

PETITION FOR *INTER PARTES* REVIEW
U.S. PATENT NO. 7,790,869

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US. Patent of Jingyue Ju. *et al.*
Patent No.: 7,790,869
Appl. No.: 11/810,509
Issue Date: September 7, 2010
For: MASSIVE PARALLEL METHOD FOR DECODING DNA
AND RNA

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PAT. No. 7,790,869

Inter partes review of U.S. Patent 7,790,869 ("the '869 patent") pursuant to 35 U.S.C. § 311 and 37 C.F.R. §§ 42.1 *et seq.* is respectfully requested by Petitioner Illumina, Inc. ("Petitioner"). Petitioner submits that the attached prior art (attached as Exhibits 1002 to 1020) renders claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent invalid under 35 U.S.C. §§ 102(a), 102(b), 102(e), and 103(a) and raises a reasonable likelihood that Petitioner will prevail with respect to at least one of claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent. Accordingly, it is requested that *inter partes* review be instituted and that claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent be found invalid.

Columbia Exhibit 2034
Illumina, Inc. v. The Trustees of Columbia
University in the City of New York
IPR2018-00322

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TABLE OF PRIOR ART REFERENCES

- Exhibit 1001 - The '869 patent (U.S. Patent 7,790,869 to Jingyue Ju et al.)
- Exhibit 1002 - Tsien (PCT Publication WO 91/06678 to Tsien et al.)
- Exhibit 1003 - Prober I (Prober et al., *Science* 238, 336-341 (1987))
- Exhibit 1004 - Prober II (U.S. Patent No. 5,242,796 to Prober)
- Exhibit 1005 - Dower (U.S. Patent No. 5,547,839 to Dower et al.)
- Exhibit 1006 - Rabani (PCT Publication WO 96/27025 to Rabani)
- Exhibit 1007 - Stemple II (PCT Publication WO 00/53805 to Stemple et al.)
- Exhibit 1008 - Stemple III (U.S. Patent No. 7,270,951 to Stemple et al.)
- Exhibit 1009 - Stemple I (U.S. application serial no. 09/266,187 to Stemple et al.)
- Exhibit 1010 - PCT Publication WO 98/33939 to Anazawa et al. (Japanese language version)
- Exhibit 1011 - Anazawa (English translation of WO 98/33939)
- Exhibit 1012 - Translation Affidavit for Anazawa
- Exhibit 1013 - Hobbs (U.S. Patent No. 5,047,519 to Hobbs et al.)
- Exhibit 1014 - Seela I (U.S. Patent No. 4,804,748 to Seela et al.)
- Exhibit 1015 - Seela II (U.S. Patent No. 5,844,106 to Seela et al.)
- Exhibit 1016 - Saiki (WO 89/11548 to Saiki)
- Exhibit 1017 - P. Williams (U.S. Pat. No. 7,037,687 to Williams et al.)
- Exhibit 1018 - J. Williams (U.S. Pat. No. 6,255,083 to Williams)

Exhibit 1019 - Canard (U.S. Pat. No. 6,001,566 to Canard)

Exhibit 1020 - Rosenthal (PCT Publication WO 93/21340 to Rosenthal et al.)

Exhibit 1021 - Declaration of George Weinstock, Ph.D.

Exhibit 1022 - Excerpts from the '869 Patent File History

I. INTRODUCTION

Inter partes review of U.S. Patent No. 7,790,869 ("the '869 patent") and cancellation of at least claims 12-13, 15-17, 20-26, 28-29, 31, and 33 ("the challenged claims") under 35 U.S.C. §§ 102 and 103 is respectfully requested. A copy of the '869 patent is attached as Exhibit 1001. Petitioner respectfully urges that this Petition be granted and examination conducted not only with "special dispatch," but also with "priority over all other cases" in accordance with MPEP § 2661, due to the ongoing nature of the underlying litigation, discussed below.

II. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. § 312 and 37 C.F.R. §§ 42.1 - 42.123

A) **Showing of a Reasonable Likelihood of Prevailing** - the Petitioner submits that for the reasons discussed in detail below, there is a reasonable likelihood that the Petitioner will prevail with respect to the invalidity of at least one of the challenged claims as required under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108. In particular, the prior art references accompanying this Petition show that the subject matter of the challenged claims was identically disclosed in the prior art and also that each of the challenged claims would have been obvious to a person of ordinary skill in the art. Further, none of the references accompanying this petition were substantively considered by the Examiner (although several of the references, including Dower, Tsien, Rabani, and Stemple II, were only

provided as part of a 11 page information disclosure statement listing 161 references). Accordingly, Petitioner respectfully requests that the *inter partes* review of the '869 patent be granted.

B) **Format Requirements** - This Petition meets the paper, font, line spacing and margin requirements set forth 37 C.F.R. § 42.6(a).

C) **Certificate of Service** - Pursuant to 37 C.F.R. § 42.6(e), a certificate of service in compliance with 37 C.F.R. § 42.6(e)(iii) is located at the end of this document showing that pursuant to 35 U.S.C. § 312(a)(5) and 37 C.F.R. § 42.105(a), a copy of this petition, including all supporting documents, have been served in its entirety on the patent owner at the correspondence address of record: COOPER & DUNHAM, LLP, 30 Rockefeller Plaza, 20th Floor, New York, NY 10112. Pursuant to 37 C.F.R. § 42.105(a), additional copies have been served on the patent owner at the following additional addresses: SHAW KELLER LLP, 300 Delaware Avenue, Suite 1120, Wilmington, DE 19801, and MEDLEN & CARROLL, LLP, 100 Grandview Road, Suite 403, Braintree, MA 02184.

D) **Mandatory Notices** - As required by 37 C.F.R. § 42.8, Petitioner hereby files the following notices:

i) Real party-in-interest under 37 C.F.R. § 42.8(b)(1) - The real party in interest is Petitioner, Illumina, Inc. ("Illumina").

ii) Related matters under 37 C.F.R. § 42.8(b)(2) - The '869 patent is the

subject of the litigation styled *The Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 1:12-cv-00376-UNA, currently pending in the United States District Court for the District of Delaware. The Patent Owner alleges that Illumina has and continues to infringe the '869 patent.

Further, a petition for *inter partes* review of legally related U.S. Patent No. 7,713,698 has been contemporaneously filed with the present petition.

iii) Lead and backup counsel under 37 C.F.R. § 42.8(b)(3) - Pursuant to 37 C.F.R. § 42.10, Petitioner designates Robert Lawler, Registration No. 62,075, as lead counsel, and James Morrow, Registration No. 32,505, as back-up counsel. The requisite power of attorney accompanies this petition.

iv) Service Address under 37 C.F.R. § 42.8(b)(4) - Petitioner may be served electronically at ipadmin@reinhardtlaw.com, and by postal mail and by hand delivery at Reinhart, Boerner, Van Deuren s.c., 1000 North Water St., Suite 1700, Milwaukee, WI 53202. The attorneys of record may be contacted by phone at 414-298-1000.

E) **Required Fee** - Pursuant to 35 U.S.C. § 312(a)(1) and 37 C.F.R. § 42.103, the required petition fee has been paid from deposit account no. 18-0882. If additional fees are due or if an overpayment has been made, the Commissioner is authorized to deduct or credit the proper amount to deposit account no. 18-0882.

F) **Grounds for Standing** - Pursuant to 37 C.F.R. § 42.104(a), Petitioner

certifies that the '869 patent is eligible for *inter partes* review, and that Petitioner is not barred or estopped from requesting *inter partes* review of the '869 patent.

G) **Identification of Challenges** -Pursuant to 35 U.S.C. § 312(a)(3) and 37 C.F.R. § 42.104(b)(1) and (2), the Petitioner requests review of claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent. The grounds on which the challenges to each claim are based are identified below:

1. Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 are anticipated under 35 U.S.C. § 102(b) by PCT Publication WO 91/06678 to Tsien et al. published **May 16, 1991** entitled **DNA Sequencing** ("Tsien," Exhibit 1002).

2. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Tsien in view of **A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides**, by Prober et al., *Science* 238, 336-341 (1987) published in **1987** ("Prober I"; Exhibit 1003).

3. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Tsien in view of U.S. Patent No. 5,242,796 issued **September 7, 1993** to Prober entitled **Method, System and Reagents for DNA Sequencing** ("Prober II"; Exhibit 1004).

4. Claims 12-13, 17, 20-26, 28-29, 31, and 33 are anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 5,547,839 issued **August 20, 1996** to Dower et al. entitled **Sequencing of Surface Immobilized Polymers Utilizing Microfluorescence Detection** ("Dower," Exhibit 1005).

5. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Dower in view of Prober I.

6. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Dower in view of Prober II.

7. Claims 12-13, 17, 20-26, 28-29, 31, and 33 are anticipated under 35 U.S.C. § 102(b) by PCT Publication WO 96/27025 to Rabani published **September 6, 1996** entitled **Device, Compounds, Algorithms, and Methods of Molecular Characterization and Manipulation with Molecular Parallelism** ("Rabani," Exhibit 1006).

8. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Rabani in view of Prober I.

9. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Rabani in view of Prober II.

10. Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 are anticipated under 35 U.S.C. § 102(a) by International Application Publication WO 00/53805 to Stemple et al. published **September 14, 2000** entitled **A Method for Direct Nucleic Acid Sequencing** ("Stemple II," Exhibit 1007).

11. Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 are anticipated under 35 U.S.C. § 102(e) by U.S. Patent No. 7,270,951 issued September 18, 2007 to Stemple et al. entitled **Method for Direct Nucleic Acid Sequencing**, ("Stemple

III," Exhibit 1008), which claims priority under 35 U.S.C. § 120 as a continuation-in-part application of U.S. application serial no. 09/266,187 ("Stemple I," Exhibit 1009), filed **March 10, 1999**.

12. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple II in view of PCT Publication WO 98/33939 to Anazawa et al., published August 6, 1998, entitled **Method for Determining Nucleic Acids Base Sequence and Apparatus Therefor** (Exhibit 1010). An English translation of WO 98/33939 ("Anazawa") is attached as Exhibit 1011, and an affidavit under 37 C.F.R. § 42.63(b) is attached as Exhibit 1012.

13. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Anazawa.

14. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Prober I.

15. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Prober I.

16. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Tsien in view of U.S. Patent No. 5,047,519 issued September 10, 1991 to Hobbs et al. entitled **Alkynylamino-Nucleotides** ("Hobbs," Exhibit 1013).

17. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Dower in view of Hobbs.

18. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Hobbs.

19. Claims 15 and 16 are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Hobbs.

Pursuant to 37 C.F.R. §§ 42.104(b)(4) and 42.104(b)(5), the details of how each challenged claim is unpatentable in view of each prior art reference, at least one instance of where each claim element can be found in the prior art and the supporting evidence relied upon are set forth in Section V below.

H) **Claim Construction** - For purposes of this *inter partes* review Petition, the Patent Office will give the claim terms the "broadest reasonable construction in light of the specification of the patent in which it appears" (e.g., the ordinary and customary meaning) as required by 37 C.F.R. § 42.100(b) which states "A claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100. The interpretation and/or construction of the claims in the '869 patent relevant to this *inter partes* review should not be viewed as constituting, in whole or in part, Petitioner's own interpretation and/or construction of such claims. Furthermore, Petitioner expressly reserves the right to present its own interpretation of such claims at a later time, which interpretation may differ, in whole or in part, from that presented herein.

I) **Copies of Submitted Prior Art** - Pursuant to 35 U.S.C. § 312(a)(3), a copy of every patent and printed publication relied upon in this petition is submitted herewith.

III. OVERVIEW OF THE '869 PATENT AND SUMMARY OF INVALIDATING PRIOR ART REFERENCES

A. Summary of the '869 Patent and Invalidating Prior Art

The '869 patent issued on September 7, 2010 from U.S. Application No. 11/810,509 filed June 5, 2007. The '869 patent was filed as a continuation of application No. 10/702,203, filed on Nov. 4, 2003, now Pat. No. 7,345,159, which is a division of application No. 09/972,364, filed on Oct. 5, 2001, now Pat. No. 6,664,079, claiming the benefit of provisional application No. 60/300,894, filed June 26, 2001, and is a continuation-in-part of application No. 09/684,670, filed on Oct. 6, 2000, now abandoned.

The '869 patent is generally directed to a "sequencing by synthesis" method of determining the sequence of a polynucleic acid, such as DNA or RNA. See '869 Abstract. In the sequencing by synthesis method of the '869 patent, 1) a nucleic acid template is attached to a solid support, 2) a primer hybridizes to the template, 3) a polymerase adds a 3'-OH blocked and labeled nucleotide (*i.e.*, a nucleotide including a capping group at the 3 position on the ribose of the nucleotide and a label that identifies the nucleotide base) to form a primer extension strand, 4) the unique label on the nucleotide is detected to determine the type of nucleotide that

was added by the polymerase, 5) removing the group capping the 3'-OH of the nucleotide that was incorporated into the primer extension strand, thereby permitting addition of further nucleotides, and 6) repeating the process to add and detect additional nucleotides added to the primer extension strand to determine the sequence of the nucleic acid template. See '869 patent, col. 8, lines 8-52. But see also Dower, Tsien, Rabani, and Stemple II and III. The 3'-OH capping group acts to ensure that only one base is incorporated into the growing primer extension strand at a time, and removal of the 3'-OH capping group then allows the next the nucleotide to be added by the polymerase. See '869 patent, col. 19, lines 52-65.

A "nucleotide analogue" is defined in the '869 specification as "...a chemical compound that is structurally and functionally similar to the nucleotide, i.e. the nucleotide analogue can be recognized by polymerase as a substrate." '869 patent, col. 7, ll. 48-51. Specific examples provided in the '869 patent of "nucleotide analogues" are nucleotides having 7-deaza-adenine and 7-deaza-guanine as the nucleobase. See '869 patent, col. 7, ll. 58-63. The cleavable chemical group that "caps" or "blocks" the -OH group at the 3'-position of the sugar of the nucleotide analogue (*i.e.*, prevents polymerase extension beyond a single base) can be any group that "1) is stable during the polymerase reaction, 2) does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate, and 3) is cleavable." See '869 patent, col. 9, ll. 52-58. The only examples of 3'-OH

cleavable groups are $\text{-CH}_2\text{OCH}_3$ and $\text{-CH}_2\text{CH=CH}_2$. Id. The disclosed labels that may be attached to the nucleotide analogues include a fluorescent moiety. Id. at col. 9, l. 59 to col. 10, l. 35. The linker attaching the label to the nucleotide analogue is a cleavable linker that can be cleaved by "...one or more of a physical means, a chemical means, a physical chemical means, heat, and light." Id. at col. 10, ll. 45-48. The only specific example of a cleavable linker in the '869 patent is a photocleavable 2-nitrobenzyl linker. See, e.g., id. at col. 23, ll. 29-35. The label can be attached to the base of the nucleotide via a linker. The specific example given in the '869 patent specification is "...a label is attached through a cleavable linker to the 5-position of cytosine or thymine or to the 7-position of deaza-adenine or deaza-guanine." Id. at col. 7, ll. 63-66. But see also Dower, Tsien, Rabani, and Stemple II and III.

The '869 patent claims priority to Pat. No. 6,664,079. However, the '869 patent was not filed until well after Illumina announced and launched the first commercial sequencing by synthesis system. While both the '869 patent and its parent '079 patent are directed to sequencing by synthesis methods, the '869 patent removed many of the original limitations of the '079 patent that the patentee argued were important to their invention when prosecuting the '079 patent.

Independent claim 12, the only independent claim of the '869 patent challenged in this petition for *inter partes* review, relates to nucleotide analog

usable in sequencing by synthesis methods and is reproduced in **Claim Chart 1** below. Challenged claims 13, 15-17, 20-26, 28-29, 31, and 33 add additional limitations to the nucleotide of claim 12.

However, the prior art submitted with this Petition shows that all of the elements of the unjustifiably broadened claims of the '869 patent were both identically disclosed and well known in the prior art. For example, Dower, Tsien, Rabani and Stemple II and III all disclose nucleotides for use in sequencing by synthesis methods identical to at least independent claim 12 of the '869 patent in which 3'-OH capped (e.g., chain terminating) and labeled nucleotide analogs are mixed with a primed nucleic acid template attached to a solid surface.

In fact, the Background of the Invention section of the '869 patent itself confirms the teachings of the prior art submitted herewith. The '869 patent Background section demonstrates that sequencing by synthesis was known at least by 1988, stating: "The concept of sequencing DNA by synthesis without using electrophoresis was first revealed in 1988 (Hyman, 1988)." See '869 patent, col. 2, lines 9-10 (emphasis added). The '869 Applicant further admits that it was known to couple the DNA template to a chip and to use labeled nucleotides, stating "Such a scheme coupled with the chip format and laser-induced fluorescent detection has the potential to markedly increase the throughput of DNA sequencing projects. Consequently, several groups have investigated such a system with an aim to

construct an ultra high-throughput DNA sequencing procedure (Cheeseman 1994, Metzker et al. 1994)." See '869 patent, col. 2, lines 13-19 (emphasis added).

Further, the '869 patent Background section demonstrates that it was known to attach label groups to the nucleotide base, stating "it is known that modified DNA polymerases (Thermo Sequenase and Taq FS polymerase) are able to recognize nucleotides with extensive modifications with bulky groups such as energy transfer dyes at the 5-position of the pyrimidines (T and C) and at the 7-position of purines (G and A) (Rosenblum et al. 1997, Zhu et al. 1994)." See '869 patent, col. 2, lines 45-51 (emphasis added). The '869 Applicant admits that it was known to use small chemical groups as 3'-OH blocking groups on nucleotides during sequencing reactions stating "It is known that MOM ($--CH_2OCH_3$) and allyl ($--CH_2CH=CH_2$) groups can be used to cap an --OH group, and can be cleaved chemically with high yield (Ireland et al. 1986; Kamal et al. 1999)." See '869 patent, col. 3, lines 26-29 (emphasis added). In fact, the MOM and allyl groups identified as prior art in the background section of the '869 patent are the very 3'-OH capping groups that the '869 patent identifies as "embodiments of the invention." See '869 patent, col. 12, lines 50-53, and FIG. 7.

