



08/03/06

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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 JMCDOUGB2006000001 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 and select option 2.

Columbia Exhibit 2022

Illumina, Inc. v. The Trustees of Columbia
University in the City of New York
IPR2018-00322

12. <input checked="" type="checkbox"/> 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. <input type="checkbox"/> A proposed amendment is included (only where the patent owner is the requester). 37 CFR 1.510(e)		
14. <input checked="" type="checkbox"/> 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 & Mentlik		
600 South Avenue West		
Westfield, NJ 07090		
Date of Service: August 4, 2006; or		
<input type="checkbox"/> b. A duplicate copy is enclosed since service on patent owner was not possible.		
15. Correspondence Address: Direct all communication about the reexamination to:		
<input type="checkbox"/> The address associated with Customer Number: <input type="text"/>		
OR		
<input checked="" type="checkbox"/> Firm or Individual Name Howard M. Gitten		
Address Edwards Angell Palmer & Dodge LLP 350 East Las Olas Blvd., Suite 1150		
City Ft. Lauderdale	State FL	Zip 33331 33301
Country USA		
Telephone 954-667-6130		Email hgitten@eapdlaw.com
16. <input type="checkbox"/> The patent is currently the subject of the following concurrent proceeding(s):		
<input type="checkbox"/> a. Copending reissue Application No. _____		
<input type="checkbox"/> b. Copending reexamination Control No. _____		
<input type="checkbox"/> c. Copending Interference No. _____		
<input type="checkbox"/> 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 Signature		AUGUST 4, 2006 Date
Howard M. Gitten Typed/Printed Name		32,138 Registration No. <input type="checkbox"/> For Patent Owner Requester <input checked="" type="checkbox"/> For Third Party Requester

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
(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
:
:
:

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.

Application No.: 08/486,536

Docket No.: SOLEXA 3.5-001 CIP IV

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

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: March 7, 2008

Signature:

Shawn P. Foley
(Shawn P. Foley)

RECEIVED

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

MAR 11 2008

CENTRAL REEXAMINATION UNIT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination Application of:
Hiatt et al.

Application No.: 90/008,152

Filed: August 3, 2006

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

:
:
:
:
: Group Art Unit: 3991
:
: Examiner: G. L. Kunz
:
:
:

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

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R.

§ 1.116

Dear Sir:

This is in response to the Office communication mailed January 7, 2008, which has been made final. This response is being submitted within the 2-month response period set out in the Communication. The patent owner hereby submits the following amendments and remarks.

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 negatived 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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CENTRAL REEXAMINATION UNIT

CERTIFICATE OF SERVICE

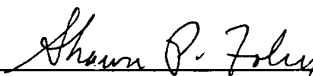
I hereby certify that a true copy of the following documents:

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.



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FT. LAUDERDALE, FL 33301

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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)).

<p align="center">Notice of Intent to Issue Ex Parte Reexamination Certificate</p>	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 --


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/88) 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

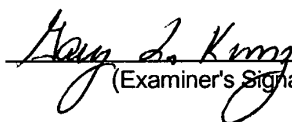
Attachment to Paper No. 20080408-B.


Art Unit 3991.

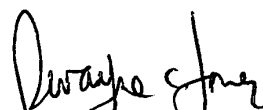
(1) The Patent Owner has obviated the rejection of claim 19 under 35 USC 305 by cancelling claim 19.

(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



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.**(56) References Cited****U.S. PATENT DOCUMENTS**

