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08/03/06

(Also referred to as FORM PTO-1465)

REQUEST FOR EX PARTE REEXAMINATION TRANSMITTAL FORM

71338 U.S. PTO

90008152

Address to:
Mail Stop Ex Parte Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket No.: None

Date: August 4, 2006



08/03/06

1. ☒ This is a request for *ex parte* reexamination pursuant to 37 CFR 1.510 of patent number 6,232,465 issued MAY 15, 2001. The request is made by:

☐ patent owner.
 ☒ third party requester.
2. ☒ The name and address of the person requesting reexamination is:

Howard M. Gitten
Edwards Angell Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150
Ft. Lauderdale, FL ~~33331~~ 33301
3. ☐ a. A check in the amount of \$_____ is enclosed to cover the reexamination fee, 37 CFR 1.20(c)(1);
☒ b. The Director is hereby authorized to charge the fee as set forth in 37 CFR 1.20(c)(1) to Deposit Account No. 04-1105 (submit duplicative copy for fee processing); or
☐ c. Payment by credit card. Form PTO-2038 is attached.
4. ☒ Any refund should be made by ☐ check or ☒ credit to Deposit Account No. 04-1105 37 CFR 1.26(c). If payment is made by credit card, refund must be to credit card account.
5. ☒ A copy of the patent to be reexamined having a double column format on one side of a separate paper is enclosed. 37 CFR 1.510(b)(4)
6. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
☐ Landscape Table on CD
7. ☒ Nucleotide and/or Amino Acid Sequence Submission
If applicable, items a. - c. are required.
 - a. ☒ Computer Readable Form (CRF)
 - b. Specification Sequence Listing on:
 - i. ☐ CD-ROM (2 copies) or CD-R (2 copies); or
 - ii. ☒ paper
 - c. ☒ Statements verifying identity of above copies
8. ☒ A copy of any disclaimer, certificate of correction or reexamination certificate issued in the patent is included.
9. ☒ Reexamination of claim(s) 1, 2, 3, 4, 5, and 6 is requested.
10. ☒ A copy of every patent or printed publication relied upon is submitted herewith including a listing thereof on Form PTO/SB/08, PTO-1449, or equivalent.
11. ☐ An English language translation of all necessary and pertinent non-English language patents and/or printed publications is included.

08/10/2006 JMCDOUSA200000001 041105

90008152

[Page 1 of 2]

This collection of information is required by 37 CFR 1.510. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Ex Parte Reexam, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. If you need assistance in completing the form, call 1-800-PTO-9199

Columbia Exhibit 2065

Illumina, Inc. v. The Trustees
of Columbia University in the
City of New York
IPR2018-00291, 318, 322 & 385

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2. ☒ The name and address of the person requesting reexamination is:

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6. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
☐ Landscape Table on CD
7. ☒ Nucleotide and/or Amino Acid Sequence Submission
If applicable, items a. - c. are required.
 - a. ☒ Computer Readable Form (CRF)
 - b. Specification Sequence Listing on:
 - i. ☐ CD-ROM (2 copies) or CD-R (2 copies); or
 - ii. ☒ paper
 - c. ☒ Statements verifying identity of above copies
8. ☒ A copy of any disclaimer, certificate of correction or reexamination certificate issued in the patent is included.
9. ☒ Reexamination of claim(s) 1, 2, 3, 4, 5, and 6 is requested.
10. ☒ A copy of every patent or printed publication relied upon is submitted herewith including a listing thereof on Form PTO/SB/08, PTO-1449, or equivalent.
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12. ☒ The attached detailed request includes at least the following items:

- a. A statement identifying each substantial new question of patentability based on prior patents and printed publications. 37 CFR 1.510(b)(1)
- b. An identification of every claim for which reexamination is requested, and a detailed explanation of the pertinency and manner of applying the cited art to every claim for which reexamination is requested. 37 CFR 1.510(b)(2)

13. ☐ A proposed amendment is included (only where the patent owner is the requester). 37 CFR 1.510(e)14. ☒ a. It is certified that a copy of this request (if filed by other than the patent owner) has been served in its entirety on the patent owner as provided in 37 CFR 1.33(c).

The name and address of the party served and the date of service are:

Lerner, David, Littenberg, Krumholz & Mentlik600 South Avenue WestWestfield, NJ 07090Date of Service: August 4, 2006; or☐ b. A duplicate copy is enclosed since service on patent owner was not possible.

15. Correspondence Address: Direct all communication about the reexamination to:

☐ The address associated with Customer Number:

OR

☒ Firm or Individual Name Howard M. GittenAddress Edwards Angell Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150City Ft. LauderdaleState FLZip 33331 33301Country USATelephone 954-667-6130Email hgitten@eapdlaw.com16. ☐ The patent is currently the subject of the following concurrent proceeding(s):

- ☐ a. Copending reissue Application No. _____
- ☐ b. Copending reexamination Control No. _____
- ☐ c. Copending Interference No. _____
- ☐ d. Copending litigation styled: _____

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Howard M. Gitten
Authorized SignatureAUGUST 4, 2006
DateHoward M. Gitten
Typed/Printed Name32,138
Registration No.☐ For Patent Owner Requester
☒ For Third Party Requester



08/03/06

Express
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ED 332072 925 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

71338 U.S. PTO
90008152

08/03/06

PATENTEE: Hiatt et al.

SERIAL NO.: 08/486,536

PATENT NO.: 6,232,465

FILING DATE: June 7, 1995

ISSUE DATE: May 15, 2001

TITLE: *Composition for Enzyme Catalyzed Template-Independent Creation of Phosphodiester Bonds Using Protected Nucleotides*

Mail Stop Ex Parte Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR EX PARTE REEXAMINATION PURSUANT TO 37 C.F.R. § 1.510

Reexamination under 35 U.S.C. §§ 302 - 307 and 37 C.F.R. § 1.510 is requested of United States Patent Number 6,232,465, which issued on May 15, 2001, to Hiatt, *et al.* (hereinafter the "'465 patent").

Pursuant to 37 C.F.R. § 1.510(a), the Director is hereby authorized and requested to charge Deposit Account No. 04-1105 in the amount of \$2,520.00 to cover the reexamination fee prescribed by 37 C.F.R. § 1.20(c)(1). If for any reason the fee paid is inadequate or credit is owed for any excess fee paid, the Director is hereby authorized and requested to charge or make deposit to Deposit Account No. 04-1105 as appropriate.

SUMMARY OF THIS REEXAMINATION REQUEST

Pursuant to 37 C.F.R. §§ 1.510(b)(1) and (b)(2), reexamination of *all of the claims* of the '465 patent is hereby requested. Substantial new questions of patentability exist for *all of the claims* of the '465 patent, including independent claims 1, 2, 5, and 6 from which all of the other

claims depend, in light of the prior art patents and printed publications listed below.

The substantial new questions of patentability are summarized as follows, and the roman numerals used immediately below (i.e., I, II, III, IV, V and VI) are used hereinafter to identify the corresponding more detailed sections of this request.

(I) Claims 1-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the prior art printed publication International Patent Application WO 91/06678 to Tsien, *et al.* (the "Tsien PCT application").

(II) Claims 1-3 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the prior art printed publication of A.A. Kraevskii *et al.*, *Molecular Biology* 21:25-29 (1987) (the "Kraevskii publication").

(III) Claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the prior art patent U.S. Patent No. 4,711,955 to Ward, *et al.* (the "Ward patent").

(IV) Claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the prior art printed publication International Patent Application WO 92/10587 to Dower, *et al.* (the "Dower PCT application").

(V) Claims 1-4 of the '465 patent would have been obvious under 35 U.S.C. §103(a) in view of the prior art patents or printed publications (i) International Patent Application WO 91/06678 to Tsien, *et al.* (the "Tsien PCT application") and/or (ii) International Patent Application WO 92/10587 to Dower, *et al.* (the "Dower PCT application") and/or (iii) U.S. Patent No. 4,711,955 to Ward, *et al.* (the "Ward patent") and/or (iv) the prior art printed publication of A.A. Kraevskii *et al.*, *Molecular Biology* 21:25-29 (1987) (the "Kraevskii publication").

(VI) Claims 5-6 of the '465 patent would have been obvious under 35 U.S.C. §103(a) in view of the prior art patents or printed publications (i) International Patent Application WO 91/06678 to Tsien, *et al.* (the "Tsien PCT application") and/or (ii) International Patent Application WO 92/10587 to Dower, *et al.* (the "Dower PCT application"), optionally further in view of the prior art patent U.S. Patent No. 4,711,955 to Ward, *et al.* (the "Ward patent") and/or the prior art printed publication of A.A. Kraevskii *et al.*, *Molecular Biology* 21:25-29 (1987) (the "Kraevskii publication").

Pursuant to 37 C.F.R. §1.510(b)(3), enclosed herewith is a copy of each of the below-listed prior art printed publications and patents.

International Patent Application WO 91/06678 to Tsien, *et al.* (the "Tsien PCT application");

International Patent Application WO 92/10587 to Dower, *et al.* (the "Dower PCT application");

U.S. Patent No. 4,711,955 to Ward, *et al.* (the "Ward patent");

A.A. Kraevskii *et al.*, *Molecular Biology* 21:25-29 (1987); and

Henner *et al.*, *Journal of Biological Chemistry*, 258:15198-15205 (1983).

The '465 patent issued from U.S. patent application Serial No. 08/486,536 (the "'536 application"). The '536 application is a continuation-in-part of U.S. patent application Serial No. 08/300,484 ("the '484 application"), filed September 2, 1994 (and which issued as U.S. Patent No. 5,990,300). The earliest possible filing date to which the claims of the '465 patent may be entitled is therefore September 2, 1994¹.

¹ It is not conceded, however, that any claim of the '465 patent is enabled by either the '536 application or the '484 application, or that any claim would have been entitled to a priority date of September 2, 1994.

I. FIRST SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 1-4 of the '465 patent in view of International Patent Application WO 91/06678 to Tsien, *et al.* (the "Tsien PCT application").

B. DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 1-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the Tsien PCT application. Claims 1-4 of the '465 patent are set forth in the following chart along with a side-by-side explanation of how the Tsien PCT application disclosed all the recited features of the claims. For ease of reference, paragraphing and other formatting has been added to the claims of the '465 patent².

² In this chart (and all other charts in this Request), the claims are set forth as corrected by Certificate of Correction dated February 19, 2002 (a copy of which is enclosed herewith).

CHART COMPARING CLAIMS 1-4 WITH THE TSIEN PCT APPLICATION

U.S. PATENT NUMBER 6,232,465	International Patent Application WO 91/06678 to Tsien
Claim of the '465 patent	Tsien PCT application disclosure
1. A nucleoside 5'-triphosphate	The Tsien PCT application describes methods for determining the sequence of deoxyribonucleotides within DNA molecules. (Tsien PCT application, Abstract).
having a removable blocking moiety protecting the 3' position	<p>The Tsien PCT application discloses "3' hydroxyl-blocked dNTPs [deoxynucleotide triphosphates]." (Tsien PCT application, page 20, lines 25-26).</p> <p>The Tsien PCT application discloses that "[t]he criteria for the successful use of 3'-blocking groups include: [. . .] (2) the availability of mild conditions for rapid and quantitative deblocking, and (3) the ability of a polymerase enzyme to reinitiate the cDNA synthesis subsequent to the deblocking stage." (Tsien PCT application, page 21, line 28 through page 22, line 3).</p> <p>The Tsien PCT application discloses that the 3'-blocked dNTPs are easily deblocked to yield a viable 3'-OH terminus. (Tsien PCT application, page 21, lines 9-12).</p>
which is a hydrocarbyl	The Tsien PCT application discloses that "the most common 3'-hydroxyl blocking groups are esters and ethers" and that modifications to the 3'-OH include -OCH ₃ . (Tsien PCT application, page 21, lines 9-17). At the least, ethers are hydrocarbyl groups under the '465 patent definition of that term.
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Tsien PCT application discloses "3' hydroxyl-blocked dNTPs [deoxynucleotide triphosphates]." (Tsien PCT application, page 20, lines 25-26).
2. A nucleoside 5'-triphosphate	The Tsien PCT application describes methods for determining the sequence of deoxyribonucleotides within DNA molecules. (Tsien PCT application, Abstract).

U.S. PATENT NUMBER 6,232,465	International Patent Application WO 91/06678 to Tsien
Claim of the '465 patent	Tsien PCT application disclosure
having a removable blocking moiety protecting the 3' position	<p>The Tsien PCT application discloses “3’ hydroxyl-blocked dNTPs.” (Tsien PCT application, page 20, lines 25-26).</p> <p>The Tsien PCT application discloses that “[t]he criteria for the successful use of 3’-blocking groups include: [. . .] (2) the availability of mild conditions for rapid and quantitative deblocking, and (3) the ability of a polymerase enzyme to reinitiate the cDNA synthesis subsequent to the deblocking stage.” (Tsien PCT application, page 21, line 28 through page 22, line 3).</p> <p>The Tsien PCT application discloses that the 3’-blocked dNTPs are easily deblocked to yield a viable 3’-OH terminus. (Tsien PCT application, page 21, lines 9-12).</p>
which is selected from the group consisting of an ester, an ether, and a phoshate [sic],	The Tsien PCT application discloses that “the most common 3’-hydroxyl blocking groups are esters and ethers” and that modifications to the 3’-OH include -OCH ₃ , and -OPO ₃ ²⁻ . (Tsien PCT application, page 21, lines 9-17).
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Tsien PCT application discloses “3’ hydroxyl-blocked dNTPs [deoxynucleotide triphosphates].” (Tsien PCT application, page 20, lines 25-26).
3. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U).	The Tsien PCT application discloses that “dNTP” is an abbreviation of deoxynucleotide triphosphate and includes the deoxynucleotide triphosphates dATP, dCTP, dGTP, and dTTP, depending on whether the base portion of the nucleotide is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. (Tsien PCT application, page 9, line 32 through page 10, line 1).
4. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said removable blocking moiety is enzymatically removable.	The Tsien PCT application discloses that “[e]nzymatic deblocking of the 3’-OH blocking groups is also possible.” (Tsien PCT publication, page 25, lines 13-14).

C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

1. The Tsien PCT Application Raises a Substantial New Question of Patentability Because the Tsien PCT Application Disclosed Compounds Meeting the Limitations of Claims 1-4 of the '465 Patent.

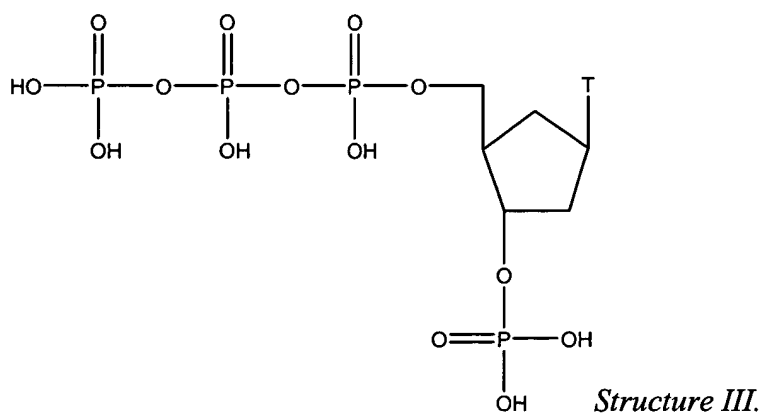
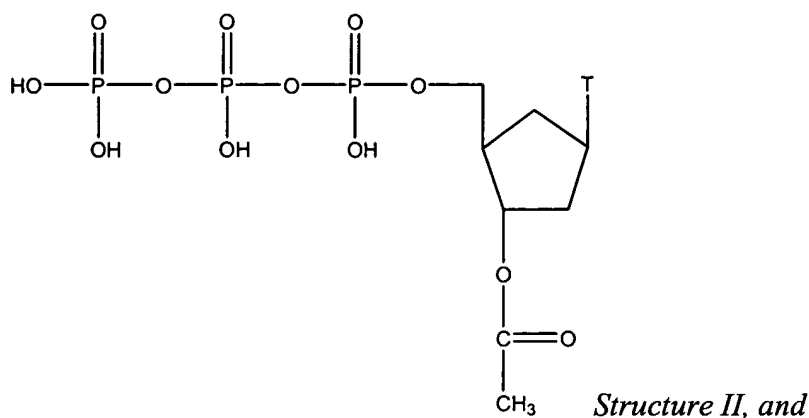
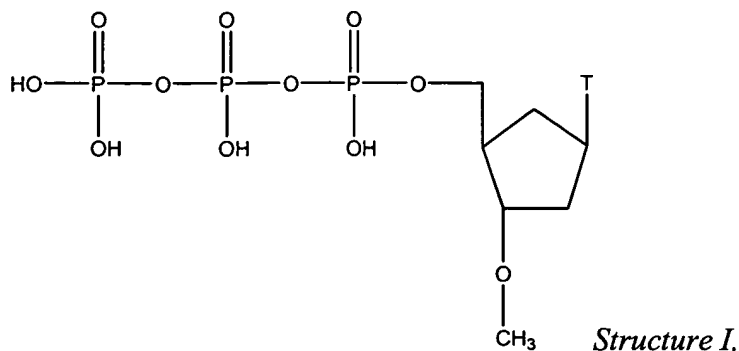
The Tsien PCT application was published on May 16, 1991, more than one year before the filing date of the '465 patent. The Tsien PCT application raises a substantial new question of patentability as to at least claims 1-4 of the '465 patent and, in particular, independent claims 1 and 2 (and dependent claims 3-4) of the '465 patent for the reasons given below.

As can be seen from the claim chart above, and as further discussed below, *all of the elements* of claims 1-4 were disclosed in the Tsien PCT application, as indicated in the right hand column of the chart.

1. Independent Claims 1 and 2

The '465 patent defines "nucleotide" as "[a] subunit of a nucleic acid comprising a phosphate group, a five-carbon sugar, and nitrogen containing base." ('465 patent, Col. 5, lines 61-63). The Tsien PCT application describes methods for determining the sequence of deoxyribonucleotides within DNA molecules. (Tsien PCT application, Abstract). According to the Tsien PCT application, the sequence of deoxyribonucleotides is determined using a polymerase and four labeled dNTPs, where the labeled dNTPS are blocked at the 3' position with a removable blocker. (Tsien PCT application, page 10, lines 1-4, and page 12, lines 11-23).

The Tsien PCT application also discloses at least the following compounds:



a) Nucleoside 5'-Triphosphate

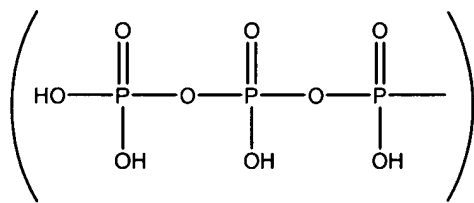
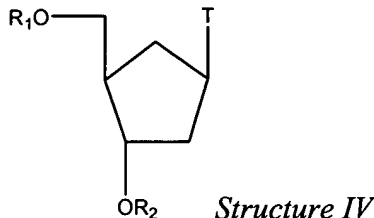
The published Tsien PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent claims (see, e.g., the Tsien PCT application at page 9, lines 35-36 and page 21, lines 9-31). As discussed in the Tsien PCT application, "dNTP" is an abbreviation of deoxynucleotide triphosphate and includes the deoxynucleotide triphosphates dATP, dCTP, dGTP, and dTTP, depending on whether the base portion of the nucleotide is

adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. (Tsien PCT application, page 9, line 32 through page 10, line 1).

Further, the Tsien PCT application discloses the compounds 3'-PO₃ thymidine triphosphate (see Example 1 of the Tsien PCT application) and a 3'-labelled (fluorescent) thymidine triphosphate (see Example 2 of the Tsien PCT application).

In addition, the Tsien PCT publication describes the structures of Figures 5 and 6 as deoxynucleotide triphosphates (dNTPs) and defines "T" as thymidine. (Tsien PCT application, page 22, line 1 through page 23, line 21 and page 9, lines 32-35).