Given the Applicant's understanding of the prior art as set forth in the Applicant's own Background section and art of which they were aware, it is unclear how the broadened claims of the '869 patent could be patentable.

B. Scope and Content of the Prior Art Relating to Nucleotides and dNTPs Having Deaza-Substituted Bases

Claims 15 and 16 of the '869 patent specify that the nucleotide "base is a deazapurine" (claim 15) and that the deazapurine is one of "deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine." (claim 16). In a "7-deazapurine," the natural 7-position nitrogen atom is replaced with a carbon atom. For reference, the nucleobase adenine is show below with standard position numbers shown in red:



However, recitation of a nucleotide or dNTP having a "deazapurine" base and labeling at the 7-position of the deazapurine, as recited in claims 15 and 16, does not render the claims patentable: use of nucleotide analogs including deazapurine, and a label attached at the 7-position thereof, was well known in the nucleic acid sequencing field at least as early as the late 1980s as shown in a wide variety of prior art documents. See Weinstock Decl. ¶ 37. For example, it would have been obvious to substitute deaza bases for the regular bases of the SBS patents in view of the express motivation provided by U.S. Pat. No. 4,804,748 to

Seela ("Seela I," Exhibit 1014). Seela I states that deaza bases can advantageously be used in place of regular bases in polymerase-based sequencing methods. See, e.g., id. at col. 4, lines 4-6; see also col. 2, lines 6-11 and 23-29. While much of Seela I is directed to Sanger sequencing, Seela I states that this teaching about using deaza bases is not limited to Sanger sequencing. See, e.g., id. at col. 4, lines 4-10.

In addition to the express statement in Seela I, multiple prior art references recognized a number of advantages for using deazapurines as the base in nucleotide analogs for sequencing. For example, the prior art teaches that deazaguanine-based nucleotides allow for effective sequencing of cytosine-guanine rich areas. See e.g., Seela I, col. 2, lines 31-33. Similarly, Prober I shows that labels attached to the 7-position of deaza purines could be successfully incorporated by polymerase. Prober I, page 340, col. 1.

Also, Hobbs reflects the synthesis scheme used to make the nucleotides of Prober I. Hobbs teaches that the 7 position of a purine base is a particularly advantageous location to place a label, as that location least interferes with the incorporation of the nucleotide into a DNA strand by a polymerase. Hobbs, col. 8, lines 54-60. Hobbs also teaches that when a label is placed at the advantageous 7 position of a purine base, the 7 position needs to be converted from an N to a C (i.e. needs to be "deaza") in order to form a stable glycosidic linkage between the

base and ribose portions of the nucleotide. See, e.g., Hobbs, col. 10, lines 67 - col. 11, line 4. In light of this express motivation in Hobbs, a person of ordinary skill in the art would have been motivated to make the nitrogen to carbon substitution (i.e. make the base a “deaza” base) when attaching a label to the 7 position of a purine base of a nucleotide, as disclosed in the prior art discussed in the '869 patent Background section. See '869 patent, col. 2, lines 45-51.

Third, the obvious interchangeability of regular and deaza bases is reflected in the art. For example, Dower teaches that sequencing by synthesis methods employing modified nucleotides having a 3'-OH "blocking agent" are "analogous to the dideoxy nucleotides used in the Sanger and Coulson sequencing procedure, but in certain embodiments here, the blockage is reversible." Dower, col. 14, ll. 53-56. Thus, Dower expressly teaches that art related to dideoxy nucleotides (i.e., Prober I, Prober II, Hobbs) is pertinent to the disclosed methods using nucleotide that is "blocked at the position of '3 elongation." Id., col. 15, lines 33-35. Similarly, Tsien teaches that the synthesis scheme for ddNTPs used in Prober I should be used in Tsien to produce "fluorescent dNTPs." Tsien, p. 29, ll. 10-19.

C. Summary of the Prosecution History of the '869 Patent

The '869 patent issued on Sep. 7, 2010 from an application filed Jun. 5, 2007. The '869 patent is a continuation of application No. 10/702,203, filed on Nov. 4, 2003, now Pat. No. 7,345,159, which is a division of application No.

09/972,364, filed on Oct. 5, 2001, now Pat. No. 6,664,079, and a continuation-in-part of application No. 09/684,670, filed on Oct. 6, 2000, now abandoned.

The prosecution history of the '869 patent is remarkably sparse: the Examiner did not make a single rejection over any prior art reference discussed in this Petition, or any reference submitted during prosecution. In fact, the Examiner entered only a single, non-final office action rejecting all claims for obviousness-type double patenting over claims 1-18 of U.S. Patent No. 7,345,159 ("the '159 patent"). (*See* Exhibit 1022, Office Action dated 2009-07-10.) The Examiner described both the pending '869 claims and those of the '159 patent as "not patentably distinct from each other because they both claim nucleotide having a base linked to a label via a cleavable linker and wherein the deoxyribose comprises a chemical cleavable group capping the 3'OH group. Wherein the linkers can be cleaved by one or more of a physical means, a chemical means, a physical chemical means, heat, or light." (*Id.*) The prosecution history does not indicate that the Examiner analyzed the pending claims of the '869 patent and applicable references describing methods for sequencing by synthesis - and the nucleotide analogs used in such methods - at any higher level of detail than the cited passage.

IV. STATEMENT REGARDING CONSTRUCTION OF THE CHALLENGED CLAIMS

A. Claim Construction Standard

For purposes of this *inter partes* review Petition, the Patent Office will give

the claim terms the "broadest reasonable construction in light of the specification of the patent in which it appears" (e.g., the ordinary and customary meaning) as required by 37 C.F.R. § 42.100(b) which states "A claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100. The interpretation and/or construction of the claims in the '869 patent relevant to this *inter partes* review should not be viewed as constituting, in whole or in part, Petitioner's own interpretation and/or construction of such claims for any other purpose, including litigation. Furthermore, Petitioner expressly reserves the right to present its own interpretation of such claims in any other proceeding, which interpretation may differ, in whole or in part, from that presented herein.

B. Discussion of Individual Claim Terms

For purposes of this *inter partes* review, Petitioner believes that the majority of the claims of the '869 patent do not require construction. Pursuant to 37 C.F.R. § 42.104, Petitioner provides specific comments to assist in determining the scope of individual claim terms.

Claim 12, the sole independent claim challenged in this *inter partes* petition, is a means-plus-function claim under 35 U.S.C. § 112(f). Claim 12 recites a nucleotide analog having a "cleavable linker" and a "cleavable chemical group," wherein both the cleavable linker and the cleavable chemical group are "cleaved by

a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light" (emphasis added). Claim 12 recites no specific structure for the recited "means," and defines those features solely by relation to their function - cleavage of the "cleavable linker" and the "cleavable chemical group" respectively. The Federal Circuit notes that "[t]ypically, if the word "means" appears in a claim element in combination with a function, it is presumed to be a means-plus-function element to which 35 U.S.C. § 112, ¶ 6 applies." *Signtech USA, Ltd., v. Vutek, Inc.*, 174 F.3d 1352, 1357 (Fed. Cir. 1999). Thus, Petitioner contends Claim 12 should be construed as a means-plus-function claim under 35 U.S.C. § 112(f). However, as none of Illumina's products and services accused of infringing the '869 patent use any of the corresponding structures disclosed in the '869 patent, Patentee may assert Claim 12 is not, in fact, a means-plus-function claim. If so, the claims are invalid as discussed in further detail below.

Pursuant to 37 C.F.R. § 42.104(b)(3), Petitioner is unable to identify any disclosure in the '869 specification of the claimed "physical means" or "physical chemical means" corresponding to the structure, material, or acts related to the claimed cleaving function. Petitioner is unable to identify any disclosure of a cleavage "means selected from the group consisting of ... heat," (i.e., a "heat means") for example temperature ranges or conditions that would result in heat-

directed cleavage of the "cleavable linker" and the "cleavable chemical group."

The only "chemical means" identifiable in the specification are two reaction conditions capable of cleaving the "cleavable chemical group capping the 3' OH group". (See Fig. 14 and col. 25, ll. 7-17). However, there is no disclosure of a corresponding "chemical means" associated with, or capable of cleaving, the "linker between the unique label and the nucleotide analogue," as the only linker disclosed to link the nucleotide to the label is a photocleavable linker.

Petitioner identifies the following disclosures in the '869 specification as disclosing cleavage "by a means selected from the group consisting of ... light" (i.e., a "light means"): FIG. 9, step 4 (showing dye cleavage, i.e. cleavage of the cleavable linker, "with light at 350 nm"); FIG. 10; col. 10, lines 53-56 and 61-61.

V. DETAILED EXPLANATION OF PETITIONER'S BASIS FOR CHALLENGING CLAIMS 12-13, 15-17, 20-26, 28-29, 31, and 33 OF THE '869 PATENT DEMONSTRATING A REASONABLE LIKELIHOOD OF PREVAILING AGAINST THE CLAIMS OF THE '869 PATENT

Pursuant to 35 U.S.C. § 312(a)(3) and 37 C.F.R. § 42.104(b), this Petition presents a detailed explanation of the basis of each challenge to claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent and where each element of each claim can be found in each prior art reference.

