide analogue at the end of a growing strand.	Does not disclose incorporation of such a nucleotide analogue at the end of a growing strand.	No	Does not disclose incorporation of such a nucleotide analogue at the end of a growing strand.

¹ Qualified by fact that reference doesn't disclose a compound having other features of the claimed structure or a rationale to use or achieve the specific feature in question

October 26, 2016

<p>iii) produces a 3'-OH group on the deoxyribose upon cleavage of R,</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide at all (let alone one containing the structure $\boxed{Y}-\boxed{\text{Tag}}$).</p> <p>Does not disclose producing a 3'-OH group on such an analogue upon cleavage of R.</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.</p> <p>Does not disclose producing a 3'-OH group on such a compound upon cleavage of R.</p>
<p>iv) no longer includes a tag on the base upon cleavage of Y, and</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide at all (let alone one containing the structure $\boxed{Y}-\boxed{\text{Tag}}$).</p> <p>Does not disclose what would happen upon cleavage of a linker Y attached to such an analogue</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.</p> <p>Does not disclose what would happen upon cleavage of a linker Y attached to such an analogue.</p>
<p>v) is capable of forming hydrogen bonds with cytosine or a cytosine nucleotide analogue.</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide at all (let alone one containing the structure $\boxed{Y}-\boxed{\text{Tag}}$).</p> <p>Does not disclose the ability of such an analogue to form hydrogen bonds with cytosine or a cytosine analogue.</p>	<p>No</p> <p>Does not disclose a 7-deazaguanine deoxyribonucleotide analogue containing the structure $\boxed{Y}-\boxed{\text{Tag}}$.</p> <p>Does not disclose the ability of such an analogue to form such hydrogen bonds with cytosine or a cytosine analogue.</p>

¹ Qualified by fact that reference doesn't disclose a compound having other features of the claimed structure or a rationale to use or achieve the specific feature in question