Still further, the Tsien PCT application discloses the following structure:



where R₁ is P₃O₉H₄

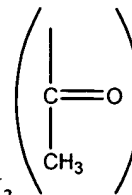
(Tsien PCT application, Figures 5 and

6).

Therefore, the Tsien PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent and claimed in independent claims 1 and 2.

b) Removable Blocking Moiety

The Tsien PCT application discloses "3' hydroxyl-blocked dNTPs." (Tsien PCT application, page 20, lines 25-26). The Tsien PCT application discloses that "the most common 3'-hydroxyl blocking groups are esters and ethers" and that modifications to the 3'-OH include -OCH₃, and -OPO₃²⁻ (phosphate). (Tsien PCT application, page 21, lines 9-17). In addition, the



Tsien PCT application discloses that R₂ of Structure VI can be COCH₃ (Tsien PCT application, Figure 5). As shown in Structures I and II, above, the –O-CH₃ group forms an ether with the 3' position of the nucleotide 5'-triphosphate and the COCH₃ group forms an ester.

The '465 patent defines "hydrocarbyl" as follows:

Hydrocarbyl: An organic radical composed of carbon and hydrogen which may be aliphatic (including alkyl, alkenyl, and alkynyl groups and groups which have a mixture of saturated and unsaturated bonds), alicyclic (carbocyclic), aryl (aromatic) or combination thereof; and may refer to straight-chained, branched-chain, or cyclic structures or to radicals having a combination thereof, as well as to radicals substituted with halogen atom(s) or heteroatoms, such as nitrogen, oxygen, and sulfur and their functional groups (such as amino, alkoxy, aryloxy, lactone groups and the like), which are commonly found in organic compounds and radicals.

'465 Patent at Col. 6, lines 25-36. A methyl group is a well-known example of an alkyl group, and the '465 patent specifically discloses that a hydrocarbyl group can be alkyl ('465 Patent at Col. 6, line 26).

Therefore, the Tsien PCT application discloses a removable blocking moiety protecting the 3' position which is hydrocarbyl linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 1 and discloses ester, ether, and phosphate blocking moieties protecting the 3' position and linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 2.

The blocking moieties disclosed in the Tsien PCT application are removable. The Tsien PCT application discloses that "[t]he criteria for the successful use of 3'-blocking groups include: [. . .] (2) the availability of mild conditions for rapid and quantitative deblocking, and (3) the ability of a polymerase enzyme to reinitiate the cDNA synthesis subsequent to the deblocking stage." (Tsien PCT application, page 21, line 28 through page 22, line 3). In addition, the Tsien PCT application discloses that the 3'-blocked dNTPs are easily deblocked to yield a viable 3'-OH terminus. (Tsien PCT application, page 21, lines 8-12).

Example 1 of the Tsien PCT application discloses a synthetic pathway to 3'-blocked dNTPs (see the Tsien PCT application at pages 35-36). Examples 5 and 6 of the Tsien PCT application describe the chemical and enzymatic removal of 3'-blocking moieties (see the Tsien PCT application at pages 38-40).

Accordingly, independent claims 1 and 2 of the '465 patent are invalid under 35 U.S.C. § 102(b) because the removable blocking moieties disclosed in the Tsien PCT application include hydrocarbyl and ether, ester, and phosphate moieties that are linked to the 3' carbon of the nucleoside 5'-triphosphate. Therefore, the Tsien PCT application discloses nucleoside 5'-triphosphates that have at least one of the removable blocking moieties protecting the 3' position that is claimed in each of independent claims 1 and 2 of the '465 patent.

2. Dependent Claims 3 - 4

Dependent claim 3 further limits independent claim 1 or 2, and requires that the nucleoside contain a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U). The Tsien PCT application discloses that "dNTP" is an abbreviation of deoxynucleotide triphosphate and includes the deoxynucleotide triphosphates dATP, dCTP, dGTP, and dTTP, depending on whether the base portion of the nucleotide is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. (Tsien PCT application, page 9, line 32 through page 10, line 1). Therefore, the Tsien PCT application discloses a nucleoside 5'-triphosphate that includes every element of dependent claim 3.

Dependent claim 4 further limits independent claim 2, and requires that the removable blocking moiety be enzymatically removable. The Tsien PCT application discloses that "[e]nzymatic deblocking of the 3'-OH blocking groups is also possible." (Tsien PCT publication, page 25, lines 13-14). According to the Tsien PCT application, T4 polynucleotide kinase converts 3'-phosphate termini to 3'-hydroxyl termini, and that this phenomenon was published as early as 1983 (Tsien PCT application, page 25, lines 14-17). Furthermore, the Tsien PCT application discloses a method for using T4 polynucleotide kinase to remove a 3'-phosphate blocking group from nucleotide. (Tsien PCT application, page 39, lines 11-22). Therefore, the Tsien PCT application discloses a nucleoside 5'-triphosphate that includes every element of

dependent claim 4.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, at least claims 1-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) by the Tsien PCT application. Consequently, the Tsien PCT application raises a substantial new question of patentability of claims 1-4 of the '465 patent.

II. SECOND SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 1-3 of the '465 patent in view of the prior art publication of A.A. Kraevskii *et al.*, *Molecular Biology* 21:25-29 (1987) (the "Kraevskii publication").

B. DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 1-3 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the Kraevskii publication. Claims 1-3 of the '465 patent are set forth in the following chart along with a side-by-side explanation of how the Kraevskii publication disclosed all the recited features of the claims. For ease of reference, paragraphing and other formatting has been added to the claim of the '465 patent.

CHART COMPARING CLAIM 1 WITH THE KRAEVSKII PUBLICATION

U.S. PATENT NUMBER 6,232,465	A.A. Kraevskii et al., <i>Molecular Biology</i> <u>21</u>:25-29 (1987)
Claim of the '465 patent	Kraevskii Publication disclosure
1. A nucleoside 5'-triphosphate	The Kraevskii publication discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Kraevskii publication discloses a series of dNTPs. The term "dNTP" is a conventional abbreviation for a deoxynucleotide triphosphate.
having a removable blocking moiety protecting the 3' position	The Kraevskii publication discloses deoxynucleotide triphosphate chain terminators including 3'-O-methyl-dNTP.
which is a hydrocarbyl	The Kraevskii publication discloses 3'-O-methyl-dNTP (Kraevskii publication, page 27 and Table 1). The 3'-O-methyl group is a methyl ether. A methyl group is a hydrocarbyl according the '465 patent definition of that term.
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Kraevskii publication discloses "3'-O-methyl-dNTP" (Kraevskii publication, page 27 and Table 1). The 3'-O-methyl group is linked to the 3' carbon of the nucleoside 5'-triphosphate.
2. A nucleoside 5'-triphosphate	The Kraevskii publication discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. The term "dNTP" is a conventional abbreviation for a deoxynucleotide triphosphate.
having a removable blocking moiety protecting the 3' position	The Kraevskii publication discloses deoxynucleotide triphosphate chain terminators including 3'-O-methyl-dNTP.
which is selected from the group consisting of an ester, an ether, and a phoshate [sic],	The Kraevskii publication discloses 3'-O-methyl-dNTP (Kraevskii publication, page 27 and Table 1). The 3'-O-methyl group is a methyl ether.
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Kraevskii publication discloses "3'-O-methyl-dNTP" (Kraevskii publication, page 27 and Table 1). The 3'-O-methyl group is linked to the 3' carbon of the nucleoside 5'-triphosphate
3. A nucleoside 5'-triphosphate	The term "dNTP" is a well-known abbreviation of

U.S. PATENT NUMBER 6,232,465	A.A. Kraevskii et al., <i>Molecular Biology</i> <u>21</u>:25-29 (1987)
Claim of the '465 patent	Kraevskii Publication disclosure
of claim 1 or 2 wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U).	deoxynucleotide triphosphate and includes deoxynucleotide triphosphates in which the base is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. (See, e.g., the Tsien PCT application, page 9, line 32 through page 10, line 1).

C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

1. The Kraevskii Publication Raises a Substantial New Question of Patentability Because the Kraevskii Publication Disclosed Compounds Meeting the Limitations of Claim 1 of the '465 Patent.

The Kraevskii Publication was published in 1987, more than one year before the filing date of the '465 patent. The Kraevskii Publication raises a substantial new question of patentability as to at least claims 1-3 of the '465 patent because as shown in the claim chart above, and as further discussed below, *all of the elements* of claims 1-3 were disclosed in the Kraevskii Publication, as indicated in the right hand column of the chart.

The Kraevskii Publication describes substrate analogs which are inhibitors of DNA biosynthesis. (Kraevskii Publication, Abstract). The Kraevskii Publication discloses at least the compound 3'-O-methyl-dNTP which includes all of the limitations of independent claims 1-3.

1. Independent Claims 1 and 2

The '465 patent defines "nucleotide" as "[a] subunit of a nucleic acid comprising a phosphate group, a five-carbon sugar, and nitrogen containing base." ('465 patent, Col. 5, lines 61-63). The Kraevskii Publication describes substrate analogs which are inhibitors of DNA biosynthesis. (Kraevskii Publication, Abstract). The Kraevskii Publication describes substrate analogs which are inhibitors of DNA biosynthesis. (Kraevskii Publication, Abstract). The

Kraevskii Publication discloses at least the compound 3'-O-methyl-dNTP.

1. Nucleoside 5'-Triphosphate

The Kraevskii Publication discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Kraevskii Publication discloses "substrate analogs" including ddNTPs and dNTPs (Kraevskii Publication, page 27, Table 1). The terms "ddNTP" and "dNTP" are conventional abbreviations for "dideoxynucleoside 5'-triphosphate" and "deoxynucleoside 5'-triphosphate," respectively. Therefore, the Kraevskii Publication discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent.

2. Removable Blocking Moiety

The Kraevskii Publication discloses deoxynucleotide triphosphate substrate analogs including "3'-O-methyl-dNTP" (Kraevskii Publication, page 27, Table 1). This compound is a dNTP having a methyl ether on the 3' hydroxyl group. According to the '465 patent, removable blocking moieties for protecting the 3' position include ethers, including methyl ether (see, e.g., the '465 patent at Col. 12, line 14 to Col. 13, line 11).

Therefore, the Kraevskii Publication discloses a removable blocking moiety protecting the 3' position which is hydrocarbyl (a methyl ether) linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 1 of the '465 application, and discloses an ester, ether, or phosphate blocking moieties protecting the 3' position and linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 2.

Accordingly, independent claims 1 and 2 of the '465 patent are invalid under 35 U.S.C. § 102(b) because the removable blocking moieties disclosed in the Kraevskii Publication include hydrocarbyl and ether, ester, and phosphate moieties that are linked to the 3' carbon of the nucleoside 5'-triphosphate. Therefore, the Kraevskii Publication discloses nucleoside 5'-triphosphates that have at least one of the removable blocking moieties protecting the 3' position that is claimed in each of independent claims 1 and 2 of the '465 patent.

2. Dependent Claim 3

Dependent claim 3 further limits independent claim 1 or 2, and requires that the nucleoside contain a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U). The Kraevskii Publication discloses that dNTPs. The term “dNTP” is a well-known abbreviation of deoxynucleotide triphosphate and includes the deoxynucleotide triphosphates dATP, dCTP, dGTP, and dTTP, depending on whether the base portion of the nucleotide is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. (See, e.g., the Tsien PCT application, page 9, line 32 through page 10, line 1³). Therefore, the Kraevskii Publication discloses a nucleoside 5'-triphosphate that includes every element of dependent claim 3.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, at least claims 1-3 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) by the Kraevskii Publication. Consequently, Kraevskii Publication raises a substantial new question of patentability of claim 1 of the '594 patent.

³ The Tsien PCT application is cited in this context only to demonstrate that the Kraevskii Publication fully discloses dNTPs as claimed in the '465 patent. See, e.g., MPEP 2131.01 and In re Baxter Travenol Labs, 952 F.2d 388, 21 USPQ2d 1281 (1991) ("Extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.")

III. THIRD SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 2-4 of the '465 patent in view of U.S. Patent No. 4,711,955 to Ward *et al.* (the “Ward patent”).

B. DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the Ward patent. Claims 2-4 of the '465 patent are set forth in the following chart along with a side-by-side explanation of how the Ward patent disclosed all the recited features of the claim. For ease of reference, paragraphing and other formatting has been added to the claim of the '465 patent.

CHART COMPARING CLAIMS 2-4 OF THE '934 WITH THE WARD PATENT

U.S. PATENT NUMBER 6,232,465	U.S. Patent No. 4,711,955 to Ward <i>et al.</i>
Claim of the '465 patent	Ward patent disclosure
2. A nucleoside 5'-triphosphate	The Ward patent discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent.
having a removable blocking moiety protecting the 3' position	The Ward patent discloses 3'-phosphate blocking moieties, which are removable.
which is selected from the group consisting of an ester, an ether, and a phoshate [sic],	<p>The Ward patent discloses the following chemical structure that includes a 5-carbon sugar:</p> <div style="text-align: center;"> <p><i>Structure XIV</i></p> </div> <p>Referring to Structure XIV, above, the Ward patent teaches that "y" (the moiety attached to the 3' position) can be "either mono-, di-, or triphosphate." (Ward patent, col. 9, lines 56-57).</p>
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Ward patent teaches that "y" can be "either mono-, di-, or triphosphate." (Ward patent, col. 9, lines 56-57). The "y" group is linked to the 3' position of the nucleoside 5'-triphosphate.
3. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U).	The term "dNTP" is a well-known abbreviation of deoxynucleotide triphosphate and includes deoxynucleotide triphosphates in which the base is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. The Ward patent discloses that "preferred bases [of the nucleotide] are cytosine [and] uracil." (Ward patent at Col. 8, lines 8-9).
4. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said removable blocking moiety is enzymatically removable.	Referring to Structure XIV, above, the Ward patent teaches that "y" (the moiety attached to the 3' position) can be "either mono-, di-, or triphosphate." (Ward patent, col. 9, lines 56-57). A phosphate group is enzymatically removable.

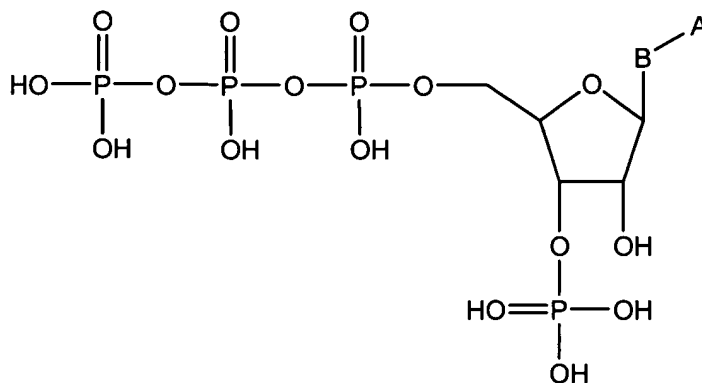
C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

1. The Ward Patent Raises a Substantial New Question of Patentability Because the Ward Patent Disclosed Compounds Meeting the Limitations of Claims 2-4 of the '465 Patent.

The Ward patent issued on December 8, 1987, more than one year before the earliest priority date of the '465 patent. The Ward patent raises a substantial new question of patentability as to at least claims 2-4 of the '465 patent for the reasons given below.

As can be seen from the claim chart above, and as further discussed below, all of the elements of claims 2-4 were disclosed in the Ward patent, as indicated in the right hand column of the chart.

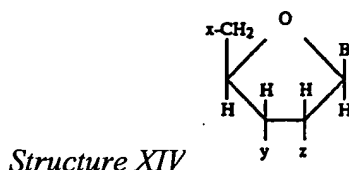
The Ward patent discloses the following compound, which includes each and every limitation of independent claim 2:



Structure XIII

a) Nucleoside 5'-Triphosphate

The Ward patent discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent and claimed in independent claims 1 and 2. Specifically, the Ward patent discloses the following chemical structure that includes a 5-carbon sugar:



The Ward patent teaches that B can represent purine, 7-deazapurine, or pyrimidine covalently bonded to the C^{1'}-position of the sugar moiety. (Ward patent, col. 7, lines 27-57). As described above, the bases C, T, and U are pyrimidines, and the bases A and G are purines. Thus, the Ward patent teaches the same bases that are included in the term “nucleoside” as defined in the ‘465 patent. In addition, the Ward patent teaches that both “y” and “z” can be -H or -OH. (Col. 7, lines 46-50). A five carbon sugar where “y” and “z” are -OH is known as ribose, and a five carbon sugar shown where “y” is -OH and “z” is H is known as 2'-deoxyribose. Thus, the Ward patent teaches the same 5-carbon sugars included in the term “nucleoside” as defined in the ‘465 patent.

Furthermore, the Ward patent teaches that “x” can represent a number of different moieties, including “mono-, di-, or triphosphate.” (Ward patent, col. 9, lines 56-57). Therefore, the Ward patent discloses nucleosides that include nucleoside 5'-triphosphates as defined in the ‘465 patent and claimed in independent claim 2.

b) Removable Blocking Moiety

Referring to Structure XIV, above, the Ward patent teaches that “y” can be “mono-, di-, or triphosphate.” (Ward patent, col. 9, lines 56-57). As shown in Structure XIV (above), “y” is linked to the 3' carbon of the nucleoside 5'-triphosphate. Therefore, the Ward patent discloses a blocking moiety (phosphate) linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 2 of the '465 patent.

It is well known that 3' terminal phosphate groups can be removed from nucleosides using enzymes such as T4 polynucleotide kinase (see, e.g., Henner, *et al.* Journal of Biological Chemistry, 258:15198-15205, 1983 (cited in the Tsien PCT application); Carmeron, *et al.*, Nucleic Acids Research, 5:825-833, 1978).

Accordingly, at least independent claim 2 of the ‘465 patent is invalid under 35 U.S.C. § 102(b) because the Ward patent discloses a nucleoside 5'-triphosphate that has a removable

blocking moiety (phosphate) protecting the 3' position where the phosphate is linked to the 3' carbon of the nucleoside 5'-triphosphate.

2. Dependent Claims 3 and 4

Dependent claim 3 further limits independent claim 1 or 2, and requires that the nucleoside contain a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U). The term "dNTP" is a well-known abbreviation of deoxynucleotide triphosphate and includes deoxynucleotide triphosphates in which the base is adenine (A), cytidine (C), guanosine (G), or thymidine (T), respectively. The Ward patent discloses that "preferred bases [of the nucleotide] are cytosine [and] uracil." (Ward patent at Col. 8, lines 8-9). Therefore, the Ward patent discloses a nucleoside 5'-triphosphate that includes every element of claim 3 of the '465 patent.

Dependent claim 4 further limits independent claim 2, and requires that the removable blocking moiety be enzymatically removable. It is well known that 3' terminal phosphate groups can be removed from nucleosides using enzymes such as T4 polynucleotide kinase. Therefore, by disclosing the use of phosphate moieties at 3' blocking groups, the Ward patent inherently discloses a removable blocking moiety that is enzymatically removable. Therefore, the Ward patent discloses a nucleoside 5'-triphosphate that includes every element of claim 4 of the '465 patent.

Accordingly, at least claims 3-4 of the '465 patent are invalid under 35 U.S.C. § 102(b) because the Ward patent discloses a nucleoside 5'-triphosphate that has a removable blocking moiety (phosphate) protecting the 3' position where the phosphate is linked to the 3' carbon of the nucleoside 5'-triphosphate.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, at least claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) by the Ward patent. Consequently, the Ward patent raises a substantial new question of patentability of claims 2-4 of the '465 patent.

IV. FOURTH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 2-4 of the '465 patent in view of International Patent Application WO 92/10587 to Dower, *et al.* (the “Dower PCT application”).

B. DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) in view of the Dower PCT application. Claims 2-4 of the '465 patent are set forth in the following chart along with a side-by-side explanation of how the Dower PCT application disclosed all the recited features of the claim. For ease of reference, paragraphing and other formatting has been added to the claim of the '465 patent.

CHART COMPARING CLAIM 1 WITH THE DOWER PCT APPLICATION

U.S. PATENT NUMBER 6,232,465	International Patent Application WO 92/10987 to Dower
Claim of the '465 patent	Dower PCT application disclosure
2. A nucleoside 5'-triphosphate	The Dower PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Dower PCT application discloses "[f]luorescent chain terminators (analogs of dATP, dCTP, dGTP, and TP (sic))" for use with "[a] DNA-dependent, DNA polymerase such as those used for conventional DNA sequencing." (Dower PCT application, page 43, lines 5-15; and page 44 lines 19-22). The terms "dATP," "dCTP," and "dGTP" are conventional abbreviations for <u>d</u> eoxy <u>a</u> denosine <u>t</u> riphosphate, <u>d</u> eoxy <u>c</u> ytidine <u>t</u> riphosphate, and <u>d</u> eoxy <u>g</u> uanosine <u>t</u> riphosphate, respectively.
having a removable blocking moiety protecting the 3' position	<p>The Dower PCT application discloses deoxynucleotide triphosphates having "small blocking groups such as acetyl, tBOC, NBOC, and NVOC on the 3'OH." (Dower PCT application, page 44, lines 20-22). The structures for the "small blocking groups" include acetyl, t-butyloxycarbonyl, 6-nitrobenzyloxycarbonyl, and 6-nitroveratryloxycarbonyl.</p> <p>The Dower PCT application discloses that "[t]hese groups [acetyl, tBOC, NBOC, and NVOC] are easily and efficiently removed under conditions of high or low pH, exposure to light or heat, etc." (Dower PCT application, page 44, lines 22-24).</p>
which is selected from the group consisting of an ester, an ether, and a phoshate [sic],	The Dower PCT application discloses deoxynucleotide triphosphates having "small blocking groups such as acetyl, tBOC, NBOC, and NVOC on the 3'OH." (Dower PCT application, page 44, lines 20-22). The structures for the "small blocking groups" include acetyl (an ester), t-butyloxycarbonyl (an ester), 6-nitrobenzyloxycarbonyl (an ester), and 6-nitroveratryloxycarbonyl (an ester).

U.S. PATENT NUMBER 6,232,465	International Patent Application WO 92/10987 to Dower
Claim of the '465 patent	Dower PCT application disclosure
wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate.	The Dower PCT application discloses deoxynucleotide triphosphates having "small blocking groups such as acetyl, tBOC, NBOC, and NVOC on the 3'OH." (Dower PCT application, page 44, lines 20-22). According to Dower, each of the blocking groups forms an ester with the 3' carbon of the nucleoside sugar.
3. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U).	The Dower PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Dower PCT application discloses "[f]luorescent chain terminators (analogs of dATP, dCTP, dGTP, and TP (sic)" for use with "[a] DNA-dependent, DNA polymerase such as those used for conventional DNA sequencing." (Dower PCT application, page 43, lines 5-15; and page 44 lines 19-22). The terms "dATP," "dCTP," and "dGTP" are conventional abbreviations for <u>d</u> eoxy <u>a</u> denosine <u>t</u> riphosphate, <u>d</u> eoxycytidine triphosphate, and <u>d</u> eoxyguanosine triphosphate, respectively.
4. A nucleoside 5'-triphosphate of claim 1 or 2 wherein said removable blocking moiety is enzymatically removable.	The Dower PCT application discloses deoxynucleotide triphosphates having "small blocking groups such as acetyl, tBOC, NBOC, and NVOC on the 3'OH." (Dower PCT application, page 44, lines 20-22). According to Dower, each of the blocking groups forms an ester with the 3' carbon of the nucleoside sugar. Esters are enzymatically removable.

C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

1. The Dower PCT Application Raises a Substantial New Question of Patentability Because the Dower PCT Application Disclosed Compounds Meeting the Limitations of Claim 1 of the '465 Patent.

The Dower PCT application was published on June 25, 1992, more than one year before the filing date of the '465 patent. The Dower PCT application raises a substantial new question

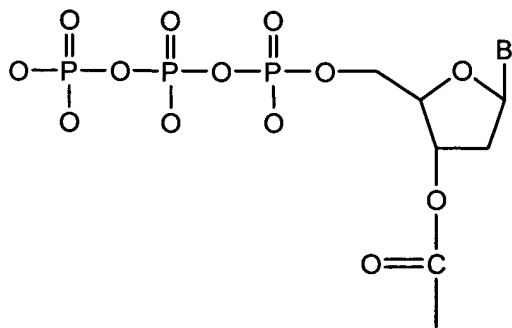
of patentability as to at least claims 2-4 of the '465 patent for the reasons given below.

As can be seen from the claim chart above, and as further discussed below, *all of the elements* of claims 2-4 were disclosed in the Dower PCT application, as indicated in the right hand column of the chart.

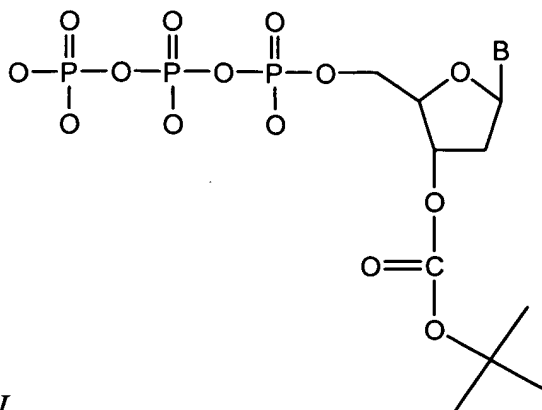
1. Independent Claim 2

The '465 patent defines "nucleotide" as "[a] subunit of a nucleic acid comprising a phosphate group, a five-carbon sugar, and nitrogen containing base." ('465 patent, Col. 5, lines 61-63). The Dower PCT application describes methods for sequencing surface immobilized polymers using microfluorescence detection. (Dower PCT application, Title and Abstract). Where the polymer is nucleic acid, a polymerase is used to extend a primer complementary to a target template by use of a "particular modified nucleotide analog to which a blocking agent is added and which prevents further elongation." (Dower PCT application, page 24, line 36 through page 25, line 1).

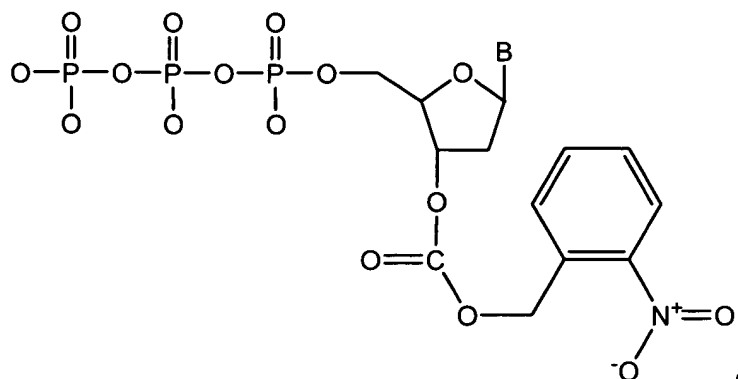
The Dower PCT application at least discloses the following compounds, each of which includes all of the limitations of independent claim 2:



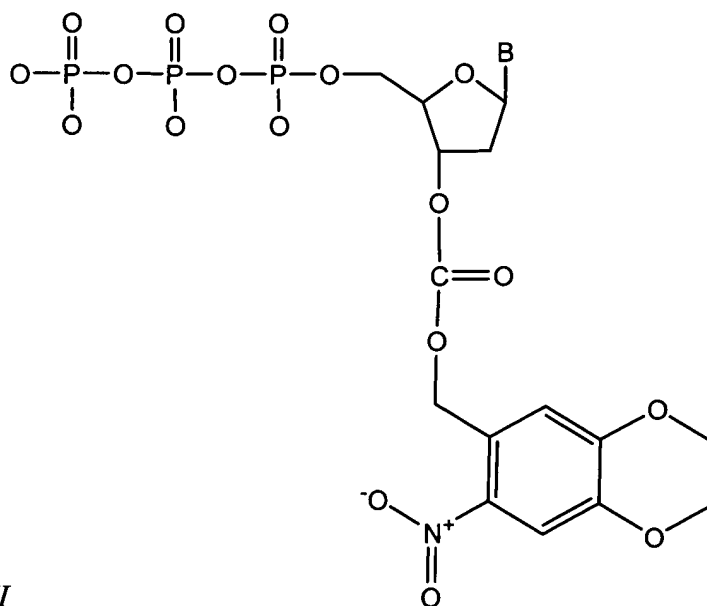
Structure V



Structure VI



Structure VII



Structure VIII

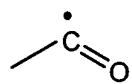
a) Nucleoside 5'-Triphosphate

The Dower PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Dower PCT application discloses “[f]luorescent chain terminators (analogs of dATP, dCTP, dGTP, and TP (sic)” for use with “[a]

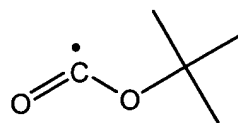
DNA-dependent, DNA polymerase such as those used for conventional DNA sequencing.” (Dower PCT application, page 43, lines 5-15; and page 44 lines 19-22). The terms “dATP,” “dCTP,” and “dGTP” are conventional abbreviations for deoxyadenosine triphosphate, deoxycytidine triphosphate, and deoxyguanosine triphosphate, respectively. Therefore, the Dower PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent.

b) Removable Blocking Moiety

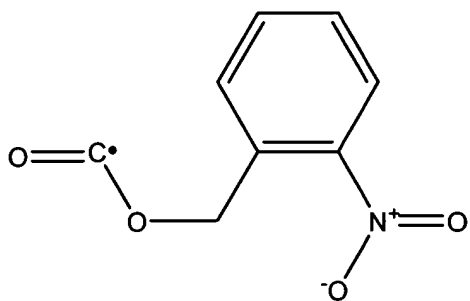
The Dower PCT application discloses deoxynucleotide triphosphates having “small blocking groups such as acetyl, tBOC, NBOC, and NVOC on the 3'OH.” (Dower PCT application, page 44, lines 20-22). The structures for the “small blocking groups” are as follows:



acetyl *Structure IX*

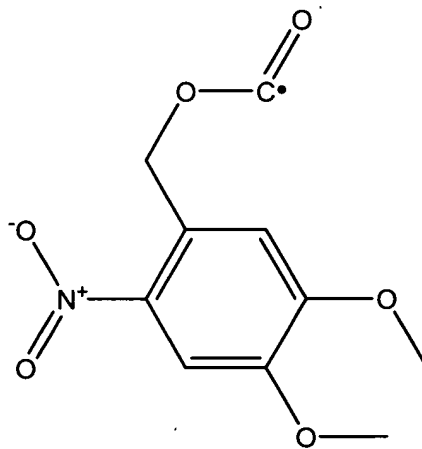


tert-butyloxycarbonyl (tBOC) *Structure X*



6-nitrobenzyloxycarbonyl (NBOC)

Structure XI



6-nitroveratryloxycarbonyl (NVOC)

Structure XII.

Each of the blocking groups shown in Structures IX-XII forms an ester with the 3' carbon of the nucleoside sugar. Therefore, the Dower PCT application discloses blocking moieties (esters) linked to the 3' carbon of the nucleoside 5'-triphosphate.

Furthermore, the Dower PCT application discloses that “[t]hese groups [acetyl, tBOC,

NBOC, and NVOC] are easily and efficiently removed under conditions of high or low pH, exposure to light or heat, etc.” (Dower PCT application, page 44, lines 22-24).

Therefore, the Dower PCT application discloses a removable ester blocking moieties protecting the 3' position and linked to the 3' carbon of the nucleoside 5'-triphosphate, as claimed in independent claim 2.

Accordingly, independent claim 2 of the '465 patent is invalid under 35 U.S.C. § 102(b) because the Dower PCT application discloses nucleoside 5'-triphosphates that have removable blocking moieties (esters) protecting the 3' position where the ester moieties are linked to the 3' carbon of the nucleoside 5'-triphosphate.

2. Dependent Claims 3 - 4

Dependent claim 3 further limits independent claim 1 or 2, and requires that the nucleoside contain a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytidine (C) and uracil (U). The Dower PCT application discloses compounds that include nucleoside 5'-triphosphates as defined in the '465 patent. Namely, the Dower PCT application discloses “[f]luorescent chain terminators (analogs of dATP, dCTP, dGTP, and TP (sic))” for use with “[a] DNA-dependent, DNA polymerase such as those used for conventional DNA sequencing.” (Dower PCT application, page 43, lines 5-15; and page 44 lines 19-22). The terms “dATP,” “dCTP,” and “dGTP” are conventional abbreviations for deoxyadenosine triphosphate, deoxycytidine triphosphate, and deoxyguanosine triphosphate, respectively. Therefore, the Dower PCT application discloses a nucleoside 5'-triphosphate that includes every element of dependent claim 3.

Dependent claim 4 further limits independent claim 2, and requires that the removable blocking moiety be enzymatically removable. It is well known that ester groups, such as acetyl groups as disclosed by Dower, can be enzymatically removed, as disclosed by the '465 patent itself (see, e.g., the '465 patent at Col. 16, lines 55-57). Therefore, the Dower PCT application discloses a nucleoside 5'-triphosphate that includes every element of dependent claim 4.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, at least claims 2-4 of the '465 patent would have been anticipated under 35 U.S.C. §102(b) by the Dower PCT application. Consequently, the Dower PCT application raises a substantial new question of patentability of claim 2-4 of the '465 patent.

V. FIFTH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 1-4 of the '465 patent in view of the Ward patent and/or the Tsien PCT application and/or the Dower PCT publication and/or the Kraevskii publication; and/or the Tsien PCT application in view of the Ward patent and/or the Dower PCT application and/or the Kraevskii publication.

B. EXPLANATION OF PERTINENCY OF CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 1-4 of the '465 patent would have been obvious under 35 U.S.C. §103(a) over any one of the Ward patent, the Tsien PCT application, the Dower PCT publication or the Kraevskii publication, for at least the reasons discussed above in Sections I – IV. See, e.g., *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"). In addition, claims 1-4 would have been obvious under 35 U.S.C. §103(a) in view of the Tsien PCT application in view of the Ward patent and/or the Dower PCT application and/or the Kraevskii publication, for at least the reasons discussed above in Sections I – IV.

C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 1-4 of the '465 patent would have been obvious under 35 U.S.C. §103(a) in view of the Ward patent, the Tsien PCT application, the Dower PCT publication or the Kraevskii publication, for at least the reasons discussed above in Sections I – IV. See, e.g., *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"). In addition, claims 1-4 would have been obvious under 35 U.S.C. §103(a) in view of the Tsien PCT application in view of the Ward patent and/or the Dower PCT application and/or the Kraevskii publication, for at least the reasons discussed above in Sections I – IV.

Even if, *arguendo*, claims 1-4 of the '465 patent are not anticipated by the Ward patent, the Tsien PCT application, the Dower PCT publication or the Kraevskii publication, claims 1-4 would have been obvious under 35 U.S.C. §103(a) in view of the Tsien PCT application optionally in view of the Ward patent and/or the Dower PCT application and/or the Kraevskii publication, because Tsien, alone or taken in any combination with the Ward patent and/or the Dower PCT application and/or the Kraevskii publication, teaches or suggests all the limitations of claims 1-4 of the '465 patent.

As discussed above, the Tsien application discloses “3’ hydroxyl-blocked dNTPs [deoxynucleotide triphosphates]” (Tsien PCT application, page 20, lines 25-26), in which a removable blocking moiety protects the 3' position and is linked to the 3' carbon of the nucleoside 5'-triphosphate. The removable blocking moiety can be an ester, an ether (e.g., a hydrocarbyl group such as a methyl ether), or a phosphate.

Each of the Ward patent, the Dower PCT application and the Kraevskii publication also discloses 3’ hydroxyl-blocked dNTPs in which a removable blocking moiety protects the 3' position and is linked to the 3' carbon of the nucleoside 5'-triphosphate. It would have been obvious to the skilled artisan to modify the teachings of the Tsien PCT application in view of the teachings of the Ward patent, the Dower PCT application and/or the Kraevskii publication to arrive at the claimed invention of claims 1-4 of the '465 patent.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, claims 1-4 would have been obvious under 35 U.S.C. §103(a) in view of the Tsien PCT application optionally in view of the Ward patent and/or the Dower PCT application and/or the Kraevskii publication. Consequently, these prior art references raise a substantial new question of patentability of claims 1-4.

VI. SIXTH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

A. CLAIMS FOR WHICH RE-EXAMINATION IS REQUESTED

Pursuant to 37 C.F.R. §1.510 (b)(2), reexamination is requested of claims 5-6 of the '465 patent in view of the Tsien PCT application in view of the Dower PCT application, optionally further in view of the Ward patent or the Kraevskii publication.

B. EXPLANATION OF PERTINENCY OF CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claims 5 and 6 of the '465 patent would have been obvious under 35 U.S.C. §103(a) as unpatentable over the Tsien PCT application in view of the Dower PCT application, optionally further in view of the Ward patent or the Kraevskii publication. The added limitations of claims 5 and 6 are merely obvious variations that were well known to those of ordinary skill in the art at the time the application was filed.

C. FURTHER DETAILED EXPLANATION OF PERTINENCY AND MANNER OF APPLYING CITED PRIOR ART TO EVERY CLAIM FOR WHICH REEXAMINATION IS REQUESTED

Claim 5 of the '465 patent is an independent claim as set forth below:

5. A composition of matter, comprising:
(a) a nucleoside [sic] 5'-triphosphate having a removable hydrocarbyl blocking moiety linked to a 3' carbon of said nucleoside 5'-triphosphate; and
(b) a solid support linked to said removable blocking moiety.

The Tsien PCT application (which, as discussed above, discloses nucleoside 5'-triphosphates that have a removable blocking moiety protecting the 3' position) further teaches that

single-point covalent attachment of DNA to a solid polymer or glass support is possible. Such single-point methods are preferred for immobilizing the subject DNA, since this leaves the chain free for interactions with the polymerase and similar enzymes.

(Tsien PCT application at page 32, lines 26-30).

The Tsien PCT application also discusses immobilization of DNA on membranes, quartz, plastic, or particles of resin or polymer microspheres (see, e.g., Tsien PCT application at pages 32 – 34). Moreover, the Tsien PCT application discloses that a removable blocking moiety can be an ether (e.g., a hydrocarbyl group).

It is known that immobilization of polynucleotides, such as DNA, is useful for the preparation of synthetic polynucleotides, as disclosed by the Dower PCT application. For example, the Dower PCT application discloses that DNA can be synthesized on a solid support using nucleotides having a blocking agent on the 3' hydroxyl group (Dower PCT application at page 42, line 29 through page 44, line 12).

Both the Tsien PCT application and the Kraevskii publication disclose nucleoside 5'-triphosphates having a removable hydrocarbyl blocking moiety linked to a 3' carbon of the nucleoside 5'-triphosphate.

Therefore, it would have been obvious to the one of ordinary skill in the art, more than one year prior to the earliest effective filing date of the '465 patent, to attach a nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3' position, as disclosed by the Tsien PCT application, to a solid support, as disclosed by the Dower PCT application, to arrive at the compound of claim 6 of the '465 patent. It would have been obvious to link the removable blocking moiety to the solid support so as to achieve simultaneous deblocking and release of the deblocked dNTP from the solid support. Moreover, it would have been obvious to use a hydrocarbyl blocking group as disclosed by the Tsien PCT application and/or the Kraevskii publication. Thus, claim 5 is obvious under 35 U.S.C. §103(a) as unpatentable over the Tsien PCT application in view of the Dower PCT application and optionally further in view of the Kraevskii publication.