In particular, these claims are anticipated by at least four separate references. As shown by the references accompanying this petition and the Declaration of

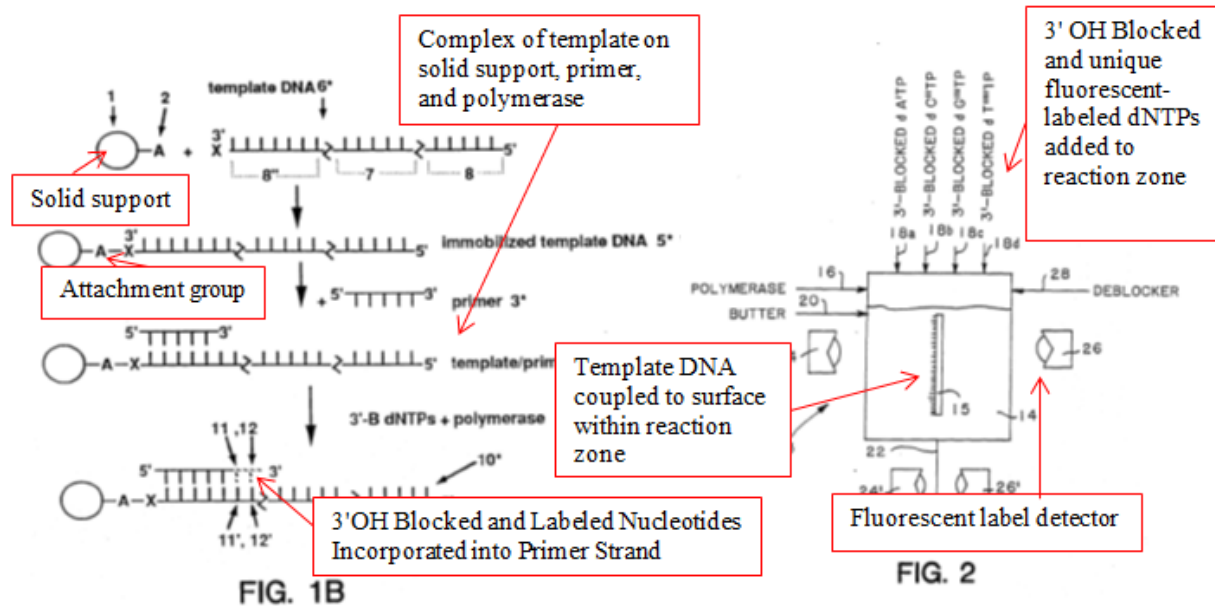
George Weinstock, Ph.D. (Exhibit 1021), the claimed elements were well known in the art and there were clear motivations to use those elements as claimed as reflected in the discussions below.

1. Ground for Challenge 1 - Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Tsien

Tsien published **May 16, 1991**, and thus is prior art under 35 U.S.C. § 102(b). *There is no indication that Tsien was considered in detail by the Examiner.*

Tsien generally discloses a sequencing by synthesis method in which a template DNA strand is coupled to a solid support, and 3' OH blocked and fluorescent labeled nucleotides are sequentially added to a primer during sequencing. Tsien first steps through the sequencing method generally, and then discusses the details of each element in the subsections that follow the general discussion. See p. 9, lines 10-27. The relevant general sequencing method of Tsien is disclosed at p. 11, line 28 to p. 15, line 5. The detailed discussions of each element of the method are disclosed starting at page 19. Of particular relevance, Tsien discloses 3' OH capping groups for nucleotides and methods for their removal at pages 23-25, and nucleotide labeling groups and methods for attachment and removal at pages 28-29. Additionally, Tsien expressly cites to Prober I for at least its disclosure of deazapurine-based, fluorescence-labeled nucleotides, as recited in dependent claims 15 and 16.

Annotated versions of FIG. 1B and FIG. 2 of Tsien are shown below:



The analysis and claim charts below demonstrate that claims 12-13, 15-17, 20 26, 28 29, 31 and 33 of the '869 patent are invalid as anticipated by Tsien:

Claim Chart 1

Claim in 7,790,869	Disclosure and Explanation of <u>Tsien</u> .
12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group,	Tsien discloses addition of a "polymerase and ... <i>four labeled dNTPs</i>" to a template-primer pair.... The <i>blocking group present on the 3'-hydroxyl position</i> of the added dNTP prevents inadvertent multiple additions." <u>Tsien</u>, p. 12, 22 to p. 13, l. 13 (emphasis added). Tsien further discloses a "<i>fluorescent moiety attached to the base moiety. The tag may be chemically cleaved</i> (either separately from or simultaneously with the deblocking step)." <i>Id.</i>, p. 28, ll. 5-8; see also p. 28, ll. 19-23 (emphasis added). Because the label and blocking group may be removed separately, <u>Tsien</u> teaches deoxyribonucleotides having both a "cleavable linker" and "cleavable chemical

	group." See also <u>Tsien</u> at p. 27, line 33 to p. 28, line 35 (describing placing the label on the base of the nucleotide or other position not on the 3' OH) and p. 14, lines 19-26 (describing the label as "otherwise incorporated" – at a position other than the 3' OH).
wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and	"the fluorescent moiety or other innocuous label can be attached to the dNTP through a spacer or tether. <u>The tether can be cleavable if desired to release the fluorophore or other label on demand.</u> " <u>Tsien</u> , p. 28, ll. 19-23 (emphasis added) <u>Tsien</u> discloses that "cleavable tethers" for fluorescent tags may be removed by a variety of chemical methods, including bases, fluoride, and thiols or thiosulfate. <i>Id.</i> , p. 28, ll. 23-29; see also p. 31, lines 33 - page 32, line 7.
wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.	<u>Tsien</u> discloses use of " <u>3'-O-acyl blocking groups</u> and other blocking groups <u>hydrolysable under basic conditions.</u> " <u>Tsien</u> , p. 22, l. 34 to p. 23, l. 2 (emphasis added) <u>Tsien</u> further discloses removal of 3'-OH blocking groups using other chemistries, light, and enzymes. (<i>Id.</i> , p. 23, l. 27 to p. 25, l. 34.).
13. The nucleotide of claim 12, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3' OH group is cleaved by chemical means.	As set forth with respect to claim 12, <u>Tsien</u> discloses that both the cleavable linker and the cleavable chemical group may be removed by, <i>inter alia</i> , basic conditions. <u>Tsien</u> , p. 28, ll. 19-29 and p. 22, l. 34 to p. 23, l. 2, respectively. <u>See also</u> p. 23, l. 27 - p. 25, l. 34.
15. The nucleotide of claim 12, wherein the base is a deazapurine.	As set forth above, <u>Tsien</u> discloses all elements of claim 12. In discussing methods utilizing a dNTP in which the fluorescent label group is coupled to the base of the dNTP, <u>Tsien</u> incorporates the disclosure of <u>Prober I</u> , stating "[o]ne method involves the use of a fluorescent

	tag attached to the base moiety. ... This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. ... Prober et al. (1987) show enzymatic incorporation of fluorescent ddNTPs by reverse transcriptase and Sequenase™." <u>Tsien</u> p. 28, l. 5-18; <u>see also Tsien</u>, page 5, lines 22-23 (citing to <u>Prober I</u>). <u>Prober I</u> discloses "the set of four fluorescence-tagged chain-terminating reagents we have designed and synthesized is shown in FIG. 2. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... the linker is attached ... to the 7 position in the <u>7-deazapurines</u>." <u>Prober I</u>, page 337, col. 1 (emphasis added).
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.	As set forth above, <u>Tsien</u>, through incorporation of <u>Prober I</u>, discloses each element of claim 15. <u>Prober I</u> discloses "the set of four fluorescence-tagged chain-terminating reagents we have designed and synthesized is shown in FIG. 2. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... <u>the linker is attached ... to the 7 position in the 7-deazapurines</u>." <u>Prober I</u>, page 337, 1st column (emphasis added) <u>see also</u> Fig. 2. "The dyes and bases were ... paired for maximum distinguishability...." <u>Id.</u>, p. 337, col. 1; <u>see also</u> Fig. 2 (showing different dyes attached to A-512 and G-505).
Claim 17. The nucleotide of claim 12, wherein the detectable label is a fluorophore.	As set forth with respect to claim 12, <u>Tsien</u> discloses nucleotides labeled with a fluorescent label. <u>Tsien</u> , p. 27, l. 36 to p. 28, l. 12; <u>see also</u> p. 26, ll. 16-36 and p. 13, ll. 4-13.
Claim 20. The nucleotide of claim 12, wherein said cleavable chemical group has a molecular weight of 300 Daltons or less.	<u>Tsien</u> discloses numerous 3'-OH blocking groups having a weight of less than 300 Daltons, including "lower (1-4 carbon) alkanolic acid ... esters, for example formyl, acetyl, isopropanol ... esters." <u>Tsien</u> , p. 21, ll. 20-31; <u>see also</u> p. 20, l. 24 to p. 23, l. 25, and specifically page 21, ll. 9-17.
Claim 21. The nucleotide of claim 12,	<u>Tsien</u> discloses use of modified nucleotides having as their nucleoside bases "adenosine, cytidine, guanosine

wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine.	and thymidine." <u>Tsien</u> , p. 9, ll. 30-36; <u>see also</u> p. 12, ll. 227, and FIGS. 2-3 (showing addition of blocked and labeled dNTPs) and 5-8.
Claim 22. The nucleotide of claim 21, wherein said nucleotide analog is incorporated in a primer.	<u>Tsien</u> discloses addition of a labeled dNTP to the "the first available template nucleotide following the primer." <u>Tsien</u> , p. 12, ll. 22-27; <u>see also</u> p. 10, l. 27 to p. 11, l. 27 and FIGS. 1A and 1B. The nucleotides disclosed by <u>Tsien</u> are thus incorporated in a primer.
Claim 23. The nucleotide of claim 22, wherein said primer is in a complex with a nucleic acid template.	<u>Tsien</u> disclose "the template 6* carries the reactive group X which bonds to the substrate via the A-X bond to <u>form an immobilized template 5*</u> . <u>This is then hybridized with primer 3* to give the immobilized, primed template 9*</u> ." <u>Tsien</u> , p. 11, ll. 14-21 (emphasis added); <u>see also</u> p. 12, ll. 22-27 and Figs. 1A and 1B.
Claim 24. The nucleotide of claim 23, wherein said template is immobilized on a solid surface.	<u>Tsien</u> discloses " the template 6* carries the reactive group X which bonds to the substrate via the A-X bond <u>to form an immobilized template 5*</u> <u>The chemistry for such an attachment is known in the art.</u> " <u>Tsien</u> , p. 11, ll. 14-27 (emphasis added); <u>see also</u> p. 11, ll. 34-36; p. 32, l. 9 - p. 34, l. 34; and FIG. 1B.
Claim 25. The nucleotide of claim 23, wherein said template is part of array.	" Figure 3 shows a schematic representation of a device 30 which has the four reaction zone configuration.... each of the four reaction zones contains a surface 34a-d to which is immobilized numerous copies of a primed subject single stranded DNA" <u>Tsien</u> , p. 15, ll. 6-16. Multiple "reaction zones" constitute an array.
Claim 26. The nucleotide of claim 23, wherein said nucleic acid template is derived from genomic nucleic acid.	<u>Tsien</u> discloses that a "goal of the biological community ... is the <u>determination of the complete structure of the DNA of a number of organisms</u> , including man." <u>Tsien</u> , p. 1, ll. 18-21 (emphasis added).
Claim 28. The nucleotide of claim 12, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a	<u>Tsien</u> discloses that a "criteria for successful use of 3'-OH blocking groups include[s]: (1) the <u>ability of a polymerase enzyme to accurately and effectively incorporate the dNTPs carrying the 3'-OH blocking groups into the cDNA chain.</u> " <u>Tsien</u> , p. 20, ll. 28-32; <u>see also</u> p. 19, ll. 4-18; p. 12, ll. 11-18; and p. 13, ll. 8-13 (emphasis added).

polymerase.	
Claim 29. The nucleotide of claim 23, wherein said complex further comprises a polymerase.	<u>Tsien</u> discloses that the template "hybridized with primer 3* to give the immobilized, primed template 9* <i>upon which the desired adding of dNTPs takes place to add units 11 and 12</i> and thus identify the sequence and identity of units 11' and 12'." <u>Tsien</u> , p. 11, ll. 14-21 (emphasis added); <u>see also</u> p. 15, l. 32 - p. 16, l. 7; p. 19, ll. 4-18; FIGS. 1A and 1B.
Claim 31. The nucleotide of claim 12, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.	<u>Tsien</u> discloses numerous 3'-OH blocking groups that are small chemical moieties, including "lower (1-4 carbon) alkanolic acid ... esters, for example formyl, acetyl, isopropanol ... esters." <u>Tsien</u> , p. 21, ll. 20-31; <u>see also</u> p. 20, l. 24 to p. 23, l. 25. "Other blocking modifications to the 3'-OH position of dNTPs include the introduction of groups such as <i>-F, -NH₂, -OCH₃, -N₃, -OPO₃⁼...</i> " <u>Tsien</u> , p. 21, ll. 9-17 (emphasis added).
Claim 33. The nucleotide of claim 24, wherein the template is attached to the solid surface via an attachment group.	<u>Tsien</u> discloses that "the template ... <i>bonds to the substrate via the A-X bond</i> to form an immobilized template 5*... <i>The chemistry for such an attachment is known in the art.</i> ." <u>Tsien</u> , p. 11, ll. 14-27 (emphasis added); <u>see also</u> FIG. 1B; p. 10, ll. 27-34; p. 11, ll. 34-36; p. 32, l. 19 - p. 34, l. 34

Regarding claims 15 and 16, Tsien incorporates the disclosure of Prober I, *Science* 238, 336-341 (1987) for its teaching of preparing nucleotides with fluorescent tags that can be successfully incorporated by Tsien's preferred polymerase, Sequenase™. See Tsien, page 5, lines 22-23, page 19, lines 4-18; and page 28, lines 5-18; see also Weinstock Decl. ¶ 63. Tsien also provides express instruction that documents identified in the specification are used "for their teaching of synthetic methods, coupling and detection methodologies, and the like." See Tsien, page 3, lines 13-16.

Prober I expressly discloses attaching a fluorescent label to the 7 position of a 7 deazapurine. Since the attachment to purine bases (A and G) in Prober I is required to be to a carbon rather than a nitrogen at the 7 position of the base, following the teaching of Prober I requires the use of a 7-deaza purine base. Thus, Tsien specifically references Prober I's teaching of using a 7-deazapurine as an effective way to couple a fluorescent label to a nucleic acid base for use in a sequencing method. The disclosure of Prober I incorporated by Tsien is sufficient to meet the all elements rule of anticipation under 35 U.S.C. § 102(b). *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1383 (Fed. Cir. 2007) (stating "material not explicitly contained in the single, prior art document may still be considered for purposes of anticipation if that material is incorporated by reference into the document" (internal quotations and citations omitted)).

2. Ground for Challenge 2 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Tsien and Prober I

Prober I is entitled "A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides," and was published in 1987, and therefore is prior art under 35 U.S.C. § 102(b). Petitioner has demonstrated that Tsien, through incorporation of Prober I, anticipates claims 15 and 16. In the alternative, Tsien in view of Prober I renders claims 15 and 16 of the '869 invalid for obviousness under 35 U.S.C. § 103. Tsien states that Prober I is used "for [its] teaching of synthetic methods, coupling and detection methodologies, and the

like." Tsien, p. 3, ll. 11-16. With specific reference to Prober I, Tsien states that:

One method involves the use of a fluorescent tag attached to the base moiety.... This method is included because a number of base moiety derivatized dNTP analogues have been reported to exhibit enzymatic competence. Prober et al. (1987) [Prober I] show enzymatic incorporation of fluorescent ddNTPs by ... Sequenase™

Tsien thus provides an express teaching, suggestion, and motivation to combine Tsien with the disclosures of Prober I with respect to "base moiety derivatized" nucleotide analogues. See Tsien at page 3, ll. 14-16 and page 28, ll. 16-18, respectively; see Weinstock Decl. ¶¶ 64-67. Tsien further states that the synthesis scheme for ddNTPs used in Prober I should be used in Tsien to produce "fluorescent dNTPs." Tsien, p. 29, ll. 10-19. Prober I specifically teaches that nucleotide analogues incorporating 7-deazapurines may be used in sequencing reactions. In fact, using the synthetic methods of Prober I to attach labels to purine bases requires and necessarily results in the use of 7 deazapurines. See Weinstock Decl. ¶ 66. Thus, it would have been obvious for one of ordinary skill in the art to combine Tsien's teachings with the 7-deazapurine feature disclosed in Prober I because it is merely the use of known techniques to improve similar Tsien systems and methods in the same way that the known features improve the methods and reagents of Prober I, and as expressly taught by Tsien. See Weinstock Decl. ¶ 66; see also, reasons in Section **Error! Reference source not found.**, above.

As disclosed above in **Claim Chart 1**, Tsien discloses each element of claim 12. Should it be determined, however, that Tsien does not anticipate claims 15 and 16, the claim chart below demonstrates that Prober I discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Tsien under 35 U.S.C. § 103.

Claim Chart 2

15. The nucleotide of claim 12, wherein the base is a deazapurine.	<u>Prober I</u> discloses "the set of four fluorescence-tagged chain-terminating reagents we have designed and synthesized is shown in FIG. 2. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... the linker is attached ... to the 7 position in the <i>7-deazapurines</i> ." <u>Prober I</u> , page 337, 1st column (emphasis added).
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.	<u>Prober I</u> discloses "the set of four fluorescence-tagged chain-terminating reagents we have designed and synthesized is shown in FIG. 2. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... the linker is attached ... to the 7 position in the <i>7-deazapurines</i>." <u>Prober I</u>, page 337, 1st column (emphasis added) <u>see also</u> Fig. 2. <u>Prober I</u> discloses unique fluorescent labels: "The dyes and bases were therefore paired for maximum distinguishability and for balanced net fluorescence sensitivities." <u>Id.</u>, p. 337, col. 1; <u>see also</u> Fig. 2 (showing different dyes attached to A-512 and G-505).

3. Ground for Challenge 3 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Tsien and Prober II

Claims 15 and 16 are also obvious in view of Tsien combined with Prober II under 35 U.S.C. § 103. Prober II is entitled "Method, System, and Reagents for

DNA Sequencing" and was issued on **September 7, 1993**, and is therefore prior art under 35 U.S.C. § 102(b).