4,711,955 A 12/1987 Ward et al.
 5,872,244 A * 2/1999 Hiatt et al. 536/26.26

FOREIGN PATENT DOCUMENTS

WO 90/15070 12/1990
 WO WO 91/06678 5/1991
 WO WO 92/10587 6/1992
 WO 04/018497 3/2004

OTHER PUBLICATIONSGreene, Theodora W., and Wuts, Peter G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991, pp. 42-45 and 413.**Substrate Inhibitors of DNA Biosynthesis* by A. A. Kraevskii et al., *Molecular Biology* 21:25-29 (1987) (5 pages).*Enzyme Action at 3' Termini of Ionizing Radiation-Induced DNA Strand Breaks* by William D. Henner et al., *The Journal of Biological Chemistry*, vol. 258, No. 24, Issue of Dec. 25, 1983, pp. 15198-15205 (8 pages).Welch et al., "Syntheses of Nucleosides Designed for Combinatorial DNA Sequencing", *J. Chem. Eur.*, 5: 3; 951-960 (1999).Gait, M J; *Oligonucleotide synthesis a practical approach*, IRL Press, Oxford, 1984.Amit, Boaz et al.; *Photosensitive Protecting Groups of Amino Sugars and Their Use in Glycoside Synthesis. 2-Nitrobenzyloxycarbonylamino and 6-Nitroveratryloxy-carbonylamino Derivatives*, *J. Org. Chem.*, vol. 39, No. 2, 1974; pp. 192-196.Patchornik, et al., *Photosensitive Protecting Groups*; *J. Am. Chem. Soc.*, 92(21):6333-35 (1970).Hovinen, Jari et al.; *Synthesis of 3'-O-(ω -Aminoalkoxymethyl)thymidine 5'-Triphosphates, Terminators of DNA Synthesis that Enable 3'-Labelling*; *J. Chem. Soc. Perkins Trans.* 1994; Issue 2, pp. 211-217.Chinault, A. Craig et al.; *Preparation of Escherichia coli tRNAs Terminating in Modified Nucleosides by the Use of CTP(ATP):tRNA Nucleotidyltransferase and Polynucleotide Phosphorylase*; *Biochemistry*, vol. 16, No. 4, 1977; pp. 756-765.Katz, Sidney; *The Reversible Reaction of Sodium Thymonucleate and Mercuric Chloride*; *J. Am. Chem. Soc.*, vol. 74(9); pp. 2238-2245, 1952.Eichhorn, Gunther L., et al.; *The Reaction of Mercury (II) with Nucleosides*; *J. Am. Chem. Soc.*; 85(24): 4020-24, Jul. 1, 1963.Yamane, Tetsuo; *On the Complexing of Desoxyribonucleic Acid (DNA) by Mercuric Ion*; *Journal of the American Chemical Society*; Jun. 30, 1961; vol. 83; No. 12; pp. 2599-2607.Gruenwedel, Dieter W. et al.; *Mercury-Induced DNA Polymorphism: Probing the Conformation of Hg(II)-DNA via Staphylococcal Nuclease Digestion and Circular Dichroism Measurements*; *Biochemistry*, vol. 29, No. 8, Jul. 25, 1989; pp. 2111-2116.Young, Peter R. et al.; *Binding of Mercury(II) to Poly-(dA-dT) Studied by Proton Nuclear Magnetic Resonance*; *Biochemistry*; 1982; vol. 21, pp. 62-66.

(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.

OTHER PUBLICATIONS

- Dale, R. M. K. et al.; Conversion of covalently mercurated nucleic acids to tritiated and halogenated derivatives; *Nucleic Acids Res.*, Apr. 21, 1975; vol. 2; No. 6; pp. 915-930.
- Dale, et al.; The Synthesis and Enzymatic Polymerization of Nucleotides Containing Mercury: Potential Tools for Nucleic Acid Sequencing and Structural Analysis; *Proc. Nat. Acad. Sci. USA*; Aug. 1973; vol. 70; No. 8; pp. 2238-2242.
- Ruparel, et al.; Design and synthesis of a 3'-O-allyl photo-cleavable fluorescent nucleotide as a reversible terminator for DNA sequencing by synthesis; *PNAS*; Apr. 26, 2005; vol. 102; No. 17; 5932-5937.
- Gigg, Roy et al.; The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part II; *J. Chem. Soc. (C)*; 1968; pp. 1903-1911.
- Cantoni, Orazio et al.; Mechanism of HgCl₂ Cytotoxicity in Cultured Mammalian Cells; *Molecular Pharmacology*; Feb. 15, 1984; 26:360-368.
- Cantoni, Orazio et al.; Characterization of DNA Lesions Produced by HgCl₂ in Cell Culture Systems; *Chem. Biol. Interactions*; 49 (1984) 209-224.
- Costa, Max et al.; DNA Damage by Mercury Compounds: An Overview; In *Advances in Mercury Toxicology*; 1991; pp. 255-273, Plenum Press, New York.
- Honda, Masanori et al.; Deprotection of Allyl Groups with Sulfenic Acids and Palladium Catalyst; *J. Org. Chem.* 1997; 62, 8932-8936.
- Karakawa, Makoto et al.; The Utility of a 3-O-Allyl Group as a Protective Group for Ring-Opening Polymerization of α -D-Glucopyranose 1,2,4-Orthopivalate Derivatives; *Biomacromolecules* 2002; 3, 538-546.
- Matsuoka, Masato et al.; Mercury Chloride Activates c-Jun N-Terminal Kinase and Induces c-jun Expression in LLC-PK₁ Cells; *Toxicological Sciences*; 2000; 53; 361-368.
- Metzker, Michael L.; Emerging technologies in DNA sequencing; *Genome Res.* 2005 15: 1767-1776.
- Hayakawa et al. 'O-Allyl Protection of Guanine and Thymine Residues in Oligodeoxyribonucleotides'; *J. Org. Chem.*; 1993; 58; 5551-5555.
- Ju et al.; 'Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators'; *PNAS*; Dec. 26, 2006; vol. 103, No. 52; 19635-19640.
- Letsinger et al., '2,4-Dinitrobenzenesulfonyl as a Blocking Group for Hydroxyl Functions in Nucleosides', *J. Am. Chem. Soc.*; Sep. 1964; vol. 29; 2615-2618.
- Kruse et al., "Use of (Thio)Acetal Esters as Reagents for the Protection of Alcohols. Synthesis of 2-Tetrahydrothienyl Ethers", *J. Org. Chem.* 43(18):3548-53 (1978).

* cited by examiner

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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*

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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).*

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