Claim 6 of the '465 patent is an independent claim as set forth below:

6. A composition of matter, comprising:
 - (a) a nucleoside 5'-triphosphate having a removable blocking moiety selected from the group consisting of an ester, an ether and a phosphate linked to a 3' carbon of said nucleoside 5'-triphosphate [sic]; and
 - (b) a solid support linked to said removable blocking moiety.

As described above, the Tsien PCT application discloses nucleoside 5'-triphosphates that have a removable blocking moiety protecting the 3' position, and further teaches that DNA can be attached to a solid support such as a solid polymer or glass support, membranes, quartz, plastic, or particles of resin or polymer microspheres. Moreover, the Tsien PCT application discloses that a removable blocking moiety can be an ester, an ether (e.g., a hydrocarbyl group) or a phosphate.

As also disclosed above, it is known that immobilization of polynucleotides, such as DNA, is useful for the preparation of synthetic polynucleotides, as disclosed by the Dower PCT application. For example, the Dower PCT application discloses that DNA can be synthesized on a solid support using nucleotides having a blocking agent on the 3' hydroxyl group (Dower PCT application at page 42, line 29 through page 44, line 12).

Both the Tsien PCT application and the Kraevskii publication disclose nucleoside 5'-triphosphates having a removable hydrocarbyl blocking moiety linked to a 3' carbon of the nucleoside 5'-triphosphate.

Therefore, it would have been obvious to the one of ordinary skill in the art, more than one year prior to the earliest effective filing date of the '465 patent, to attach a nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3' position, as disclosed by the Tsien PCT application, to a solid support, as disclosed by the Dower PCT application, to arrive at the compound of claim 6 of the '465 patent. It would have been obvious to link the removable blocking moiety to the solid support so as to achieve simultaneous deblocking and release of the deblocked dNTP from the solid support. Moreover, it would have been obvious to use an ester blocking group as disclosed by the Tsien PCT application or the Dower PCT application, an ether blocking group as disclosed by as disclosed by the Tsien PCT application patent and/or the Kraevskii publication, or a phosphate blocking group as disclosed by the Tsien PCT application or the Ward patent. Thus, claim 6 is obvious under 35 U.S.C. §103(a) as unpatentable over the Tsien PCT application in view of the Dower PCT application and optionally further in view of the Ward patent or the Kraevskii publication.

D. STATEMENT POINTING OUT SUBSTANTIAL NEW QUESTION OF PATENTABILITY

In view of the foregoing, claims 5 and 6 of the '465 patent would have been obvious under 35 U.S.C. §103(a) as unpatentable over the Tsien PCT application in view of the Dower PCT application, optionally further in view of the Ward patent or the Kraevskii publication. . Consequently, these prior art references raise a substantial new question of patentability of claims 5 and 6 of the '465 patent.

***Request for Reexamination of
U.S. Patent Number 6,232,465***

Pursuant to 37 C.F.R. §1.501(b)(4), enclosed is an entire copy of U.S. Patent 6,232,465, including the front face, drawings, and specification/claims, in double column format, with each page of the copy plainly written on only one side of a sheet of paper. The one-page Certificate of Correction of the '465 patent also is enclosed.

Pursuant to 37 C.F.R. §1.510(b)(5), the undersigned hereby certifies that a copy of this Request for Reexamination has been served in its entirety on Patentee's attorney of record at the following address:

LERNER, DAVID, LITTENBERG, KRUMHOLZ, & MENTLICK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

All correspondence should be sent to:

Howard M. Gitten, Esq.
Edwards Angell Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150
Ft. Lauderdale, FL 33301
(954) 667-6130

In view of the foregoing, it is respectfully requested that an order be issued granting reexamination.

Respectfully submitted,

Date

August 4, 2006

By



Howard M. Gitten, Esq.
Reg. No. 32,138

Edwards Angell Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150
Ft. Lauderdale, FL 33301
(954) 667-6130

CERTIFICATE OF SERVICE

I hereby certify that on this 4th day of August 2006 a true and correct copy of the foregoing Request for Reexamination was served, in its entirety, by certified mail (return receipt requested), postage prepaid, on Patentee's attorney of record at the following address:

LERNER, DAVID, LITTENBERG, KRUMHOLZ, & MENTLICK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090



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08/03/06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

71338 U.S. PTO
90008152



08/03/06

In re patent application of

HIATT, ANDREW C. et al.

Serial No. 08/486,536

Filed: June 7, 1995

For: COMPOSITIONS FOR ENZYME CATALYZED TEMPLATE-INDEPENDENT CREATION OF
PHOSPHODIESTER BONDS USING PROTECTED NUCLEOTIDES

STATEMENT TO SUPPORT FILING AND SUBMISSION IN
ACCORDANCE WITH 37 C.F.R. §§ 1.821-1.825

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Mail Stop SEQUENCE

Sir:

In connection with a Sequence Listing submitted concurrently
herewith, the undersigned hereby states that:

1. the submission, filed herewith in accordance with 37
C.F.R. § 1.821(g), does not include new matter;
2. the content of the attached paper copy and the
attached computer readable copy of the Sequence Listing, submitted in
accordance with 37 C.F.R. § 1.821(c) and (e), respectively, are the same.

Respectfully submitted,

July 31, 2006
Date


James A. Coburn

HARBOR CONSULTING IP SERVICES, INC.
1500A Lafayette Road, #262
Portsmouth, N.H. 03801
800-318-3021

SEQUENCE LISTING

<110> HIATT, ANDREW C.
ROSE, FLOYD

<120> COMPOSITIONS FOR ENZYME CATALYZED TEMPLATE-INDEPENDENT
CREATION OF PHOSPHODIESTER BONDS USING PROTECTED
NUCLEOTIDES

<130>

<140> 08/486,536

<141> 1995-06-07

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,152	08/03/2006	6232465	None	5197

530 7590 09/29/2006

LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

EXAMINER

ART UNIT PAPER NUMBER

DATE MAILED: 09/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.



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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

HOWARD M. GITTEN
EDWARDS ANGELL PALMER & DODGE LLP
350 EAST LAS OLAS BLVD., SUITE 1150
FT. LAUDERDALE, FL 33301

***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/008,152.

PATENT NO. 6232465.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting / Denying Request For Ex Parte Reexamination	Control No. 90/008,152	Patent Under Reexamination 6232465	
	Examiner Gary L. Kunz	Art Unit 3991	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed 03 August 2006 has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a) ☐ PTO-892, b) ☐ PTO/SB/08, c) ☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

- a) ☐ by Treasury check or,
b) ☐ by credit to Deposit Account No. _____, or
c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

cc:Requester (if third party requester)

DETAILED ACTION: Reexamination: Granting of Request
Procedural Posture

The Third Party Request filed 03 August 2006 for *ex parte* reexamination of claims 1 - 6 of United States Patent Number 6,232,465 is acknowledged.

Decision Granting the Order

A substantial new question of patentability affecting claims 1 - 6 of United States Patent Number 6,232,465 (Hiatt et al.) is raised by the request for reexamination.

Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,232,465 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282, and 2286.

Substantial New Question of Patentability (SNQ) Raised by the Request

For "a substantial new question of patentability" to be present, it is only necessary that:

- A. The prior art patents and/or printed publications raise a substantial new question of patentability regarding at least one claim, i.e., the prior art

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teaching is such that there is a substantial likelihood that a reasonable examiner would consider the teaching to be important in deciding whether or not the claim is patentable; and it is not necessary that the prior art establish a *prima facie* case of patentability and;

B. The same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim. See MPEP § 2242.

For a reexamination that was ordered on or after November 2, 2002 (the date of enactment of Public Law 107-273); see Section 13105, of the Patent and Trademark Office Authorization Act of 2002), reliance *solely* on old art (as basis for a rejection) does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Determination on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. For example, a SNQ may be based upon a fact-specific inquiry done on a case-by-case basis. For example, a SNQ may be based solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in the earlier concluded examination(s), in view of a material new argument or interpretation presented in the request. MPEP § 2258.01.

Priority of claims 1 - 6 of US Patent No. 6,232,465 (Hiatt et al.)

The Hiatt et al. patent (6,232,465; hereinafter "Hiatt") issued from application serial number 08/486,536 filed 07 June 1995, which is a continuation-in-part of application serial number 08/300,484 filed 02 September 1994, which issued as U.S.

Patent No. 5,990,300 on 23 November 1999. Therefore, the earliest possible priority date is 02 September 1994.

The Hiatt et al. 6,232,465 Patented Invention

The Hiatt invention is drawn to nucleoside 5'-triphosphates having a removable blocking group at the 3'-OH position wherein the blocking group can be an ester, and ether, or a phosphate moiety. Representative claims 2 and 6 are presented below.

Claim 2. A nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3'-position which is selected from the group consisting of an ester, an ether and a phosphate, where said removable blocking moiety is linked to a 3'-carbon of said nucleoside 5'-triphosphate.

Claim 6. A composition of matter, comprising:

- (a) a nucleoside 5'-triphosphate having a removable blocking moiety selected from the group consisting of an ester, an ether, and a phosphate linked to a 3'-carbon of said nucleoside 5'-triphosphate; and
- (b) a solid support linked to said removable blocking moiety.

Documents Cited by the Requester:

1. Tsien et al. WO 91/06678 (filed 26 October 1990): published 16 May 1991.
2. Dower et al. WO92/10587 (filed 06 December 1991): published 25 June 1992.
3. Ward et al., U.S. Patent No. 4,711,955 issued 08 December 1987.
4. Kraevskii et al., *Molecular Biology* 21 : 25 - 29, 1987.
5. Henner et al., *Journal of Biological Chemistry*, 258: 15198-15205, 1983.

Discussion of the Cited Documents and an SNQ

1. Tsien et al. WO 91/06678

The request indicates the applicability of the Tsien reference to claims 1 - 4 at request pages 4 - 12 as anticipatory; or alternatively at request pages 31 - 32 as obvious in combination with Ward and/or Dower and/or Kraevskii; The request also indicates the applicability of the Tsien reference to claims 5 - 6 at request pages 33 - 36 as obvious in combination with Dower and optionally further in view of Ward or Kraevskii.

The Tsien reference was not cited during the prosecution of the Hiatt '465 patent.

The Tsien reference teaches the four traditional 2'-deoxyribonucleotides-5'-triphosphates (e.g., 2'-deoxyadenosine-5'-triphosphate, 2'-deoxyguanosine-5'-triphosphate, thymidine-5'-triphosphate, and 2'-deoxycytidine 5'-triphosphate) with a blocking group at the 3'-OH. (See page 9, line 30 to page 10, line 3.) Tsien further discloses that the blocking group at the 3'-OH position may be methyl, acetyl, or phosphate. (See page 22, line 1 - 25.) Tsien also discloses thymidine-3'-O-phosphate-5'-triphosphate as compound no. 9 in Figure 5. Tsien discloses 3'-hydroxyl-blocked dNTP's (page 20, lines 25 - 26) and indicates that "the most common blocking groups are esters and ethers" and that modifications to the 3'-OH include -OCH₃ and -OPO₃⁻² (phosphate). (See page 21, lines 9 - 17.) Finally, Tsien teaches that these 3'-hydroxyl protecting groups are removable by chemical or enzymatic means. See Examples 5 and 6 of Tsien at pages 38 - 40.

It is agreed that there is a substantial likelihood that a reasonable examiner would consider the Tsien reference to be important in deciding whether or not one or more claims of US Patent No. 6,232,465 are patentable, and thus raises a substantial new question of patentability.

2. Dower et al. WO 92/10587

The request indicates the applicability of the Dower reference to claims 2 - 4 at request pages 23 - 30 as anticipatory. The request also indicates the applicability of the Dower reference to claims 1 - 4 at request pages 31 - 32 as obvious when combined with Tsien, Ward, or Kraevskii; or alternatively to claims 1 - 4 as obvious over Ward in view of Tsien and/or Dower and/or Kraevskii. The request further indicates the applicability of the Dower reference to claims 5 - 6 at request pages 33 - 38 as obvious over Tsien and/or Dower, and optionally further in view of Ward and/or Kraevskii.

The Dower reference was not cited during the prosecution of the Hiatt '465 patent.

The Dower reference discloses the four standard 2'-deoxyribonucleotide'-5'-triphosphates: 2'-deoxyadenosine -5'-triphosphate (dATP), 2'-deoxycytidine-5'-triphosphate (dCTP), 2'-deoxyguanosine-5'-triphosphate (dGTP), and thymidine-5'-triphosphate (TTP)--used as fluorescent chain terminators with their 3'-hydroxyl groups protected or blocked by acetyl, t-butyloxycarbonyl, 6-nitrobenzyloxycarbonyl, and 6-nitroveratryloxycarbonyl (page 44, lines 20 - 22). Each of these blocking groups can be easily removed under conditions of high or low pH or exposure to light or heat. (page 44, lines 22 - 24). The carboxylic acid ester blocking groups can be removed

enzymatically by non-specific esterases.

It is agreed that there is a substantial likelihood that a reasonable examiner would consider the teachings of the Dower reference to be important in deciding whether or not one or more claims of US Patent No. 6,232,465 are patentable, thus raising a substantial new question of patentability.

3. Ward et al. U.S. Patent No. 4,711,955

The request indicates the applicability of the Ward reference to claims 2 - 4 of the 6,232,465 patent at request pages 18 - 22 as anticipatory; or alternatively to claims 1 - 4 as obvious at pages 31 - 32 in view of Ward and/or Tsien and/or Dower and/or Kraevskii; or alternatively to claims 1 - 4 at pages 31 - 32 of the request as obvious over Tsien in view of Ward and/or Dower and/or Kraevskii; or alternatively at pages 33 - 36 of the request claims 5 - 6 as obvious over Tsien in view of Dower and optionally further in view of Ward or Kraevskii.

The Ward patent was not cited during the prosecution of the Hiatt '465 patent.

The Ward patent teaches 2'-deoxyribonucleotide-3'-phosphate-5'-triphosphates of purines (adenine and guanine) and pyrimidines (uracil and cytidine) at column 3, lines 20 - 68. Ward further teaches that these 2'-deoxyribonucleotide-5'-triphosphates can be blocked at the 3'-hydroxyl by either a mono-, di-, or triphosphate group which are enzymatically removable.

It is agreed that there is a substantial likelihood that a reasonable examiner would consider the teachings of the Ward patent to be important in deciding whether or

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not one or more claims of US Patent No. 6,232,465 are patentable, thus raising a substantial new question of patentability.

4. Kraevskii et al. Molecular Biology

The request indicates the applicability of the Kraevskii reference to claims 1 - 3 of the '465 patent at pages 13 - 17 of the request as anticipatory; or alternatively to claims 1 - 4 at pages 31 - 32 of the request as obvious over Ward and/or Tsien and/or Dower and/or Kraevskii; or alternatively to claims 1 - 4 at pages 31 - 32 of the request as obvious over Tsien in view of Ward, and/or Dower and/or Kraevskii; or alternatively to claims 5 - 6 at pages 33 - 36 of the request as obvious over Tsien in view of Dower and optionally further in view of Ward or Kaevskii.

The Kraevskii reference was not cited during the prosecution of the Hiatt '465 patent.

Kraevskii discloses the traditional four chain terminators of polymerase reactions: 2'-deoxyribonucleotide-5'-triphosphate having adenine, guanine, thymine, or cytidine as the base. Kraevskii further discloses each of these four deoxynucleotides with the 3'-hydroxyl blocked with a methyl group (See entry No. 7 in Table 1 on page 27).

It is agreed that there is a substantial likelihood that a reasonable examiner would consider the teachings of the Kraevskii reference to be important in deciding whether or not one or more claims of US Patent No. 6,232,465 are patentable, thus raising a substantial new question of patentability.

5. Henner et al. Journal of Biological Chemistry

The Henner reference was not cited during the prosecution of the Hiatt '465 patent.

The Henner reference does not appear to disclose any 2'-deoxyribonucleotide-5'-triphosphates with a blocked 3'-hydroxyl. It pertains to radiation-induced DNA-strand breaks.

In view of the above observations, there is not a substantial likelihood that a reasonable examiner would consider the teachings of the Henner reference to be important in deciding whether or not one or more claims of US Patent No. 6,232,465 are patentable. Therefore, the Henner et al. reference does **NOT** raise a substantial new question of patentability.

Conclusion

In view of the above, the request for reexamination is GRANTED.
Claims 1 - 6 of United States Patent Number 6,232,465 will be reexamined.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because of the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 USC 305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings have been merged) in the reexamination proceedings in the manner provided in 37 CFR 1.248. See 37 CFR 1.530(f).

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c). In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, will be governed by requirements of 37 CFR 1.116, after final rejection and 37 CFR 41.33 after appeal, which will be strictly enforced.

Further Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary L. Kunz, whose telephone number is 571-272-0887. The examiner can normally be reached on Monday through Friday (with alternative Fridays off) between 7:00 AM and 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached at 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

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Should you have questions about access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this Ex parte Reexamination proceeding should be directed to:

By Mail to:

Attn: Mail Stop "Ex Parte Reexam »
Central Reexamination Unit
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application/Control Number: 90/008,152

Page 12

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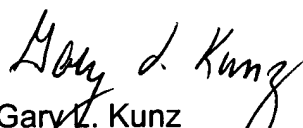
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Primary Examiner
Art Unit 3991

Conferee:





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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,152	08/03/2006	6232465	None	5197

530 7590 02/28/2007

LERNER, DAVID, LITTENBERG,
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EXAMINER

ART UNIT PAPER NUMBER

DATE MAILED: 02/28/2007

Please find below and/or attached an Office communication concerning this application or proceeding.



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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO 90/008152

PATENT NO. 6,232,465

ART UNI 3992

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,152	Patent Under R examination 6232465	
	Examiner Gary L. Kunz	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

- a ☒ Responsive to the communication(s) filed on Request of 8/3/07. b ☐ This action is made FINAL.
c ☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892. 3. ☐ Interview Summary, PTO-474.
2. ☐ Information Disclosure Statement, PTO/SB/08. 4. ☐ _____.

Part II SUMMARY OF ACTION

- 1a. ☒ Claims 1-6 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims 1-6 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have

- 1 ☐ been received.
2 ☐ not been received.
3 ☐ been filed in Application No. _____.
4 ☐ been filed in reexamination Control No. _____.
5 ☐ been received by the International Bureau in PCT application No. _____.

* See the attached detailed Office action for a list of the certified copies not received.

9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

EX PARTE REEXAMINATION

Detailed Non-Final Action

Procedural Posture

This is a re-examination of US Patent No. 6,232,465 B1, which issued on 15 May 2001.

A Request for Reexamination was filed by a Third Party Requester on 03 August 2006.

Reexamination was ordered for control number 90/008,152 on 29 September 2006.

No Patent Owner's response was received in 90/008,152.

Reexamination proceedings will be handled with "special dispatch" throughout their pendency in the Office as required by 35 USC 305 and MPEP 2261.

Priority

US Patent No. 6,232,465 B1 issued from application 08/486,536, filed 7 June 1995, which is a continuation-in-part of application number 08/300,484, filed 02 September 1994 and issued as US Patent No. 5,990,300 on 23 November 1999. Therefore, the earliest possible priority date is 02 September 1994.

Related Proceedings

Hiatt et al., the inventors of US Patent No. 6,232,465, also filed a related second application, 08/486,913, on 09 June 7 1995, which issued as US Patent No. 5,763,594

on 09 June 1998. A Third Party Requester filed a Request for Reexamination of US Patent No. 5,763,594 on 04 August 2006. This reexamination request was given the control number of 90/008,149 and was granted in the Order mailed 29 October 2006. The claims in both patents (5,763,594 and 6,232,465) are directed to nucleoside 5'-triphosphates with the 3'-hydroxyl protected by a removable blocking group.