As previously explained, Tsien teaches systems and methods for polymerase-mediated, template directed, DNA sequencing. Prober II specifically teaches that nucleotide analogues incorporating 7-deazapurines may be used in polymerase-mediated, template directed, DNA sequencing reactions. Prober II expressly teaches that "The unnatural 7-deazapurines are employed so that the reporter may be attached *without adding a net charge to the base portion or destabilizing the glycosidic linkage.*" Prober II, col. 19, lines 4-7 (emphasis added). Further, Prober II expressly teaches the advantage of attaching the label group to 7-position of purines stating "the *7-position on purines* may carry even a relatively *bulky substituent without significantly interfering with overall binding or recognition.*" Prober II, col. 18, lines 66-68 (emphasis added).

Thus, it would have been obvious for one of ordinary skill in the art to combine Tsien's teachings with the 7-deazapurine feature disclosed in Prober II because it is merely the use of known techniques to improve Tsien systems and methods. See e.g., reasons in Section **Error! Reference source not found.**, above. Furthermore, Prober II discloses the synthesis scheme underlying Prober I. As discussed in Section V.1., above, Tsien specifically states that the synthesis scheme for ddNTPs used in Prober I should be used in Tsien to produce

"fluorescent dNTPs." Tsien, p. 29, ll. 10-19.

As disclosed above in **Claim Chart 1**, Tsien discloses each element of claim 12. Should it be determined, however, that Tsien does not disclose deapaurine nucleotide analogs in its method of sequencing by synthesis, the claim chart below showss that Prober II discloses the elements of both claims 15 and 16, and thereby renders the claims obvious in combination with Tsien under 35 U.S.C. § 103.

Claim Chart 3

15. The nucleotide of claim 12, wherein the base is a deazapurine.	<u>Prober II</u> discloses that "<i>base elements are essential for incorporation of the appropriate nucleotide</i> directed by the template with the high fidelity necessary for accurate sequencing. This structural part also carries the reporter. <i>The art shows that the 5-position on the pyrimidines and the 7-position on purines may carry even a relatively bulky substituent</i> without significantly interfering with overall binding or recognition." <u>Prober II</u>, col. 18, line 61-68 (emphasis added). <u>Prober II</u> discloses that "preferred heterocyclic base parts include ... <i>7 deazaadenine [and] 7 deazaguanine</i>." <u>Id.</u>, col. 19, ll. 2-4 (emphasis added).
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.	<u>Prober II</u> discloses a linker with fluorescent label "<i>attached to the heterocyclic base at ... the 7-position (purine numbering) for the 7-deazapurines</i>." <u>Prober II</u>, col. 19, ll. 18-28 (emphasis added). <u>Prober II</u> further discloses that "fluorescent species emissions can be detected ... in a manner that differentiates spectral distributions." <u>Id.</u>, col. 20, lines 10-12.

4. Ground for Challenge 4 - Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Dower

Dower is entitled "Sequencing of Surface Immobilized Polymers Utilizing Microfluorescence Detection" and issued **August 20, 1996**, and is therefore prior art under 35 U.S.C. § 102(b) because it was patented more than one year before the earliest claimed filing date of the '869 patent. *There is no indication that Dower was considered in detail by the Examiner.*

Dower generally discloses nucleic acid sequencing by synthesis methods. Dower discloses both a degradative approach and a synthetic approach to sequencing. The synthetic approach is relevant to the '869 patent. See, generally, Dower col. 14, - col. 15 and col. 23 - col. 26. This approach uses chain-terminating nucleotide analogs having both a removable fluorescent label attached to the base of the nucleotide and a removable blocking group located at the 3'-OH of the ribose. For example, an annotated version of FIG. 8 of Dower is shown below (the two portions reproduced side by side for clarity):

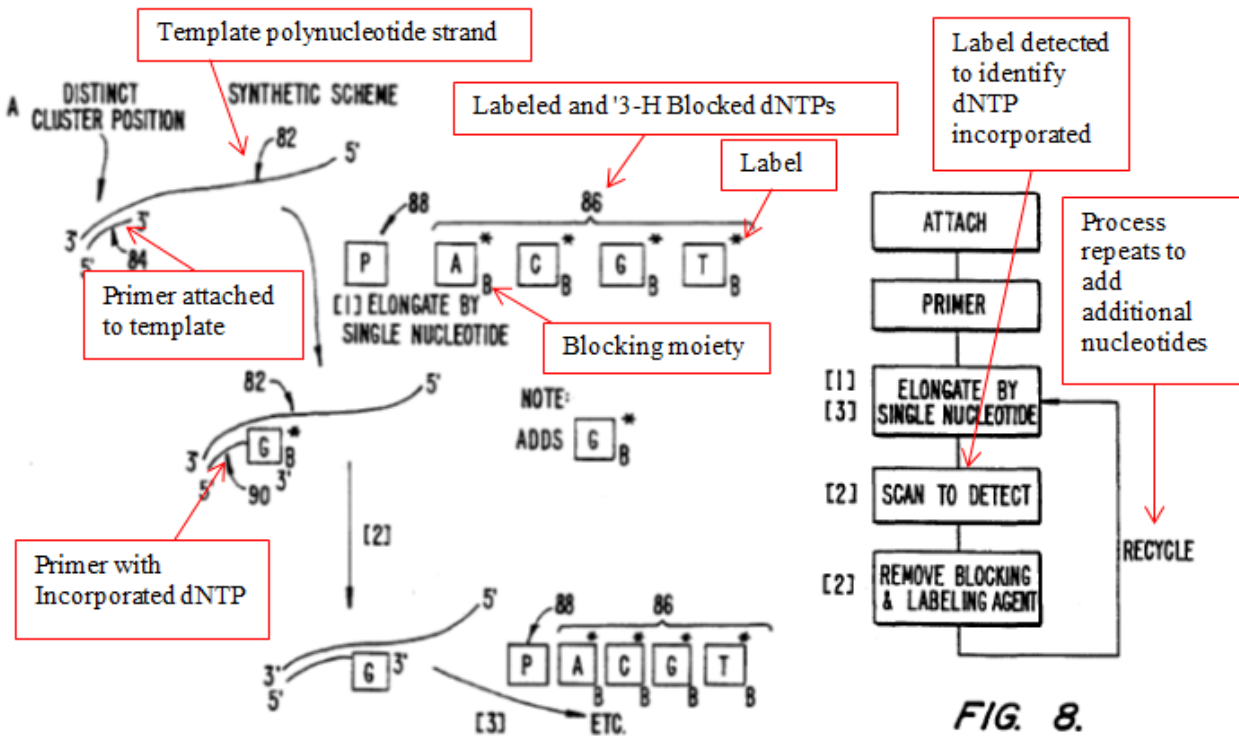
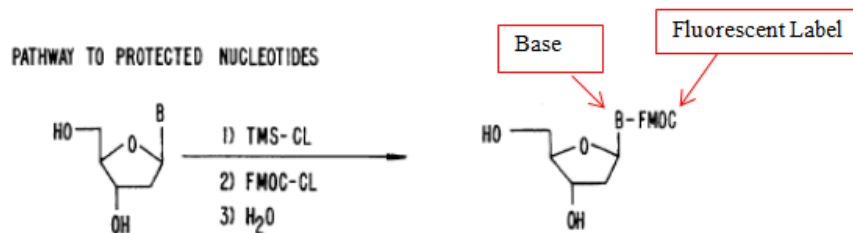


FIG. 9 of Dower shows a synthesis scheme towards production of a labeled and 3'-OH blocked nucleotide which includes a fluorescent label connected to the base. An annotated version of a portion of FIG. 9 of Dower is reproduced below:



Further Dower expressly incorporates Prober I by reference for at least its disclosure of deazapurine-based, fluorescence-labeled nucleotides, as recited in dependent claims 15 and 16.

The analysis and claim charts below demonstrate that claims 12-13, 15-17,

20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Dower.

