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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
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Conf. No.	:	1260	
For	:	MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA	

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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.

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

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

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 R_{15} 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

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

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