The Inventions in US Patent 6,232,465

There are six claims in the Hiatt '465 patent under reexamination. Independent claim 1 is directed to a nucleoside 5'-triphosphate containing a removable blocking group at the 3'-position wherein said blocking group is a hydrocarbyl linked to the 3'-carbon. Independent claim 2 is also directed to a nucleoside 5'-triphosphate having a removable 3'-OH protecting group selected from the group consisting of an ester, ether, and a phosphate. Claim 3 depends from claims 1 or 2 and specifies that the heterocyclic base moiety must be adenine, guanine, thymine, cytosine, or uracil. Claim 4 depends from claims 1 or 2 (see Certificate of Correction) and requires that the 3'-OH protecting group must be enzymatically removable. Independent claims 5 and 6 are directed to a nucleoside 5'-triphosphate having a removable solid support protecting group at the 3'-OH position. Claim 5 requires that said solid support be linked to the 3'-OH through a removable protecting group which is a hydrocarbyl group. Claim 6 requires that said solid support be linked to the 3'-OH through a removable protecting group that is an ester, an ether, or a phosphate group.

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Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,232,465 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282, and 2286.

References cited by the Third Party Requester

None of the following references cited by the Third Party Requester were cited during the prosecution of the Hiatt '465 patent.

1. **Tsien, Roger Y.**, WO 91/06678, International Publication Date of 16 May 1991.
2. **Dower et al.**, WO 92/10587, International Publication Date of 25 June 1992.
3. **Ward et al.**, U.S Patent No. 4,711,955, issued 8 December 1987.
4. **Kraevskii et al.**, "Substrate Inhibitors of DNA Biosynthesis," Mol. Biol. 21: 25 - 29, 1987.
5. **Henner et al.**, "Enzyme Action at 3'-Terminal of Ionizing Radiation-Induced DNA Strand Breaks," J. Biol. Chem. 258(24): 15198 - 15205, 1983.

Claim Rejections - 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 - 4 are rejected under 35 USC 102(b) as being unpatentable over Tsien WO 91/06678 in view of patent owner's admission.

Independent claim 1 is directed to a nucleoside 5'-triphosphate containing a removable blocking group at the 3'-O-position wherein said blocking group is a "hydrocarbyl" moiety linked to the 3'-carbon. The specification defines hydrocarbyl at column 6, lines 25 - 36:

Hydrocarbyl: An organic radical composed of carbon and hydrogen which may be aliphatic (including alkyl, alkenyl, and alkynyl group and groups which have a mixture of saturated and unsaturated bonds), alicyclic (carbocyclic), aryl (aromatic) or combination thereof; and may refer to straight-chained, branched-chain, or cyclic structures or to radicals having a combination thereof, as well as to radicals substituted with halogen atom(s) or heteroatoms, such as nitrogen, oxygen, and sulfur and their functional groups (such as amine, alkoxy, aryloxy, lactone groups and the like), which are commonly found in organic compounds and radicals.

Therefore, according to the above definition of "hydrocarbyl groups," ester and ether 3'-OH protecting groups are clearly encompassed by claim 1. Independent claim 2 is also directed to a nucleoside 5'-triphosphate having a removable 3'-OH protecting group selected from the group consisting of an ester, ether, and a phosphate. Claim 3 depends from claims 1 or 2 and specifies that the heterocyclic base moiety must be adenine, guanine, thymine, cytosine, or uracil. Claim 4 depends from claims 1 or 2 (see Certificate of Correction) and requires that the 3'-OH protecting group must be enzymatically removable.

(A) Ester Protecting Groups (anticipation of claims 1 - 4)

Claim 1 includes "esters" within the genus of any "hydrocarbyl" 3'-OH blocking groups for nucleoside 5'-triphosphates, as explained above. Claims 2 - 4 explicitly

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includes esters among the removable 3'-OH protecting groups. Claim 3 requires that the base moiety be adenine (A), guanine (G), thymine (T), cytosine (C), or uracil (U).

Tsien WO '678 discloses esters as 3'-O-protecting groups of deoxynucleoside 5'-triphosphates at page 21, lines 9 – 24. "Presently preferred embodiments focus on the ester blocking groups such as lower (1 – 4 carbon) alkanolic acid and substituted lower alkanolic acid esters, for example formyl, **acetyl**, isopropanoyl, alpha fluoro- and alpha chloroacetyl esters and the like; . . ." Tsien WO '678 also illustrates the structure of the 3'-O-protected deoxynucleoside 5'-O-triphosphates in Figure 5. Structure 6 in Figure 5 is 3'-O-acetyl 5'-triphosphate when R_1 is $P_3O_9H_4$ and R_2 is $COCH_3$. Tsien WO '678 further teaches [t]hat the criteria for successful use of 3'-O-blocking groups include: [. . .] the availability of mild conditions for rapid and quantitative deblocking. See Tsien WO '678, page 20, lines 33 - 34. In addition, the patent owner admits that the removability is an inherent property of many esters, as required by claims 1 - 3. "The chemistry of esters a protecting groups for hydrolysis is well established." See Hiatt '465 column 10, lines 49 – 59. "Esters in general are readily removed, usually in the presence of bases, to regenerate the hydroxyl group and thus are useful as removable blocking moieties" (column 10, lines 49 – 59). Thus Tsien WO '678 anticipates claim 1 which encompasses esters generally as "hydrocarbyl groups" and claims 2 - 3 which specify esters as an acceptable blocking group. Note also that Tsien WO '678 also discloses the specific bases defined in claim 3 as adenine (A), guanine (G), thymine (T), cytosine

(C), and uracil (U) at page 9, line 32 through page 10, line 3, where the meaning of dNTP is explained.

Finally, Tsien WO '678 also anticipates claim 4 which requires that the 3'-OH protecting group (esters in this case) be capable of enzymatic removal. This is also an inherent property of any specific ester as admitted by patent owner in the specification at column 13, lines 60 - 63, "Some modifications may also be removed by enzymatic digestion resulting in the regeneration of the 3'-hydroxyl. These would include phosphates, glycosides, and certain esters." Thus, the patent owner provides the evidence of the inherency that certain esters can be enzymatically removable as required by claim 4.

(B) Ether Protecting Groups (anticipation of claims 1 - 3)

Claim 1 includes ethers within the genus of any "hydrocarbyl" 3'-OH blocking moiety that is removable as previously explained. Independent claim 2 specifies that the 3'-OH protecting/blocking group may be an ether. Claim 3 which depends from claims 1 or 2 also specifies that an ether may be the removable 3'-OH blocking group.

Tsien WO '678 clearly anticipates claim 1 because this reference also discloses 3'-OH ether blocking groups for nucleoside 5'-triphosphates: "The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications to the 3'-OH position of dNTPs include the introduction of groups such as -F, -NH₂, and OCH₃ . . ." (See page 21, lines 12 - 13.) "Presently preferred embodiments focus on [. . .] ether blocking groups such as alkyl ethers; . . . " (See page 21, lines 20 - 25.) Furthermore, the patent owner admits in the specification at column 12, lines 14 - 21, that "The

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chemistry involved in using ethers as removable blocking moieties for hydroxyls is well known in the art. Numerous ethers have been described and are useful for transiently protecting hydroxyl and similar chemical groups." Thus, Tsien WO '678 clearly anticipates the 3-O-protected nucleoside 5'-triphosphates of claims 1 - 3 along with their inherent removability property.

(C) Phosphate Protecting Groups (anticipation of claims 2 - 4)

Claims 2 - 4 encompass nucleoside 5'-triphosphates wherein the 3'-OH blocking group is phosphate because claims 3 and 4 depend in the alternative from claim 2.

Tsien WO '678 discloses nucleoside 5'-triphosphates wherein the 3'-OH is blocked/protected by a phosphate group and that "[e]nzymatic deblocking of the 3'-OH blocking groups is also possible" with polynucleotide kinase at page 25, lines 13 - 14. Thus, Tsien WO '678 clearly anticipates claims 2 - 3 because it discloses nucleoside 5'-triphosphates with phosphate as the specific 3'-O-blocking group which is removable as required by claim 2. Claim 4 is also anticipated because Tsien WO '678 teaches that phosphate 3'-OH protecting groups can be removed enzymatically (Tsien WO '678 at page 25, lines 13 - 22 and pages 39 - 40, Example 6).

Claim Rejection – 35 USC 102(b)

Claims 1 - 4 are rejected under 35 USC 102(b) as being clearly anticipated by Dower PCT WO 92/10587 in view of the patent owner's admission.

Claim 1 of the Hiatt '465 patent is directed to any nucleoside 5'-triphosphate in which the 3'-hydroxyl is protected by a "hydrocarbyl" moiety which includes esters

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(possessing carbon, hydrogen, and oxygen). See column 6, lines 25 - 36. Claim 2 specifies that said 3'-OH blocking group may be an ester. Claims 3 - 4 depend from claim 2 in the alternative, and therefore, also specify that an ester may be the removable blocking group.

Dower WO '587 describes a group of esters that can be used in the protection of 3'-hydroxyls of dideoxynucleoside 5'-triphosphates on page 44, lines 20 - 24.

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

Dower WO '587, thus, anticipates claims 1 - 3 with respect to the ester 3'-OH blocking groups of nucleoside 5'-triphosphates along with their inherent chemical property of removability.

Dower PCT '587 further anticipates claim 4 which requires that the 3'-OH protecting group be enzymatically removable. This inherency is documented by the patent owner at column 13, lines 60 - 63 of the specification. "Some modifications may also be removed by enzymatic digestion resulting in the regeneration of the 3'-hydroxyl. These would include phosphates, glucosides, and certain esters."

Claim Rejection - 35 USC 102(b)

Claims 1 - 3 are rejected under 35 USC 102(b) as being clearly anticipated by Kraevskii et al. (Mol. Biol. 21: 25 - 29, 1987) in view of the patent owner's admission.

Claim 1 is directed to nucleoside 5'-triphosphates having a "hydrocarbyl" moiety as the removable blocking group at the 3'-OH. Ether protecting groups fall within the patent owner's definition of "hydrocarbyl" because it contains carbon, hydrogen and oxygen. See column 6, lines 25 - 36 for the definition of "hydrocarbyl." Claims 2 - 4 specifically indicate that the removable 3'-OH blocking group may be an ether. Claim 3 requires that the base moiety of the nucleoside 5'-triphosphate be any one of the traditional bases in DNA or RNA, i.e, adenine, guanine, cytosine, thymine, or uracil. This is exactly the traditional meaning given to the abbreviation of ddNTP disclosed by Kraevskii et al. on page 27, Table 1, entry. The ddNTP represents a genus of 2',3'-dideoxynucleoside 5'-triphosphates. This genus embraces nucleoside 5'-triphosphates with any of the five traditional bases in DNA and RNA.

Kraevskii '87 discloses generic 2'-deoxynucleoside 5'-triphosphates with a methyl ether blocking group on the 3'-OH on page 27, Table 1, seventh entry, abbreviated dNTP (3'-O-methyl) as substrate inhibitors of DNA biosynthesis. These 2'-deoxynucleoside 5'-triphosphates read on claims 1 - 3 of Hiatt '465. The only other limitation required by claims 1 - 3 is that the 3'-OH blocking group must be removable. While Kraevskii '87 is silent about the cleavage reaction for removing 3'-O-methyl protecting groups, the patent owner admits that "removability" is an inherent property of 3'-O-methyl protecting groups at column 12, lines 14 - 22 of the specification. "The chemistry involved in using ethers as removable blocking moieties for hydroxyls is well known in the art. Numerous ethers have been described and are useful for transiently protecting hydroxyls and similar chemical groups." Thus, Kraevskii '87 clearly anticipates claims

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1 - 3 because 3'-O-methyl groups in nucleoside 5'-triphosphates are readily removable; a fact that is well-known in the prior art as acknowledged by the patent owner at column 12, lines 14 - 22.

Claim Rejection -- 35 USC 103(a)

Claims 2 - 4 are rejected under 35 USC 103(a) as being unpatentable over Ward et al. (4,711,955) in view of Tsien WO '678.

The Hiatt '465 inventions as defined by claims 2 - 4 are described above.

Ward '955 discloses generically nucleoside 5'-triphosphates with phosphate as the blocking group at the 3'-OH position at column 7, lines 20 - 57. In the structure at lines 20 - 25 in column 7, "B" represents a purine base such as adenine or guanine. When variable "z" is hydrogen, variable "x" is triphosphate, and variable "y" is monophosphate, this structure becomes a nucleoside 5'-triphosphate with a phosphate group blocking the 3'-hydroxyl.

Ward '955 fails to teach that phosphate is a removable 3'-OH blocking group as required by claims 2 and 3 or that 3'-O-phosphate groups can be enzymatically removed as required by claim 4

However, Tsien WO '678 does teach that 3'-O-phosphate blocking groups can be removed enzymatically by polynucleotide kinase to leave a free 3'-OH at page 25, lines 13 - 22. Furthermore, this reaction can be accomplished within one minute as indicated at page 39, Example 6, lines 112 - 22.

Therefore, the claimed nucleoside 5'-triphosphates with phosphate blocking groups at the 3'-OH position as disclosed by Ward '955 would have been obvious to the

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person of ordinary skill in the art wanting a nucleoside 5'-triphosphate with a 3'-blocking group that can be easily and quickly removed enzymatically as taught by Tsien WO '678. Thus, the claimed 3'-O-phosphate-nucleoside 5'-triphosphates are *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

Claim Rejection -- 35 USC 103(a)

Claims 5 - 6 are rejected under 35 USC 103(a) as being unpatentable over Tsien WO 91/06678 in view of Dower WO 92/10587.

Independent claim 5 requires that the nucleoside 5'-triphosphate possess a solid support as the 3'-OH blocking group and that said support be linked to a removable "hydrocarbyl" linkage. Independent claim 6 also requires that the removable 3'-OH blocking group of the nucleoside 5'-triphosphate be a solid support. Additionally, claim 6 specifies that this solid support blocking group must be linked to the nucleoside 5'-triphosphate by an ester, ether, or phosphate linkage.

Tsien WO '678 as discussed previously discloses nucleoside 5'-triphosphates with 3'-OH removable blocking groups that are esters, ethers or phosphates (page 21, lines 9 - 19. At page 32, lines 26 - 30, Tsien WO '678 further teaches that:

Single-point covalent attachment of DNA to a solid polymer of glass support is possible. Such single-point methods are preferred for immobilizing the subject DNA, since this leaves the chain free for interactions with the polymerase and similar enzymes.

Tsien WO '678 also discloses immobilization of DNA to membranes, quartz, plastic, or particles of resin or polymer microspheres at pages 32 - 34.

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While Tsien WO '678 does not specifically disclose the immobilization of nucleoside 5'-triphosphate compounds to a solid support via the 3'-OH, Dower WO '587 does teach that immobilization of polynucleotides, such as DNA, is useful for the preparation of synthetic polynucleotides. For example, the Dower WO '587 application discloses that DNA can be synthesized on a solid support using nucleotides having a blocking agent on the 3'-hydroxyl group at page 42, lines 29 through page 44, line 12.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have attached a nucleoside 5'-triphosphate having a removable moiety protecting the 3'-position, as disclosed by Tsien WO '678 to a solid support as disclosed by Dower WO '587 to arrive at the compound of claims 5 and 6 of Hiatt '465. It would have been obvious to the person of ordinary skill in the art at the time of the invention to have linked the removable blocking moiety to the solid support in order to achieve rapid purification with simultaneous deblocking and release of the deprotected dNTP or polynucleotide from the solid support. Thus, claims 5 and 6 are *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

Conclusion

Claims 1 - 6 of the Hiatt 6,232,465 patent are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because of the provisions of 37 CFR 1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 USC 305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR

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1.550(a). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c). In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, will be governed by requirements of 37 CFR 1.116, after final rejection and 37 CFR 41.33 after appeal, which will be strictly enforced.

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After the filing of a request for reexamination by 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings have been merged) in the reexamination proceedings in the manner provided in 37 CFR 1.248. See 37 CFR 1.530(f).

Further Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary L. Kunz, whose telephone number is 571-272-0887. The examiner can normally be reached on Monday through Friday (with alternative Fridays off) between 7:00 AM and 4:30 PM.

Art Unit: 3991

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Central Reexamination Unit

Application/Control Number: 90/008,152

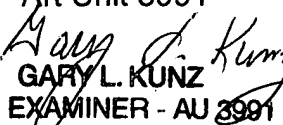
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Art Unit: 3991


By hand to:

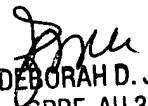
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria VA 22314

Conferee:

Gary L. Kunz
Primary Examiner
Art Unit 3991

GARY L. KUNZ
CRU EXAMINER - AU 3991

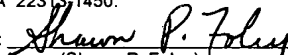
Conferee:


DWAYNE JONES
PRIMARY EXAMINER


DEBORAH D. JONES
SPRE-AU 3991
CENTRAL REEXAMINATION UNIT

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: Mail Stop Ex Parte Reexam, Central Reexamination Unit, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: April 30, 2007 Signature:


(Shawn P. Foley)

Docket No.: SOLEXA 3.5-001 CIP IV
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination Application of:
Andrew C. Hiatt, et al.

Application No.: 90/008,152

Filed: August 3, 2006

For: REEXAM OF U.S. PATENT NUMBER
6,232,465

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: Group Art Unit: 3991
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: Examiner: Gary L. Kunz
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Mail Stop Ex Parte Reexam
Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. § 1.530

Dear Sir:

In response to the Office Communication mailed February 28, 2007, the Patent Owner submits the following proposed amendments and remarks.

IN THE CLAIMS

1. (amended) A nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3' position which is [a hydrocarbyl] an allyl moiety, wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate via an ether linkage.

Cancel Claim 2.

3. (amended) [A] The nucleoside 5' triphosphate of claim 1 [or 2], wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U).

Cancel Claim 4.

5. (amended) [A composition of matter, comprising: (a) a] The nucleoside 5'-triphosphate of claim 1, [having a removable hydrocarbyl blocking moiety linked to a 3' carbon of said nucleoside 5'-triphosphate; and (b)] further comprising a solid support linked to said removable blocking moiety.

Cancel Claim 6.

Proposed Added Claims

7. The nucleoside 5'-triphosphate of claim 1, wherein said nucleoside contains a base that is an analog of adenine (A), guanine (G), thymine (T), cytosine (C) or uracil (U).

8. A composition comprising the nucleoside 5'-triphosphate of claim 1 or claim 3, or claim 7, and an initiating substrate comprising an oligonucleotide having a free and unmodified 3' hydroxyl group or a polynucleotide having a free and unmodified 3' hydroxyl group.

9. The composition of claim 8, wherein said oligonucleotide or polynucleotide is affixed to a solid support.

10. A composition comprising the nucleoside 5'-triphosphate of claim 1 or claim 3, or claim 7, a biological buffer, and an enzyme suitable for phosphodiester bond formation.

11. The composition of claim 10, further comprising an oligonucleotide or polynucleotide comprising at its 3' terminus a nucleotide having a 5-carbon sugar and a nitrogen-containing base, wherein the 3' carbon on said sugar is protected with an allyl removable blocking moiety linked to said 3' carbon via an ether linkage.

12. A composition, comprising: four nucleoside tri-phosphates, wherein each of the 3' positions is protected with an allyl removable blocking moiety linked to the 3' carbon via an ether linkage, and wherein each of the first, second, third, and fourth nucleoside tri-phosphates are different.

13. The composition of claim 12, further comprising an initiating substrate comprising an oligonucleotide having a free and unmodified 3' hydroxyl group or a polynucleotide having a free and unmodified 3' hydroxyl group.

14. The composition of claim 13, wherein said oligonucleotide or polynucleotide is affixed to a solid support.

15. The composition of claim 12 or 13, further comprising a biological buffer and an enzyme suitable for phosphodiester bond formation.

16. The composition of claim 15, further comprising an oligonucleotide or polynucleotide comprising at its 3'-terminus a nucleotide wherein the 3' position is protected with an allyl removable blocking moiety linked to the 3' carbon via an ether linkage.