Claim Chart 4

Claim in 7,790,869	Disclosure and Explanation of <u>Dower</u>
12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group,	<u>Dower</u> discloses "Nucleotide analogs used as chain-terminating reagents will <i>typically have both a labeling moiety and a blocking agent</i> while remaining compatible with the elongation enzymology.... it is also possible to put a label on another portion of the nucleotide analog than the 3' hydroxyl position of the sugar, thereby requiring a two-step reaction cycle for removing the blocking and labeling groups." <u>Dower</u>, col. 15, l. 62 to col. 16, l. 6 (emphasis added). "The fluorophore is placed in a position other than the 3'OH of the nucleoside, and a different group placed on the 3'OH of the <i>dNTPs</i> to function as a chain terminator. <i>The fluorophore and the 3' blocking group are removed by the same treatment in a single step</i> (preferably), or they may be removed in separate steps." <u>Dower</u> col. 25, ll. 35-40 (emphasis added).
wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and	<u>Dower</u> teaches that "One important functional property of the monomers is that the <i>label be removable</i>. The removal reaction will preferably be achieved using mild conditions. Blocking groups sensitive to mild <i>acidic conditions, mild basic conditions, or light</i> are preferred." <u>Dower</u>, col. 15, ll. 52-56 (emphasis added); <u>see also</u> col. 25, ll. 35-40.
wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a	"In order to ensure that only a single nucleotide is added at a time, a blocking agent is usually incorporated onto the 3' hydroxyl group of the nucleotide. Optimally, the <i>blocking agent should be removable under mild conditions (e.g., photosensitive, weak acid labile, or weak base labile groups)</i>, thereby allowing for further elongation of the primer strand with a next synthetic cycle." <u>Dower</u>, col. 18, ll. 1-7 (emphasis added); <u>see also</u>

chemical means, a physical chemical means, heat, and light.	col. 18, ll. 11-20; col. 25, ll. 15-23.
13. The nucleotide of claim 12, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3' OH group is cleaved by chemical means.	As set forth with respect to claim 12, <u>Dower</u> discloses that both the cleavable linker and the cleavable chemical group may be removed by mild acidic and basic conditions, <i>i.e.</i> a chemical method (specifically, hydrolysis). <u>Dower</u> , col. 15, ll. 52-56 and col. 25, ll. 24-40.
15. The nucleotide of claim 12, wherein the base is a deazapurine.	As set forth above, <u>Dower</u> discloses all elements of claim 12. <u>Dower</u> states that "each of the four dNTP analogs is identified by <u>a distinct dye, such as described in Prober et al. Science 238:336-341...</u>" <u>Dower</u>, col. 23, lines 18-24 (emphasis added). <u>Dower</u> further incorporates <u>Prober I</u> by reference. <u>See</u> col. 28, lines 38-41. <u>Prober I</u> teaches that a "linker is attached to ... <u>the 7 position of the 7-deazapurines.</u>" <u>Prober I</u>, p. 337, col. 1 (emphasis added); <u>see also</u> Fig. 2.
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deza-adenine and deza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deza-adenine or deza-guanine.	As set forth above, <u>Dower</u>, through incorporation of <u>Prober I</u>, discloses each element of claim 15. <u>Prober I</u> discloses "the set of four fluorescence-tagged chain-terminating reagents we have designed and synthesized is shown in FIG. 2. These are ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... the linker is attached ... to the 7 position in the <u>7-deazapurines.</u>" <u>Prober I</u>, page 337, 1st column (emphasis added) <u>see also</u> Fig. 2. Fig. 2 shows the "7-deazapurines" as 7-deazaadenosine (A-512) and 7-deazaguanosine (G-505). <u>Id.</u> <u>Prober I</u> discloses that "[t]he dyes and bases were therefore paired for <u>maximum distinguishability</u> and for balanced net fluorescence sensitivities." <u>Id.</u>, p. 337, col. 1 (emphasis added); <u>see also</u> Fig. 2 (showing

	different dyes attached to A-512 and G-505).
Claim 17. The nucleotide of claim 12, wherein the detectable label is a fluorophore.	" Although many different labels may be devised ..., <u>a fluorescent moiety is the preferred form.</u> " <u>Dower</u> , col. 20, lines 50-53 (emphasis added); <u>see also</u> col. 25, lines 4-14 and 35-40. <u>See also Prober I.</u>
Claim 20. The nucleotide of claim 12, wherein said cleavable chemical group has a molecular weight of 300 Daltons or less.	<u>Dower</u> discloses use of "appropriate blocking agents includ[ing] ... 6-nitoveratryloxycarbonyl (NVOC), 2-nitobenzylloxycarbonyl (NBOC), α,α -dimethyl-dimethoxybenzylloxycarbonyl (DDZ), 5-bromo-7-nitroindolyl, o-hydroxy-2-methyl cinnamoyl, 2-oxymethylene-anthraquinone, and t-butyl oxycarbonyl (TBOC)." <u>Dower</u> , col. 18, ll. 52-63. <u>Dower</u> further discloses the use reversible chain terminators of " <u>small blocking groups such as acetyl</u> , tBOC, NBOC and NVOC on the 3'OH." <u>Id.</u> , col. 25, ll. 48-51. An acetyl group has a molecular weight of 43 Daltons. A tBOC group has a molecular weight of 101 Daltons.
Claim 21. The nucleotide of claim 12, wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine.	<u>Dower</u> discloses and depicts examples of labeled monomers "selected from the group of nucleotides consisting of <u>adenine, cytidine, guanidine, and thymidine.</u> " <u>Dower</u> , col. 3, lines 21-26 (emphasis added); <u>see also</u> col. 3, l. 40-43; col. 4, ll. 7-10; and Figs. 6 and 9. Additionally, claim 4 recites use of "labeled and reversibly blocked adenine, cytosine, guanine, and thymine nucleotides" in the claimed sequencing method.
Claim 22. The nucleotide of claim 21, wherein said nucleotide analog is incorporated in a primer.	<u>Dower</u> discloses "using <u>primer with template which directs the addition of the nucleotide analog to be incorporated</u> will determine whether the combination is workable. Natural polymerases or variants thereof may be used under particular defined conditions." <u>Dower</u> , col. 19, ll. 11-18 (emphasis added); Fig. 8B (showing elongation of a primer); <u>see also</u> col. 14, ll. 38-59; col. 17, ll. 33-36 (citing <u>Prober I</u>); col. 18, ll. 11-32; col. 23, ll. 15-26.
Claim 23. The nucleotide of claim 22, wherein said primer is in a complex with a nucleic acid template.	<u>Dower</u> discloses "The template polymer 82 located at a particular site has already been linked to substrate. <u>The template 82 and complementary primer 84 are hybridized.</u> " <u>Dower</u> , col. 14, ll. 60-67 (emphasis added). The primer may be covalently cross-linked to the

	template. <u>Id.</u>
Claim 24. The nucleotide of claim 23, wherein said template is immobilized on a solid surface.	<u>Dower</u> discloses that sequencing methods "begin by obtaining and <i>immobilizing the target fragments ... at specific locations on [a] surface.</i> " <u>Dower</u> , col. 23, ll. 34-37 (emphasis added); <u>see also</u> col. 7, ll. 58-66 and col. 9, ll. 1-8.
Claim 25. The nucleotide of claim 23, wherein said template is part of array.	<u>Dower</u> discloses a " <i>whole matrix array of different polymers for sequencing.</i> " <u>Dower</u> , col. 9, ll. 1-8 (emphasis added); <u>see also</u> col. 6, ll. 33-35;
Claim 26. The nucleotide of claim 23, wherein said nucleic acid template is derived from genomic nucleic acid.	<u>Dower</u> discloses that techniques for DNA sequencing are "necessary for ... the successful completion of the <i>human genome project.</i> " <u>Dower</u> , col. 1, ll. 43-49 (emphasis added); <u>see also</u> col. 6, ll. 15-31 and col. 14, ll. 62-63.
Claim 28. The nucleotide of claim 12, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.	<u>Dower</u> discloses that "Preferably, where an enzymatic elongation step is used, the monomers should be <i>compatible with the selected polymerase.</i> " <u>Dower</u> , col. 18, ll. 14-16 (emphasis added).
Claim 29. The nucleotide of claim 23, wherein said complex further comprises a polymerase.	<u>Dower</u> discloses that "[t]he synthetic scheme depends, in part, on the stepwise elongation by small and identifiable units. <i>A polymerase is used to extend a primer complementary to a target template.</i> " <u>Dower</u> , col. 14, ll. 47-50 (emphasis added); <u>see also</u> col. 3, ll. 52-58.
Claim 31. The nucleotide of claim 12, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.	<u>Dower</u> discloses use of "appropriate blocking agents includ[ing] ... 6-nitroveratryloxycarbonyl (NVOC), 2-nitrobenzyloxycarbonyl (NBOC), α,α -dimethyl-dimethoxybenzyloxycarbonyl (DDZ), 5-bromo-7-nitroindoliny, o-hydroxy-2-methyl cinnamoyl, 2-oxymethylene-anthraquinone, and t-butyl oxycarbonyl (TBOC)." <u>Dower</u> , col. 18, ll. 52-63. <u>Dower</u> further discloses the use reversible chain terminators of " <i>small blocking groups such as acetyl</i> , tBOC, NBOC and NVOC on the 3'OH." <u>Id.</u> , col. 25, ll. 48-51 (emphasis

	added). An acetyl group is --CO-CH₃, and has a molecular weight of 43 Daltons. The '869 patent <u>does not provide a reference mass other than 300 Daltons for "small"</u>, making this element difficult to judge. Without a more clear definition of "small" these "small blocking groups" are "small chemical moiety[ies]".
Claim 33. The nucleotide of claim 24, wherein the template is attached to the solid surface via an attachment group.	<u>Dower</u> discloses " Although the type of linkage is dependent upon the polymer being sequenced, various types of polymers have preferred linkages.... For nucleic acids, the linkages will typically be either 5' or 3' linkages. Suitable 3' linkages include those illustrated in FIG. 6...." <u>Dower</u>, col. 10, l. 67 - col. 11, l. 13; <u>see also</u> FIG. 6 and col. 10, ll. 45-55. <u>Dower</u> further discloses that "<u>The template 82 is attached to the substrate</u>, either directly or through the primer". <u>Id.</u>, col. 15, ll. 19-24 (emphasis added).