17. The composition of claim 12, wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U).

18. The composition of claim 12, wherein said nucleoside contains a base that is an analog of adenine (A), guanine (G), thymine (T), cytosine (C) or uracil (U).

19. An oligonucleotide or polynucleotide comprising at its 3' terminus a nucleotide wherein the 3' position is protected with an allyl removable blocking moiety linked to the 3' carbon via an ether linkage.

REMARKS

By way of this submission, the Patent Owner is amending Claims 1, 3 and 5 of U.S Patent 6,232,465 (hereinafter "the '465 Patent), cancelling Claims 2, 4 and 6 of the '465 Patent, and proposing added Claims 7-19, which in accordance with 37 C.F.R. § 1.530(g), are numbered consecutively beginning after the highest numbered claim appearing in the '465 Patent. These amendments are being presented in accordance with 37 C.F.R. § 1.530(d).

Support for Claim 1 as amended can be found, for example, in the '465 Patent specification, for example, at column 7, lines 16-22; column 12, line 66; and at column 30, line 65 of the '465 Patent. The Patent Owner also directs the Examiner's attention to the fact that support for the invention as claimed herein is also contained in the parent i.e., U.S. Application No. 08/300,484, now U.S. Patent 5,990,300 (hereinafter "the '300 Patent). A copy of the '300 Patent is annexed hereto as Exh. A. Support for Claim 1 as amended can be found, for example, at column 7, lines 1-7, and at column 10, line 37 in the '300 Patent. Claim 3 has been amended to be in proper format for dependent claims, i.e., to delete reference to cancelled Claim 2. Claim 5 has been amended to depend from Claim 1.

Support for the proposed added Claims 7-19 is contained in the specification. Support for Claim 7 can be found, for example, at column 6, lines 2-6, and at column 7, lines 4-7 in the '465 Patent, and at column 5, lines 58-63, and at column 6, lines 54-57 in the '300 Patent. Support for Claim 8 can be found, for example, at columns 8, 10 and 22 in the '465 Patent, and at columns 8, 9 (e.g., lines 53-61), and 17-18 in the '300 Patent. Support for Claim 9 can be found, for example, at column 8, lines 39-40 and 51-62 in the '465 Patent, and at

column 8, lines 31-42 in the '300 Patent. Support for Claim 10 can be found, for example, at column 22, lines 1-10 in the '465 Patent, and at column 17, lines 57-66 in the '300 Patent. Support for Claim 11 can be found, for example, at column 22, lines 39-44 in the '465 Patent, and at column 18, lines 28-33 in the '300 Patent. Support for Claim 12 can be found, for example, at column 20, lines 9-12 in the '465 Patent, and at columns 15-16 in the '300 Patent. Support for Claims 13-16 can be found, for example, in the disclosures referenced in connection with Claims 8-11 which contain the same respective recitations. Claims 17 and 18 find support, for example, in the disclosures referenced in connection with claims 3 and 7 which contain the same respective recitations. Support for Claim 19 is contained, for example, at column 7, lines 25-36 in the '465 Patent and at column 7, lines 8-19 in the '300 Patent.

Since the subject matter now being claimed is also supported by the disclosure in the parent, U.S. Application No. 08/300,484 from which the '300 Patent issued, the Patent Owner submits that amended Claims 1, 3 and 5, and proposed added Claims 7-19 are entitled to the earliest priority date, namely September 2, 1994.

In view of these amendments, it is clear that pursuant to 37 C.F.R. § 1.530(j), there has been no enlargement of claim scope or introduction of new matter.

Pursuant to 37 C.F.R. § 1.550(f) and § 1.246, copies of this Amendment, all annexed exhibits and other accompanying documents, are being served upon the Requester.

The Rejections

The Office Communication sets forth five (5) different rejections of various claims, namely:

- Claims 1-4 have been rejected under 35 U.S.C. § 102(b) as being unpatentable over Tsien,

WO 91/06678 (hereinafter "*Tsien*") and within this rejection three separate grounds of rejection are enumerated, as they apply to ester protecting groups ("A"), ether protecting groups ("B"), and phosphate protecting groups ("C");

- Claims 1-4 have been rejected under 35 U.S.C. § 102(b) as anticipated by Dower, WO 92/10587 ("*Dower*");
- Claims 1-3 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Kraevskii et al., Mol. Biol. 21:25-29 (1987) ("*Kraevskii*");
- Claims 2-4 have been rejected under § 103(a) as being unpatentable over Ward et al., U.S. Pat. No. 4,711,955 ("*Ward*"), in view of *Tsien*; and
- Claims 5 and 6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Tsien* in view of *Dower*.

Response to the Rejections

In view of the fact that Claims 2, 4 and 6 have been canceled, and that amended Claims 1, 3 and 5, and proposed added Claims 7-19 share at least one common recitation, namely, that the 3' position is protected with an allyl removable blocking moiety that is linked to the 3' carbon via an ether linkage, each of these rejections is rendered moot, either in whole or in part. For the sake of completion and in the spirit of dispatch with which the instant proceeding is to be conducted, the Patent Owner responds to each of these rejections, as follows.

Rejections under 35 USC § 102

The Patent Owner submits that the rejection of Claims 1-4 under § 102(b) as being anticipated by *Tsien* is moot with respect to ground "A" directed to ester protecting groups, and

ground "C" which is directed to phosphate protecting groups, as these groups are not encompassed by the amended claims.

The ground of rejection set forth as "B" is directed to ether protecting groups. For the following reasons, the Patent Owner respectfully submits that *Tsien* does not anticipate any of Claims 1 or 3 as amended.

In support of the rejection, the Office points to page 21, lines 12-13 as allegedly describing ether blocking groups. This passage occurs in the section entitled "Blocking Groups and Methods for Incorporation". There is absolutely no disclosure at page 21, lines 12-13 or anywhere else in this section of allyl ethers as 3'-blocking groups of a nucleoside 5'-triphosphate. Thus, there is no explicit teaching in this section of a nucleoside 5'-triphosphate having an allyl removable blocking moiety protecting the 3' position which is linked to the 3' carbon via an ether linkage, as required by the present claims, or for that matter, wherein the base is adenine, guanine, thymine, cytosine or uracil as recited in Claim 3 as amended, or wherein the base is an analog of adenine, guanine, thymine, cytosine or uracil, as recited in proposed added Claim 7. (*Kraevskii* which is referenced in page 21, line 19 of *Tsien*, does not teach allyl ether blocking groups, as set forth in further detail below.) Plainly, the complete absence of any mention of allyl ethers in this section is evidence that *Tsien* did not envision the compounds which are the subject matter of Claims 1 and 3 as amended.

In the subsequent section entitled "Deblocking Methods", *Tsien* references a 1968 publication that allegedly teaches that treatment with Hg(II) in acetone/water will cleave an allyl ether. See, *Tsien*, Page 24, lines 29-30. The mere description of general deblocking methods in this section does not describe

a nucleoside 5'-triphosphate having an allyl removable blocking moiety, much less one having an allyl removable blocking moiety which is linked specifically at the 3' carbon as claimed.

Rather the only description that can be found in *Tsien* of a compound having an allyl ether group is in the next section entitled "Reporter Groups, their Incorporation and Detection." In this section *Tsien* contrasts the use of labels at different positions on a nucleoside, specifically stating:

While the above-described approaches to labeling focus on incorporating the label into the 3'-hydroxyl blocking group, there are a number of *alternatives* - particularly the formation of a 3'-blocked dNTP analogue containing a label such as a fluorescent group coupled to a *remote position* such as the base. This dNTP can be incorporated and the fluorescence measured and removed according to the methods described below.

See *Tsien*, at page 27 line 33, through page 28, line 4 (emphasis added). *Tsien* then goes on to describe chemical means by which the label can be attached to these remote positions. Specifically, *Tsien* states:

In another type of remote labeling the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. The tether can be cleavable if desired to release the fluorophore or other label on demand. There are several cleavable tethers that permit removing the fluorescent group before the next successive nucleotide is added--for example, silyl

ethers are suitable tethers which are cleavable by base or fluoride, allyl ethers are cleavable by Hg(II), or 2,4-dinitrophenylsulfenyls are cleavable by thiols or thiosulfate.

See *Tsien*, at page 28, lines 19-29(emphasis added). Although *Tsien* describes an allyl ether as a cleavable tether that can be used at the remote position, *Tsien* does not describe using an allyl ether at the 3' position, as claimed.

Therefore Patent Owner respectfully submits that any disclosure of allyl ether moieties in *Tsien* does not rise to a level to satisfy the requirements for anticipation under § 102(b).

For a claimed invention to be anticipated all claim elements must be shown in a single prior art reference. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Additionally, as determined by the Federal Circuit, every element of the claimed invention must be literally present, arranged as in the claim. *Id.*, at 1920 ("The identical invention must be shown in as complete detail as is contained in the . . . claim."); see *Brown v. 3M*, 265 F.3d 1349, 60 U.S.P.Q.2d 1375 (Fed. Cir. 2001) (to anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim); *Novo Nordisk v. Becton Dickinson & Co.*, 96 F. Supp. 2d 309, 312 (S.D. N.Y. 2000) (It is "not sufficient that each element be found somewhere in the reference, the elements must be 'arranged as in the claim'."). Thus, to be anticipatory, the prior art must describe the exact composition, or in this case, the compounds. For example, it is long-standing law that the novelty of an optical isomer is not negated by the prior art disclosure of its

racemate. *In re May*, 197 U.S.P.Q. 601, 607 (CCPA 1978) (citing *In re Williams*, 80 U.S.P.Q. 150, 151 (CCPA 1948)).

In this regard, it is clear that *Tsien* does not teach every element of the claimed invention arranged as in Claims 1 and 3 as amended, as the law requires. In view of the foregoing, the Patent Owner respectfully submits that *Tsien* does not anticipate Claims 1 or 3 as amended.

The Patent Owner also submits that *Tsien* does not anticipate Claim 5, as amended, or any of proposed added Claims 7-19, all of which require the presence of an allyl removable blocking moiety linked to the 3' carbon via an ether linkage.

The rejection of Claims 1-4 under § 102(b) as being clearly anticipated by *Dower* is now moot in view of the amendments. The Office relies upon *Dower* as allegedly describing ester blocking groups. In contrast all claims presented herein, including Claims 1 and 3 as amended, require, *inter alia*, an allyl removable blocking moiety linked to the 3' carbon via an ether linkage. Absent any description of an allyl ether group occupying the 3' position, *Dower* does not anticipate Claims 1 or 3 as amended.

The rejection of Claims 1-3 under § 102(b) as being anticipated by *Kraevskii* is also moot in view of the amendments. The Office relies upon *Kraevskii* as allegedly describing 2'-deoxynucleoside 5'-triphosphates with a methyl ether blocking group on the 3' OH. In contrast, all the claims including Claims 1 and 3 as amended, require, *inter alia*, an allyl removable blocking moiety linked to the 3' carbon via an ether linkage. Absent any description of an allyl ether group occupying the 3' position, *Kraevskii* does not anticipate Claims 1 or 3 as amended.

Response to rejections under 35 USC § 103

The rejection of Claims 2-4 under § 103(a) over *Ward* in view of *Tsien* is rendered moot by the amendments. The Patent Owner respectfully maintains, for the reasons set forth above in response to the novelty rejections, that *Tsien* does not teach or suggest all of the elements of Claim 3 as amended. For example, *Tsien* does not teach or suggest a nucleoside 5' triphosphate having an allyl removable blocking moiety protecting the 3' position linked to the 3' carbon via an ether linkage. *Ward* is relied upon by the Office as allegedly describing use of a phosphate group blocking the 3' hydroxyl of a nucleoside 5'-triphosphate. As such, *Ward* does not cure the deficiencies of *Tsien*. Accordingly, the references taken alone or in combination do not render obvious the subject matter of Claim 3 as amended.

The rejection of Claims 5 and 6 under § 103(a) over *Tsien* in view of *Dower* is rendered moot by the amendments. The Patent Owner respectfully maintains, for the reasons set forth above in response to the novelty rejections, that neither *Tsien* nor *Dower* teaches or suggests all of the elements of the claims as amended. For example, neither reference teaches or suggests a nucleoside 5' triphosphate having an allyl removable blocking moiety protecting the 3' position which is linked to the 3' carbon via an ether linkage. Accordingly, the references taken alone or in combination do not render obvious the subject matter of Claim 5 as amended.

Lastly, in view of the fact that *Tsien* has been applied to some claims under § 103, the Patent Owner wishes to bring the following evidence to the attention of the Office. It sheds light on the state of the art at the time the claimed invention was made. In particular, it speaks to the issue of whether a person of ordinary skill in the art would or would not have been

motivated, on the basis of the teachings in *Tsien*, to make a compound comprising an dNTP capped with a 3'-allyl ether group. Specifically, the evidence is probative of a determination that *Tsien* does not suggest that allyl ether 3' blocking groups would be effective from the standpoints of hydrolyzability and their steric effect on a nucleic acid polymerase during nucleic acid synthesis. Evidence in support of this position is embodied in EP 1,337,541 B1 ("the '541 patent"), in the name of The Trustees of Columbia University in the City of New York (hereinafter "Columbia University"), annexed hereto as Exh. B, and its prosecution history, relevant portions of which are annexed hereto as Exhs. C and D. Exhibit C is a copy of a Communication pursuant to Article 96(2) EPC, dated March 30, 2005, which was the first Examination Report issued by the European Patent Office (EPO). Exhibit D is a copy of the Reply to the Communication Pursuant to Article 96(2), dated October 10, 2005, including amended claims.

The '541 patent claims priority on the basis of two U.S. applications, filed in 2000 and 2001 respectively. As clearly shown on the face of the '541 patent, *Tsien* (WO-A-91/06678) was of record. In fact, the EPO considered *Tsien* to be the "closest prior art". See, Exh. C, first line in paragraph 5.1 in page 4.

As shown in Exh. B, Claim 1 of the '541 patent is directed to a method for sequencing a nucleic acid that entails use of a nucleotide analogue containing a deoxyribose having a cleavable chemical group to cap the 3' OH group, which is a $\text{CH}_2\text{-O-CH}_3$ group (referred to therein as an MOM group) or an allyl ether group (*i.e.*, $\text{CH}_2\text{CH=CH}_2$). Claim 37 is directed to the nucleotide analogue, *per se*. Claims 12 and 38, which depend from claims 1 and 37 respectively, specify that the cleavable chemical group is the allyl ether.

As originally filed, claims 1 and 37 simply recited "a cleavable chemical group to cap an OH group at a 3' position of the deoxyribose". Claims 12 and 38 recited the two specific blocking groups. At the very outset of prosecution, the European Patent Office seized on the disclosure in paragraph [0008] in page 3 of the '541 patent as an admission that the nature of the 3' blocking was essential for the invention, and that the allyl ether and the MOM groups combined the advantage of being easily cleavable and having little steric effect on the polymerase during the elongation step. See, Exh. C, paragraph 3 in page 3. More importantly, for purposes of the present matter, the EPO then stated its determination that the prior art, including *Tsien* which it considered as the "closest prior art", did not suggest that the MOM or the allyl ether groups did possess the advantages of being hydrolysable and having little steric effect on the polymerase during an elongation step. See, Exh. C, paragraph 5.1 in page 5. Columbia University expressly agreed with this determination and amended its claims. See, Exh. D, page 5 ("These features are not suggested in the prior art, as acknowledged by the Examiner...").

The Patent Owner respectfully submits that this evidence is relevant in any obviousness determination of the presently claimed invention, which of course, now also involves, *inter alia*, presence of allyl removable blocking moieties linked to the 3' carbon via an ether linkage, and interestingly enough, the very same prior art publication, *Tsien*. Basically, the evidence shows that even 6 years after the time the presently claimed invention was made, persons skilled in the art would not have been motivated to prepare the compounds of claims 1, 3 and 7, or compositions containing them, with a reasonable expectation that they could be used for DNA synthesis.

In view of the foregoing, the Patent Owner respectfully submits that Claims 1, 3 and 5 as amended, and proposed added Claims 7-19 are patentable. Withdrawal of all rejections and issuance of a Reexamination Certificate to this effect are therefore requested.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone the Patent Owner's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: April 30, 2007

Respectfully submitted,

By Shawn P. Foley
Shawn P. Foley
Registration No.: 33,071
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000

758728_1.DOC

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the following documents:

1. Amendment under 37 C.F.R. § 1.530, with Exhibits A-D and
Amendment transmittal;
2. Information Disclosure Statement Pursuant to 37 C.F.R. § 1.555; and
3. Twenty-six (26) Publications

are being served upon the Requester with respect to the reexamination of U.S. Patent No.
6,232,465, this 30th day of April, 2007, as follows:

VIA FIRST CLASS MAIL

Howard M. Gitten, Esq.
Edwards, Angell, Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150
Ft. Lauderdale, FL 33301


SHAWN P. FOLEY

Registration No. 33,071

Control No. 90/008,152



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,152	08/03/2006	6232465	None	5197

530 7590 01/07/2008

LERNER, DAVID, LITTENBERG,
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600 SOUTH AVENUE WEST
WESTFIELD, NJ . 07090

EXAMINER

ART UNIT PAPER NUMBER

DATE MAILED: 01/07/2008

Please find below and/or attached an Office communication concerning this application or proceeding.



DO NOT USE IN PALM PRINTER

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

HOWARD M. GITTEN, EQS.
EDWARDS, ANGELL, PALMER & DODGE LLP
350 EAST LAS OLAS BLVD., SUITE 1130
FT. LAUDERDALE, FL 33301

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. 90/008,152.

PATENT NO. 6,232,465.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,152	Patent Under Reexamination 6232465	
	Examiner Gary L. Kunz	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

- a ☒ Responsive to the communication(s) filed on Request of 8/3/07. b ☐ This action is made FINAL.
c ☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 3. <input type="checkbox"/> Interview Summary, PTO-474. |
| 2. <input type="checkbox"/> Information Disclosure Statement, PTO/SB/08. | 4. <input checked="" type="checkbox"/> <u>PTO/SB/42</u> . |

Part II SUMMARY OF ACTION

- 1a. ☒ Claims 1-6 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims 1-6 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
1 ☐ been received.
2 ☐ not been received.
3 ☐ been filed in Application No. _____.
4 ☐ been filed in reexamination Control No. _____.
5 ☐ been received by the International Bureau in PCT application No. _____.
* See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

EX PARTE REEXAMINATION

DETAILED ACTION

Final Rejection

This is a Final Rejection in the reexamination proceeding of claims 1 - 6 of 6,232,465, issued on 15 May 2001 to Hyatt et al.

Procedural Posture

On 03 August 2006 the request for *ex parte* reexamination by the Third Party Requester was filed.

On 29 September 2006 the request for reexamination was granted. No Patent Owner Response was submitted under 37 CFR §1.530.

On 28 February 2007 a non-final Office action was mailed.

On 02 May 2007 the Patent Owner responded to the non-final action by filing an amendment.

Information Disclosure Statement

On 2 May 2007 the Patent Owner filed an Information Disclosure Statement (IDS). Each of the documents listed on this IDS has been considered and an initialed, signed copy of this IDS is attached to the Office action.

Continuing Duty to Disclose

The Patent Owner is reminded of the continuing responsibility under 37 CFR §§1.555, 1.565(a), and 1.933 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving U. S. Patent No. 6,232,465 throughout the course of

Art Unit: 3991

the reexamination proceedings. The Third Party Requester is also reminded of the ability similarlyl apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§2684, 2280, and 2282.

Status of Claims

The Patent Owner has cancelled original patent claims 2, 4 and 6 and has added new claims 7 - 19. Therefore, claims 1, 3, 5, and 7 - 19 are pending. In each of the pending claims, the Patent Owner has narrowed the 3'-O-nucleotide protecting group to only "an allyl moiety" linked to the 3'-carbon atom via an oxygen atom.

Withdrawn Claim Rejection - 35 USC §102(b)

The rejection of claims 1 - 4 under 35 USC §102(b) as being anticipated by Tsien WO 91/06678 in view of Patent Owner's admission has been withdrawn because claims 2 and 4 have been cancelled and claims 1 and 3 have been amended to the specific allyl protecting group at the 3'-OH position of the nucleotide 5'-triphosphate.

Withdrawn Claim Rejection - 35 USC §102(b)

The rejection of claims 1 - 4 under 35 USC §102(b) as being clearly anticipated by by Dower PCT WO 92/10587 in view of Patent Owner's admission has been withdrawn because claims 2 and 4 have been cancelled and claims 1 and 3 have been narrowed to the specific allyl protecting group at the 3'-OH position of an nucleotide-5'-triphosphate.

Withdrawn Claim Rejection - 35 USC §102(b)

The rejection of claims 1 - 3 under 35 USC §102(b) as being clearly anticipated by Kraevskii et al. in view of the Patent Owner's admission has been withdrawn because claim 2 has been cancelled and claims 1 and 3 have been narrowed to the specific allyl protecting group at the 3'-OH position of a nucleotide-5'-triphosphate.

Withdrawn Claim Rejection - 35 USC §103(a)

The rejection of claims 2 - 4 under 35 USC §103(a) as being unpatentable over Ward et al. in view of Tsien WO '678 has been withdrawn because claims 2 and 4 have been cancelled and claim 3 has been narrowed to the specific allyl protecting group at the 3'-OH position of a nucleotide-5'-triphosphate.

Withdrawn Claim Rejection - 35 USC §103(a)

The rejection of claims 5 - 6 under 35 USC §103(a) as being unpatentable over Tsien WO 91/06678 in view of Dower WO 92/10587 has been withdrawn because claim 6 has been cancelled and claim 5 has been narrowed to the specific allyl protecting group for the 3'-OH position of a nucleotide-5'-triphosphate.

New Claim Rejection -- 35 USC §305

9. Claim 19 is rejected under 35 U.S.C. §305 as enlarging the scope of the claims of the patent being reexamined.

In 35 U.S.C. §305, it is stated that "[n]o proposed amended or new claim enlarging the scope of a claim of the patent will be permitted in a reexamination proceeding... ." A claim presented in a reexamination "enlarges the scope" of the patent claim(s) where the claim is broader than any claim of the patent. A claim is broader in scope than the

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original claims if it contains within its scope any conceivable product or process which would not have infringed the original patent. A claim is broadened if it is broader in any one respect, even though it may be narrower in other respects.

The following rationale supports the rejection under 35 U.S.C. 305 as enlarging the scope of the claims of the patent being reexamined.

Claim 19 is presented below.

Claim 19. An oligonucleotide or polynucleotide comprising at its 3'-terminus a nucleotide wherein the 3'-position is protected with an allyl removable blocking moiety linked to the 3'-carbon via an ether linkage.

Original claims 1 - 4 in the Hiatt '465 patent are directed to nucleoside 5'-triphosphates with a protected 3'-OH. Claims 5 - 6 are directed to compositions comprising nucleoside 5'-triphosphates with a 3'-OH protected group. However, newly submitted claim 19 is directed to a "separate and distinct" invention from the issued claims. The product inventions as issued in the '465 patent and the invention of claim 19 as presented in the amendment filed May 3, 2007 are related as different products which are regarded as "separate and distinct" inventions.

Claims to a "separate and distinct" inventions from the patent are considered to be an enlargement of the scope of the patent claims. The addition of the oligonucleotide claim in the patent (i.e., where there were no oligonucleotide or polynucleotide claims present in the original patent) is generally considered as being a broadening of the invention. See *Ex Parte Wikdahl*, 10 USPQ2d 1546 (Bd. Pat. App. & Inter. 1989) (See MPEP §§1414.031 and 2258, section IV, part C). Accordingly, newly submitted claim 19 "enlarges the scope" of the claims of the '465 patent being reexamined because this claim is broader than each and every claim of the patent.

New Claim Rejection - 35 USC §103(a)

Claims 1, 3, 5, and 7 -19 are rejected under 35 USC 103(a) as being obvious over Tsien et al. (WO 91/06678) in view of Greene et al. (Protective Groups in Organic Chemistry, John Wiley & Sons: New York, 1991, pages 42 - 45 and 413 and the Patent Owner admission at column 13, lines 55 - 64.

Claims 1, 3, 5, and 7 are directed to nucleoside 5'-triphosphates wherein the 3'-OH protecting group is allyl. Claim 3 requires that the nucleoside base is any of the five bases in DNA and RNA. Claim 5 requires that the nucleoside 5'-triphosphate is linked through the 3'-OH protecting group to a solid support. Claim 7 requires that the nucleoside base is an analog of the five bases in DNA and RNA. Claim 8 - 18 are directed to compositions comprising from one to four nucleoside 5'-triphosphates of claims 1, 3, or 7, and further comprising a buffer, an enzyme suitable for phosphodiester bond formation, and an oligonucleotide or polynucleotide which may also be attached to a solid support via the 3'-O-protecting group. Claim 19 is directed to an oligonucleotide or polynucleotide with the 3'-OH protected by an allyl group.

Tsien et al. disclose a method for sequencing DNA comprising enzymatically incorporating 3'-O-protected nucleoside 5'-triphosphates or fluorescent analogues therein (page 38, Example 4) onto a DNA template immobilized on a solid support (Example 3 and pages 32 - 34). A DNA polymerase is mixed with four fluorescent-labeled dNTP's with a protected 3'-OH along with a DNA template bound to a solid support, wherein the bound DNA has a free 3'-OH group. Once the enzyme has incorporated a specific fluorescent 3'-OH protected nucleoside 5'-triphosphate, the

composition will then further contain an oligonucleotide or polynucleotide with a protected 3'-OH. See Tsien et al. at page 12, lines 22 - 29.

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

Therefore, the claimed 3'-OH protected nucleoside 5'-triphosphates and compositions containing them along with a buffer, an enzyme capable of forming phosphodiester bonds, an oligonucleotide or polynucleotide with a free 3'-OH group bound to a solid support would have been obvious to the person of skill in the art as taught by Tsien et al. for the purpose of sequencing the nucleic acid bound to the solid support. The use of a 3'-OH allyl protecting group that is readily removable but not only implicitly disclosed in Tsien et al. is rendered obvious by Greene et al. and the Patent Owner's admission that all of the protecting groups are known in the prior art. Furthermore, the claimed oligonucleotide or polynucleotide bound to a solid support via an allyl protected 3'-OH (claim 19) is also obvious because this is the product of the enzyme

adding a 3'-OH protected nucleoside 5'-triphosphate to an oligonucleotide or polynucleotide bound to a solid support and having a free 3'-OH. Thus, claims 1, 3, 5, and 7 - 19 are *prima facie* obvious over Tsien et al. in view of Greene et al. and the Patent Owner admission at column 13, lines 55 - 64.

Response to Patent Owner's Argument

The Patent Owner's arguments traversing the new obviousness rejection have been fully considered but are not deemed persuasive.

On page 12, last six lines to the end of page 14 of the "Arguments" section of the amendment, the Patent Owner provides a preemptive explanation for the non-obviousness of the instant claims in order to obviate any potential obviousness rejection over Tsien et al. (WO 91/06678). The Patent Owner provides documentation of alleged unexpected results in the use of either allyl or methoxymethyl groups to protect the 3'-OH of nucleoside 5'-triphosphates, by referencing to the EPO prosecution history of EP 1,37,541 B1 (the '541 patent). Interestingly, the '541 patent was also claiming 3'-OH protected nucleoside 5'-triphosphates for use in a DNA sequencing process. The preferred protecting groups were allyl and methoxymethyl. Furthermore, the EPO considered that Tsien et al. (WO 91/06678) was the closest prior art. In the words of the Patent Owner at page 12, line 6 from the bottom to page 13, line 22:

Lastly, in view of the fact that Tsien has been applied to some claims under §103, the Patent Owner wishes to bring the following evidence to the attention of the Office. It sheds light on the state of the art at the time the claimed invention was made. In particular, it speaks to the issue of whether a person of ordinary skill in the art would or would

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not have been motivated, on the basis of the teachings in Tsien, to make a compound comprising an dNTP with a 3'-allyl ether group. Specifically, the evidence is probative of a determination that Tsien does not suggest that allyl ether 3'-blocking groups would be effective from the standpoints of hydrolysability and their steric effect on a nucleic acid polymerase during the nucleic acid synthesis. Evidence in support of this position is embodied in EP 1,337,541 B1 ("the '541 patent"), in the name of the Trustees of Columbia University in the City of New York (hereinafter), annexed hereto as Exh. B, and its prosecution history, relevant portions of which are annexed hereto as Exhs. C and D. Exhibit C is a copy of a Communication pursuant to Article 96(2) EPC, dated March 30, 2005, which was the first Examination Report issued by the European Patent Office (EPO). Exhibit D is a copy of the Reply to the Communication pursuant to Article 96(2), dated October 10, 2005, including amended claims.

The '541 patent claims priority on the basis of two U.S. applications, filed in 2000 and 2001, respectively. As clearly shown on the face of the '541 patent, Tsien (WO-A-91/00678) was of record. In fact, the EPO considered Tsien to be the "closest prior art." See, Exh. C, first line in paragraph 5.1 in page 4.

In effect, the Patent Owner is suggesting that the evidence from the EPO showing that this patent office considered nucleoside 5'-triphosphates having a 3'-OH protected with either allyl or methoxymethyl groups to be patentable over the prior art reference of Tsien et al. because of alleged unexpected results, should be equally applicable to the instant claims which also claim nucleoside 5'-triphosphates also possessing an allyl or methoxymethyl protecting group at the 3'-hydroxyl.

The Patent Owner's evidence and arguments regarding the non-obviousness of the claimed nucleoside 5'-triphosphates with allyl or MOM(methoxymethyl) groups protecting the 3'-hydroxyl over Tsien et al. have been fully considered but are not deemed persuasive. The central problem with the Patent Owner's arguments, which

focus on the prosecution history of the '541 patent, is the contradictory teachings of the Patent Owner in the specification of the Hiatt et al. '465 patent itself. The '465 patent provides all of the necessary information to understand the perspective of the artisan at the time of the invention.

At the time of the invention, it is clear that the Patent Owner believed that virtually any known hydroxyl protective group known in the art (See Greene et al. '91) that was easily removable without harming the growing polynucleotide would be usable in his invention of synthesis of DNA. A vast number of hydroxyl protecting groups are disclosed by the Hiatt '594 patent beginning at column 9, line 55 through column 14, line 44. The Patent Owner discloses 27 specific ester protective groups at column 11, line 1 through line 67, including the especially sterically bulky triphenylmethoxyacetate at line 17. The Patent Owner discloses 53 specific ether protecting groups at column 12, line 42 through line 65, including the especially sterically bulky (triphenylmethyl)dimethylsilyl group at line 63. Among the preferred ether protecting groups is tri(methoxyphenyl)-methyl ether at column 13, line 15. Furthermore, the Patent Owner recites a litany of other well known removable blocking moieties useful for protecting hydroxyls including carbonitriles, phosphates, carbonates, carbamates, borates, nitrates, phosphoramidates, and phenylsulfenates at column 13, lines 38 - 41.

In a related patent by the same inventor, 5,872,244, the Patent Owner not only discloses the information concerning bulky hydroxyl protecting groups, but actually claims the same nucleoside 5'-triphosphates with 3'-OH protecting groups consisting of tri(p-methoxyphenyl)methyl and (triphenylmethyl)dimethylsilyl in claims 1 and 2 of this

patent. The teachings by the Patent Owner are clear : both large and small protecting moieties are operative in his enzyme elongation method for synthesizing polynucleotides. There is no caveat in the Hiatt '465 patent against the use of bulky 3'-OH protecting groups in the enzymatic polynucleotide synthesis process. Therefore, at the time of the invention, contrary to the teaching of the '541 patent, the artisan would not have found it surprising that relative small protecting groups such as allyl and methoxymethyl would not sterically interfere with the enzyme-catalyzed elongation step in the synthesis of a polynucleotide, especially when Patent Owner discloses numerous bulky 3'-OH protecting groups that are compatible with the elongation of a polynucleotide.

Conclusion

All pending claims 1, 3, 5 and 7 - 19 are rejected.

Final Rejection

Patent owner's amendment filed 19 September 2007 necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP §706.07(a).

A shortened statutory period for response to this action is set to expire **TWO MONTHS** from the mailing date of this action.

Extensions of time under 37 CFR §1.136(a) do not apply in reexamination proceedings. The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. §305 and in 37 CFR §1.550(a), it is required that reexamination proceedings "will be conducted with special

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dispatch within the Office." Extensions of time in reexamination proceedings are provided for in 37 CFR §1.550(c). A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR §1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Service on the Other Party (3rd Party Request)

After the filing of a request for reexamination by 3rd party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings have been merged) in the reexamination proceedings in the manner provided in 37 CFR §1.248. See 37 CFR §1.530(f).

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

Effective May 16, 2007, 37 CFR §1.33(c) has been revised to provide that:

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The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Further Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary L. Kunz, whose telephone number is 571-272-0887. The examiner can normally be reached on Monday through Friday (with alternative Fridays off) between 7:00 AM and 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached at 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Should you have questions about access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this *Ex Parte* Reexamination proceeding should be directed to:

By Mail to:

Attn: Mail Stop "Ex Parte Reexam"
Central Reexamination Unit
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450


By FAX to:

(571) 273-9900
Central Reexamination Unit

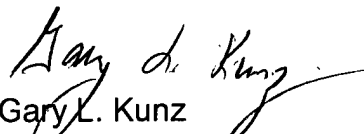
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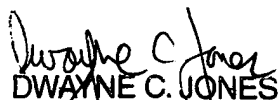
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Application No.: 90/008,152

Docket No.: SOLEXA 3.5-001 CIP IV

IN THE CLAIMS

Please cancel claim 19.

REMARKS

The indication that the documents cited on the IDS have been considered is acknowledged. The indication that all prior rejections set forth under §§ 102 and 103 have been withdrawn is acknowledged and appreciated.

Claim 19 is being cancelled. Entry of this amendment is requested because it reduces issues for purposes of appeal.

In view of the cancellation of claim 19 and the following arguments, the patent owner respectfully requests reconsideration and withdrawal of the two new rejections, namely (1) the rejection of claims 19 under 35 U.S.C. § 305, and (2) the rejection of claims 1, 3, 5 and 7-19 under § 103(a).

THE § 305 REJECTION

Claim 19 has been rejected under 35 U.S.C. § 305 as purporting to enlarge the scope of the claims of the patent being reexamined. Claim 19 is being cancelled. Withdrawal of the rejection is respectfully requested.

THE § 103 REJECTION

Claims 1, 3, 5 and 7-19 have been rejected under § 103(a) as being unpatentable over Tsien, et al., (WO 91/06678) (hereinafter "*Tsien*") in view of Greene, et al. (*Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, New York 1991, pp. 42-45 and 413) (hereinafter "*Greene*"), and the alleged admission of the patent owner at column 13, lines 55-64. The Examiner concedes that *Tsien* does not explicitly teach a nucleoside 5'-triphosphate with a 3'-allyl protective group. The Examiner alleges, however, that by referencing the ribosyl through the use of the term "remote," the person of ordinary skill in the art would immediately envision the 3'-OH protected by an allyl group because the prior

art, i.e., *Greene* at pages 42-45 and 413, clearly teaches allyl as a standard protecting group for hydroxyl groups. Thus, the Examiner has asserted that the claimed 3'-OH protected nucleoside 5'-triphosphates, and compositions containing them along with a buffer, an enzyme capable of performing phosphodiester bonds and an oligonucleotide or polynucleotide with a free 3'-OH group bound to a solid support, would have been obvious to the person of ordinary skill in the art, as taught by *Tsien* for the purpose of sequencing the nucleic acid bound to the solid support.

The Examiner has also asserted that the use of an allyl 3'-OH protecting group that is readily removable but not implicitly [*sic* specifically] disclosed in *Tsien* are rendered obvious by *Greene* and the patent owner's alleged admission that all of the protecting groups are known in the prior art. The Examiner has further asserted that the claim 19 which is directed to an oligonucleotide or polynucleotide bound to a solid support via an allyl-protected 3'-OH is also obvious because this is the product of the enzyme adding a 3'-O-protected nucleoside 5'-triphosphate to an oligonucleotide or polynucleotide bound to a solid support and having a free 3'-OH.

At pages 8-11 of the Office communication, the Examiner has attempted to rebut the patent owner's "preemptive" explanation for the non-obviousness of the instant claims over *Tsien*. The Examiner notes that the patent owner's explanation centers around European Patent 1,337,541 B1 ("the EP '541 Patent") in the name of the Trustees of Columbia University in the City of New York and the prosecution of that patent. Specifically, the Office communication states that the patent owner's arguments and evidence regarding the EP '541 Patent suggest that the European Patent Office (EPO) considered nucleoside 5'-triphosphates having a 3'-OH protected with either allyl or methoxymethyl groups to be patentable over *Tsien*

because of unexpected results, in particular with respect to hydrolysability and a lack of steric hindrance of a DNA polymerase, and that this evidence is equally applicable to the instant claims, which are also directed to nucleoside 5'-triphosphates possessing an allyl or methoxymethyl protecting group at the 3'-hydroxyl.

At Page 9 of the Office communication, the Examiner states that the foregoing evidence was fully considered but not deemed persuasive. In the Examiner's estimation, the central problem with the patent owner's argument is that the teachings in the specification of the Hiatt '465 Patent purportedly contradict the alleged unexpected results discussed in the EP '541 Patent prosecution history. In arriving at this assessment of the patent owner's arguments in connection with the issue of obviousness, as set forth at pp. 10-11 of the Official communication, the Examiner has expressed three beliefs regarding facts of this case and the law on obviousness. The first such belief is apparently that the patent owner's '465 Patent should provide all of the necessary information regarding the perspective of an artisan of ordinary skill as of the time of the invention. The second apparent belief is that at the time of the invention, the patent owner believed that virtually any known hydroxyl protective group known in the art that was easily removable without harming the growing polynucleotide, would have been operative in his invention of the enzymatic synthesis of DNA. Third, the Examiner appears to believe that the absence of any "caveat" in the Hiatt '465 Patent against the use of bulky 3'-OH protecting groups or that an allyl or methoxymethyl group would be expected to sterically hinder a DNA polymerase enzyme, coupled with the teachings of the Hiatt '465 Patent that bulky 3'-OH protecting groups will also function in the enzymatic polynucleotide synthesis process, indicate that the patent owner in essence has clearly taught that both large and small protecting moieties alike are operative in his enzyme elongation method for synthesizing polynucleotides.

The rejection is now moot with respect to claim 19. The patent owner respectfully traverses the rejection of claims 1, 3, 5 and 7-18 under 35 U.S.C. § 103. The patent owner's arguments were not cast explicitly as "unexpected results," but more generally that the evidence is probative of a determination that Tsien does not suggest that an allyl blocking moiety would have been effective for purposes of nucleic acid synthesis due to an extant belief that it caused problems from the standpoints of hydrolysability and steric hindrance. Nonetheless, any perceived or actual contradiction between the arguments and evidence of nonobviousness of record and the teachings of the Hiatt '465 Patent are simply irrelevant from the standpoint of the obviousness issue. Likewise, the three crucial presumptions or beliefs that are the underpinnings of the Examiner's assessment of the patent owner's arguments are either incorrect as a matter of fact and/or law, or are also irrelevant with respect to the determination of obviousness of the claimed invention.

In essence, the Examiner has relied on the teachings of the inventors in the present case to reject the claims at issue, contending that they have equated the use of large and small 3' blocking protecting moieties in the claimed invention. As discussed below, this approach is fundamentally improper, as the obviousness or nonobviousness of a claimed invention is never to be judged by what is or is not obvious to the inventor. Rather, it must be judged from the viewpoint of what would have been obvious to a person of ordinary skill in the relevant art. If obviousness were to be measured by what was or was not obvious to an inventor, then an argument could be made that every invention is obvious, because the inventor, in making his invention, undoubtedly proceeded along a path that was obvious to him. Simply stated, what may be apparent to an inventor does not equate to obviousness to a person of ordinary skill in the art.

Accordingly, in the present case, although Hiatt, et al., disclose in the '465 patent specification a variety and large number of different blocking moieties, and without any caveat or discriminating explanation as to the relative operability of each, the fact that the prior art discloses 3'blocked nucleoside 5'-triphosphates with certain of the blocking groups does not mean that all of the disclosed 3'blocked nucleoside 5'-triphosphates would have been obvious over the prior art. Stated somewhat differently, even if it were assumed that the Hiatt, et al. '465 patent specification (or the related Hiatt '594 specification or the specification and claims of the related U.S. Patent 5,872,244, as alleged in pages 10-11 of the Office communication) suggests that the disclosed blocking groups are interchangeable, it would be improper to deduce that the person of ordinary skill in the art would have believed that to be the case. Thus, notwithstanding the absence of any caveat in the '594 patent specification, all the disclosed 3'blocked nucleoside 5'-triphosphates do not rise or fall together for purposes of patentability under §103.

As demonstrated by the evidence submitted by the patent owner in its prior response, despite the fact that some moieties are disclosed in the prior art as being useful as "blocking moieties," it would not necessarily have been obvious to a person of ordinary skill in the relevant art that they would be operable in the more specific context of the present invention. The weight of the evidence which shows that Hiatt, et al., proceeded contrary to conventional wisdom certainly highlights the nonobviousness of claims 1, 3, 5 and 7-18. It is not relevant whether the inventors in the '465 Patent may have believed that virtually any known hydroxyl protective group known in the art would be operative in their claimed invention, and it is not relevant whether there is a caveat of purported unexpected results in the '465 Patent or the '594 or '244 Patents. At most, such facts only show that the use of large and small protecting moieties alike were known and apparent to Hiatt, et al., as operative in the disclosed enzyme-catalyzed

nucleic acid elongation methods. Such facts do not mean that they would have been known or apparent to a person of ordinary skill in the art. The analysis that must be undertaken by an examiner in considering the patentability of the claimed invention under §103 is from the standpoint of the person of ordinary skill in the art, not from the standpoint of the inventors themselves.

Turning now to the specific contentions of the Examiner, the text of the rejection demonstrates that the obviousness determination was based on a *subjective* inquiry as to what was in the mind of the inventors Hiatt, et al. As noted above, this is contrary and exactly opposite to the actual correct legal standard for obviousness which is *objective* in nature, rather than subjective. Patentability is to be assessed from the perspective of the hypothetical person of ordinary skill in the art; not from the perspective of the inventors, who are presumed to be persons of extraordinary skill. Thus, information regarding the subjective motivations of inventors is completely irrelevant, and it is improper to interject them into the obviousness determination. See *Life Technologies Inc. v. Clontech Lab, Inc.*, 224 F.3d 1320, 1325, 56 U.S.P.Q.2d 1186, 1190 (Fed. Cir. 2000) (quoting *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985) (which notes that the person of ordinary skill is an objective legal construct presumed to think along conventional lines without undertaking to innovate, whether by systematic research or by extraordinary insights). In *Life Technologies*, the Federal Circuit reiterated its statements in *Standard Oil* as follows:

Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something — call it what you will — which sets them apart from the workers of ordinary skill, and one should not go about determining

obviousness under § 103 by inquiring into what patentees . . . would have known or would likely have done, faced with the revelations of references.

Id.

Thus, the inventors' beliefs, whatever they might have been at the time they made their invention, are just not relevant to the obviousness determination under § 103. Therefore, the absence of any "caveat" in the Hiatt et al. '465 Patent to the effect that a person of ordinary skill in the art, or for that matter the inventors themselves, would have expected that blocking moieties such as allyl and methoxymethyl groups would cause hydrolysability problems or sterically hinder a DNA polymerase enzyme, is equally irrelevant in the obviousness determination. The path that leads an inventor to the invention is expressly made irrelevant to patentability by statute. See *Life Technologies*, 224 F.3d at 1325, 56 U.S.P.Q.2d at 1190 (citing 35 U.S.C. § 103(a) and stating that "[i]t does not matter whether the inventors reached their invention after an exhaustive study of the prior art, or developed [their invention] in complete isolation."); See also 35 U.S.C. § 103(a) ("Patentability shall not be negated by the manner in which the invention was made.").

Further, the patent owner is aware of no legal authority which stands for the proposition that the patent specification must provide all the necessary information regarding the perspective of the artisan at the time of the invention, or that the patent applicant was consciously aware that he arrived at his invention by deviating from any conventional wisdom in the field. The illogicality of such a proposition was certainly appreciated by the Federal Circuit in *In re Chu*, 66 F.3d 292, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995), which reads in pertinent part as follows:

We have found no cases supporting the position that a patent applicant's evidence and/or arguments traversing a

§ 103 rejection must be contained within the specification. There is no logical support for such a proposition as well, given that obviousness is determined by the totality of the record including, in some instances most significantly, the evidence and arguments proffered during the give-and-take of ex parte patent prosecution.

In re Chu, 66 F.3d at 299, 36 U.S.P.Q.2d at 1095.

Moreover, to the extent the patent owner's arguments and evidence may be characterized as probative of an "unexpected result," there is no requirement that an invention's properties and advantages have to be fully known before a patent application is filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence at a later time after the application is filed. See *Knoll Pharm. v. Teva Pharms.*, 367 F.3d 1381, 1385, 70 U.S.P.Q.2d 1957, 1960 (Fed. Cir. 2004).

In the present case, without conceding whether "unexpected results" are relevant to the determination of whether claims 1, 3, 5 and 7-18 would have been obvious over the prior art, the patent owner submits that the relevant consideration is the extent to which the arguments and evidence provided in the previous response show that the inventors proceeded contrary to an accepted wisdom in the art. That accepted wisdom, as described in the EP '541 Patent and its companion U.S. Patent 6,664,079 (annexed hereto as Exh. E), is that a person of ordinary skill in the art, at the time the claimed invention was made, would have expected that blocking moieties such as allyl and methoxymethyl groups used at the 3'-position on a nucleoside 5'-triphosphate would not have been effective in nucleic acid synthesis from the standpoints of hydrolysability or steric hindrance, and thus would not have used them in the synthesis of nucleic acids. Proceeding contrary to the accepted wisdom in the art has been held to be strong evidence of unobviousness. See *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668, 57 U.S.P.Q.2d 1161, 1169-70 (Fed. Cir. 2000) (quoting *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q.

685, 687 (Fed. Cir. 1986) (citing *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983)).

In view of the decisional authority discussed above, it is further evident that the patent specification does not have to contain evidence that the patent applicant was actually aware that he was proceeding in a direction contrary to conventional wisdom, or for that matter, that he even knew what that wisdom might have been.

In view of the foregoing, the patent owner respectfully submits that the arguments and evidence of record have not been given full weight in the determination of whether claims 1, 3, 5 and 7-18 would have been obvious over *Tsien* in view of *Greene* and the patent owner's admission. When given such weight, it becomes clear that the determination should be resolved in favor of nonobviousness. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

* * *

As it is believed that all of the rejections set forth in the Official communication have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

Application No.: 90/008,152

Docket No.: SOLEXA 3.5-001 CIP IV

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: March 7, 2008

Respectfully submitted,

By Shawn P. Foley
Shawn P. Foley
Registration No.: 33,071
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000
Attorney for Applicant

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MAR 11 2008

CENTRAL REEXAMINATION UNIT

CERTIFICATE OF SERVICE

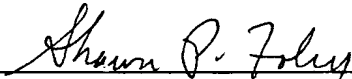
I hereby certify that a true copy of the following documents:

1. Amendment under 37 C.F.R. § 1.116, with Exhibit E and Amendment Transmittal;
2. Information Disclosure Statement Pursuant to 37 C.F.R. § 1.555; and
3. Two (2) References.

are being served upon the Requester with respect to the reexamination of U.S. Patent No. 6,232,465, this 7th day of March, 2008, as follows:

VIA FIRST CLASS MAIL

Howard M. Gitten
Edwards, Angell, Palmer & Dodge LLP
350 East Las Olas Blvd., Suite 1150
Ft. Lauderdale, FL 33301



SHAWN P. FOLEY

Registration No. 33,071

Control No. 90/008,152



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,152	08/03/2006	6232465	SOLEXA 3.5-001 CIP IV	5197
530	7590	05/20/2008	EXAMINER	
LERNER, DAVID, LITTENBERG, KRUMHOLZ & MENTLIK 600 SOUTH AVENUE WEST WESTFIELD, NJ 07090			ART UNIT	PAPER NUMBER

DATE MAILED: 05/20/2008

Please find below and/or attached an Office communication concerning this application or proceeding.



DO NOT USE IN PALM PRINTER

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

HOWARD M. GITTEN, ESQ.
EDWARDS, ANGELL, PALMER, & DODGE LLP
350 EAST LOS OLAS BLVD., SUITE 1150
FT. LAUDERDALE, FL 33301

MAILED

MAY 20 2008

CENTRAL REEXAMINATION UNIT

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. 90/008,152.

PATENT NO. 6232465.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Notice of Intent to Issue Ex Parte Reexamination Certificate	Control No.	Patent Under Reexamination	
	90/008,152	6232465	
	Examiner	Art Unit	
	GARY L. KUNZ	3991	


-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --


1. ☒ Prosecution on the merits is (or remains) closed in this *ex parte* reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. Cf. 37 CFR 1.313(a). A Certificate will be issued in view of
 - (a) ☒ Patent owner's communication(s) filed: 11 March 2008.
 - (b) ☐ Patent owner's late response filed: _____.
 - (c) ☐ Patent owner's failure to file an appropriate response to the Office action mailed: _____.
 - (d) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).
 - (e) ☐ Other: _____.

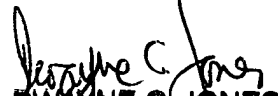
Status of *Ex Parte* Reexamination:

 - (f) Change in the Specification: ☐ Yes ☒ No
 - (g) Change in the Drawing(s): ☐ Yes ☒ No
 - (h) Status of the Claim(s):
 - (1) Patent claim(s) confirmed: NONE.
 - (2) Patent claim(s) amended (including dependent on amended claim(s)): 1,3 and 5
 - (3) Patent claim(s) cancelled: 2,4 and 6.
 - (4) Newly presented claim(s) patentable: 7-18.
 - (5) Newly presented cancelled claims: 19.
2. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."
3. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).
4. ☒ Note attached LIST OF REFERENCES CITED (PTO/SB/66). 42 2 page
5. ☐ The drawing correction request filed on _____ is: ☐ approved ☐ disapproved.
6. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
 - ☐ been received.
 - ☐ not been received.
 - ☐ been filed in Application No. _____.
 - ☐ been filed in reexamination Control No. _____.
 - ☐ been received by the International Bureau in PCT Application No. _____.

* Certified copies not received: _____.
7. ☐ Note attached Examiner's Amendment.
8. ☐ Note attached Interview Summary (PTO-474).
9. ☐ Other: _____.


 GARY L. KUNZ
 PRIMARY EXAMINER
 CRU - AU 3991


 SPE AU 3991


 DWAYNE C. JONES
 PRIMARY EXAMINER
 CRU - AU 3991

cc: Requester (if third party requester)

U.S. Patent and Trademark Office
PTOL-469 (Rev.08-06)

Notice of Intent to Issue Ex Parte Reexamination Certificate Part of Paper No 20080408-AAAA

REEXAMINATION

REASONS FOR PATENTABILITY / CONFIRMATION

Reexamination Control No. 90/008,152

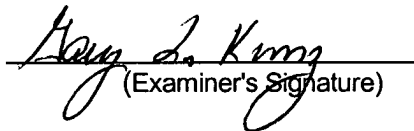
Attachment to Paper No. 20080408-B.


Art Unit 3991.

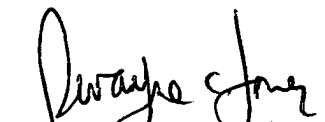
(1) The Patent Owner has obviated the rejection of claim 19 under 35 USC 305 by cancelling claim 19.

(2) In view of the Patent Owner's arguments of March 11, 2008, the Examiner withdraws the rejection of claims 1, 3, 5, and 7 - 19 under 35 USC 103(a) as being unpatentable over Tsien et al. (WO 91/06678) in view of Greene et al. (Protective Groups in Organic Chemistry, John Wiley & Sons: New York, 1991, pages 42 - 45 and 413) and the Patent Owner's admission at column 13, lines 55 - 64. The Examiner finds that the evidence submitted with regard to the prosecution history of EP 1,337,541 B1 documents that the person of skill in the art at the time of the invention would not have expected that a 3'-OH allyl protecting group or any other 3'-hydroxyl-protecting group of comparative size on a nucleoside 5'-triphosphate would have sterically permitted a nucleic acid polymerase to use said nucleoside triphosphate as an effective substrate in the elongation of a polynucleotide.

PTOL-476 (Rev. 03-98)


(Examiner's Signature)


SPE AU. 3991


DWAYNE C. JONES
PRIMARY EXAMINER
CRU - AU 3991

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS Ex Parte Reexam, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: May 27, 2008

Signature: 

(Thomas M. Palisi)

71338 U.S. PTO



05/30/08

Docket No.: SOLEXA 3.5-001 CIP IV
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination Application of:
Hiatt et al.

Application No.: 90/008,152

Confirmation No.: 5197

Filed: August 3, 2006

Art Unit: 3991

For: REEXAM OF U.S. PATENT NO.
6,232,465

Examiner: G. L. Kunz

INTERVIEW SUMMARY

Mail Stop *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present submission summarizes the telephone interview conducted between Patent Owner's representatives Shawn P. Foley and Thomas M. Palisi, and Examiner Gary L. Kunz on April 25, 2008. The Examiner's courtesy in conducting such interview is greatly appreciated.

During the interview, the Examiner stated that Patent Owner's arguments mailed March 7, 2008 were found to be persuasive. Specifically, the Examiner agreed that the specification was improperly used against Patent Owner. Moreover, the Examiner acknowledged that one of ordinary skill in the art would not have expected that a nucleoside 5'-triphosphate with a 3'-OH allyl protecting group would have been an acceptable substrate for a DNA polymerase because of steric considerations.

The interview was then concluded with Patent Owner's representatives thanking the Examiner for the interview.

Finally, Patent Owner's representatives acknowledge with appreciation the Patent Office's Reasons for Patentability/Confirmation mailed May 20, 2008.

Dated: May 27, 2008

Respectfully submitted,

By 

Thomas M. Palisi

Registration No.: 36,629

LERNER, DAVID, LITTENBERG,

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Attorney for Applicant

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US006232465C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (6356th)**United States Patent****Hiatt et al.**(10) **Number:** **US 6,232,465 C1**(45) **Certificate Issued:** **Aug. 12, 2008**

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

(75) Inventors: **Andrew C. Hiatt**, San Diego, CA (US);
Floyd Rose, Del Mar, CA (US)

(73) Assignee: **Solexa, Inc.**, Hayward, CA (US)

Reexamination Request:

No. 90/008,152, Aug. 3, 2006

Reexamination Certificate for:

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

Certificate of Correction issued Feb. 19, 2002.

Related U.S. Application Data

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

(51) **Int. Cl.**
C07H 19/00 (2006.01)
C07H 19/10 (2006.01)
C07H 19/20 (2006.01)
C07H 21/00 (2006.01)
C12P 19/00 (2006.01)
C12P 19/30 (2006.01)

(52) **U.S. Cl.** **536/26.26; 536/26.7; 536/26.71; 536/26.72; 536/26.73; 536/26.74; 536/26.8**

(58) **Field of Classification Search** None
See application file for complete search history.

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5,872,244 A * 2/1999 Hiatt et al. 536/26.26

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(Continued)

Primary Examiner—Gary L. Kunz(57) **ABSTRACT**

A method for the stepwise creation of phosphodiester bonds between desired nucleosides resulting in the synthesis of polynucleotides having a predetermined nucleotide sequence by preparing an initiation substrate containing a free and unmodified 3'-hydroxyl group; attaching a mononucleotide selected according to the order of the predetermined nucleotide sequence to the 3'-hydroxyl of the initiating substrate in a solution containing a catalytic amount of an enzyme capable of catalyzing the 5' to 3' phosphodiester linkage of the 5'-phosphate of the mononucleotide to the 3'-hydroxyl of the initiating substrate, wherein the mononucleotide contains a protected 3'-hydroxyl group, whereby the protected mononucleotide is covalently linked to the initiating substrate and further additions are hindered by the 3'-hydroxyl protecting group. Methods in which a mononucleotide immobilized on a solid support is added to a free polynucleotide chain are also disclosed.

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* cited by examiner

1
EX PARTE
REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 2, 4 and 6 are cancelled.

Claims 1, 3 and 5 are determined to be patentable as amended.

New claims 7-18 are added and determined to be patentable.

1. A nucleoside 5'-triphosphate having a removable blocking moiety protecting the 3' position which is [a hydrocarbyl] *an allyl moiety*, wherein said removable blocking moiety is linked to the 3' carbon of said nucleoside 5'-triphosphate *via an ether linkage*.

3. [A] *The nucleoside 5' triphosphate of claim 1 [or 2], wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U).*

5. [A composition of matter, comprising: (a) a] *The nucleoside 5'-triphosphate [having a removable hydrocarbyl blocking moiety linked to a 3' carbon of said nucleoside 5'-triphosphate; and (b)] of claim 1, further comprising a solid support linked to said removable blocking moiety.*

7. *The nucleoside 5'-triphosphate of claim 1, wherein said nucleoside contains a base that is an analog of adenine (A), guanine (G), thymine (T), cytosine (C) or uracil (U).*

8. *A composition comprising the nucleoside 5'-triphosphate of claim 1 or claim 3, or claim 7, and an initiating substrate comprising an oligonucleotide having a free and*

2
unmodified 3' hydroxyl group or a polynucleotide having a free and unmodified 3' hydroxyl group.

9. *The composition of claim 8, wherein said oligonucleotide or polynucleotide is affixed to a solid support.*

10. *A composition comprising the nucleoside 5'-triphosphate of claim 1 or claim 3, or claim 7, a biological buffer, and an enzyme suitable for phosphodiester bond formation.*

11. *The composition of claim 10, further comprising an oligonucleotide or polynucleotide comprising at its 3' terminus a nucleotide having a 5-carbon sugar and a nitrogen-containing base, wherein the 3' carbon on said sugar is protected with an allyl removable blocking moiety linked to said 3' carbon via an ether linkage.*

12. *A composition, comprising:*

four nucleoside tri-phosphates, wherein each of the 3' positions is protected with an allyl removable blocking moiety linked to the 3' carbon via an ether linkage, and wherein each of the first, second, third, and fourth nucleoside tri-phosphates are different.

13. *The composition of claim 12, further comprising an initiating substrate comprising an oligonucleotide having a free and unmodified 3' hydroxyl group or a polynucleotide having a free and unmodified 3' hydroxyl group.*

14. *The composition of claim 13, wherein said oligonucleotide or polynucleotide is affixed to a solid support.*

15. *The composition of claim 12 or 13, further comprising a biological buffer and an enzyme suitable for phosphodiester bond formation.*

16. *The composition of claim 15, further comprising an oligonucleotide or polynucleotide comprising at its 3'-terminus a nucleotide wherein the 3' position is protected with an allyl removable blocking moiety linked to the 3' carbon via an ether linkage.*

17. *The composition of claim 12, wherein said nucleoside contains a base selected from the group consisting of adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U).*

18. *The composition of claim 12, wherein said nucleoside contains a base that is an analog of adenine (A), guanine (G), thymine (T), cytosine (C) or uracil (U).*

* * * * *