Regarding claims 15 and 16, as shown above, Dower identically discloses formation of dNTP analogues including a deazapurine via the incorporation of the disclosure of Prober I. In describing the fluorescent labeled dNTPs analogues used during the sequencing method, Dower expressly identifies Prober I as providing additional details about the fluorescent labeled dNTPs that may be used in the sequencing method of Dower. Dower col. 23, lines 18-24. In fact, using the synthetic methods of Prober I to attach labels to purine bases requires and necessarily results in the use of 7 deazapurines. Prober I expressly discloses attaching a fluorescent label to a deazapurine stating " ddNTP's to which succinylfluorescein has been attached via a linker to the heterocyclic base ... the

linker is attached ... to the 7 position in the 7-deazapurines." Prober I, page 337, 1st column (emphasis added); see also Weinstock Decl. ¶ 45.

Dower expressly incorporates by reference Prober I stating "All publications and patent applications are herein incorporated by reference." Dower, col. 28, lines 38-39. As discussed above, the disclosure of Prober I incorporated by Dower is sufficient to meet the all elements rule of anticipation under 35 U.S.C. § 102(b). See Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1383 (Fed. Cir. 2007).

5. Ground for Challenge 5 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Dower and Prober I

Petitioner has demonstrated that Dower, through incorporation of Prober I, anticipates claims 15 and 16. In the alternative, Dower in view of Prober I renders claims 15 and 16 of the '869 invalid for obviousness under 35 U.S.C. § 103.

Dower expressly teaches the combination with Prober I to make the labeled nucleotides stating "Fluorescent chain terminators (*analogues of dATP, dCTP, dGTP, and dTTP, each labeled with fluorophore preferably emitting at a distinguishable wavelength*) are added to the reaction at a sufficient concentration and under suitable reaction conditions (time, temperature, pH, ionic species, etc., See ... Prober et al.)." Dower, col. 25, lines 4-10 (emphasis added). Thus, it would be obvious to make the combination of Dower and Prober I because Dower provides express teaching to do so. See Weinstock Decl. ¶ 72. Further, it would have been obvious to combine Dower and Prober I for all the reasons discussed in section

V.2. (Tsien and Prober I) above, including because the combination of known features with known systems and methods produces a predictable result.

Additionally, Prober I showed a linker and four label system that was compatible with extension by the Sequenase polymerase enzyme, and the Sequenase polymerase enzyme was identified as a preferred extension enzyme in Dower at col. 18, lines 21-28. See Weinstock Decl. ¶ 72.

As disclosed above in **Claim Chart 4**, Dower discloses each element of claim 12. Should it be determined, however, that Dower does not disclose use of deaza-substituted nucleotide analogs in its method of sequencing by synthesis, **Claim Chart 2** above shows that Prober I renders claims 15 and 16 obvious in combination with Dower under 35 U.S.C. § 103.

6. Ground for Challenge 6 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Dower and Prober II

As previously explained, Dower teaches systems and methods for sequencing. As shown above, Prober II specifically teaches that nucleotide analogues incorporating 7-deazapurines may be used in sequencing reactions. Prober II expressly teaches the use "the unnatural 7-deazapurines" for the labeled nucleotide analogues used during sequencing stating "The unnatural 7-deazapurines are employed so that the reporter may be attached without adding a net charge to the base portion or destabilizing the glycosidic linkage." Prober II, col. 19, lines 4-7 (emphasis added). Further, Prober II expressly teaches the

advantage of attaching the label group to 7-position of purines stating "the 7-position on purines may carry even a relatively bulky substituent without significantly interfering with overall binding or recognition." Prober II, col. 18, lines 66-68 (emphasis added).

Thus, it would have been obvious for one of ordinary skill in the art to combine the teachings of Dower with the 7-deazapurine feature disclosed in Prober II for all the reasons discussed in section V.3. (Tsien and Prober II) above, including because it is merely the use of known techniques to improve similar Dower systems and methods in the same way that the known features improve the methods and reagents of Prober II. Furthermore, it would have been obvious to use the features taught by Prober II for their intended purpose to enhance the capability of the Dower systems and methods, and because the combination merely produces a predictable result. See Weinstock Decl. ¶¶ 73, 74.

As disclosed above in **Claim Chart 4**, Dower discloses each element of claim 12. Should it be determined, however, that Tsien does not disclose use of deazapurine nucleotide analogs in its method of sequencing by synthesis, **Claim Chart 3** above demonstrates that Prober II discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Dower under 35 U.S.C. § 103.

7. Ground for Challenge 7 - Claims 12-13, 17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Rabani

Rabani entitled "Device, Compounds, Algorithms, and Methods of Molecular Characterization and Manipulation with Molecular Parallelism" and published **September 6, 1996**, and is therefore prior art under 35 U.S.C. § 102(b).

There is no indication that Rabani was considered in detail by the Examiner.

Rabani generally discloses nucleic acid sequencing by synthesis methods that utilize 3'-OH capped, chain-terminating nucleotide analogs that include a fluorescent label. As shown in the claim chart below, Rabani discloses every element of at least claims 12-13, 17, 20-26, 28-29, 31, and 33 of the '869 patent, and thus, anticipates those claims under 35 U.S.C. § 102(b):

Claim Chart 5

Claim in 7,790,869	Disclosure and Explanation of <u>Rabani</u>
12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group,	<u>Rabani</u> discloses nucleotides with "<u>labeling moieties ... coupled to nucleotides via a linker.</u>" <u>Rabani</u>, p. 32, ll. 10-13 (emphasis added). <u>Rabani</u> also discloses use of removable "<u>3' protecting groups.</u>" <u>Id.</u>, p. 7, ll. 13-18 (emphasis added). "For purposes of the present disclosure ... the term nucleotide shall comprehend both the standard four <u>deoxyribonucleotides</u> or the standard four ribonucleotides, as well as any variations thereupon which pair with similar or other bases according to definable pairing rules." <u>Rabani</u>, p. 11, ll. 26-29. <u>Rabani</u> further discloses removal of moieties attached via a "<u>photocleavable linker,</u>" and "<u>photocleavable protecting groups.</u>" <u>Id.</u> at p. 17, ll. 15-21 (emphasis added).

wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and	As <u>Rabani</u> discloses that removing the label may be a separate step from removing a 3' protecting group, <u>Rabani</u> teaches that the label/linker may be attached at a different location than the 3' protecting group. <u>Id.</u> <u>Rabani</u> discloses "<u>Cleavability may be provided for in a number of ways which will be obvious to those skilled in the arts of organic and synthetic chemistry.</u> For example, said linker may include along its length one or more <u>ester linkages, which will be susceptible to hydrolysis....</u>" <u>Id.</u>, p. 34, lines 24-29 (emphasis added); <u>see also</u> discussion of "cleavable linkers" on p. 32, line 9 to p. 33, line 32.
wherein the cleavable chemical group capping the 3' OH group is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.	<u>Rabani</u> discloses that protecting groups may be photocleavable. <u>Rabani</u>, p. 17, ll. 15-21. <u>Rabani</u> discloses that "3' protecting groups..." may be "distinct from ... cleavably linked labeling moieties." <u>Id.</u>, p. 7, lines 14-18. <u>Rabani</u> further discloses that monomers which prevent further elongation ("chain terminators") may be "chemically or photochemically modified" to permit later elongation <u>Id.</u> at p. 38, ll. 16-24; <u>see also</u> p. 38, line 5 to p. 39, line 31 and claim 11.
13. The nucleotide of claim 12, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3' OH group is cleaved by chemical means.	<u>Rabani</u> discloses "<u>Cleavability may be provided for in a number of ways which will be obvious to those skilled in the arts of organic and synthetic chemistry.</u> For example, said linker may include along its length one or more <u>ester linkages, which will be susceptible to hydrolysis....</u>" <u>Id.</u>, p. 34, lines 24-29 (emphasis added); <u>see also</u> discussion of "cleavable linkers" on p. 32, line 9 to p. 33, line 32. <u>"Numerous monomers which may thus be added but do not provide an appropriate chemical functional group for subsequent elongation</u> of the polynucleotide strand to which they have been enzymatically added <u>are known within the relevant arts</u>, and are generally referred to as

	chain terminators. <u>Any such terminators which may be chemically</u> or photochemically <u>modified</u> ... to a form which may support subsequent addition of comonomers in the usual manner, may be employed...." <u>Id.</u> , p. 38, lines 16-23 (emphasis added).
Claim 17. The nucleotide of claim 12, wherein the detectable label is a fluorophore.	" molecules may be labeled by a first label, for example with a particular fluorescent dye incorporated by nick translation, in a manner identifying a portion of the molecule near the site of polymerization, and proximity of said first label to the perceptibly distinct labeling moieties used for nucleotide incorporation detection." <u>Rabani</u> , p. 14, lines 12-16; <u>see also</u> p. 24, lines 10-11 and p. 12, l. 37 - p. 13, l. 2.
Claim 20. The nucleotide of claim 12, wherein said cleavable chemical group has a molecular weight of 300 Daltons or less.	" Enzymological evidence concerning binding of <u>3' acetate esterified nucleotides</u> ... to the triphosphate binding site of <i>E. coli</i> Polymerase I <u>supports the acceptability of 3' modified nucleotides as substrates for this enzyme. Such protecting groups should therefore be compatible with either naturally occurring or genetically modified polymerases.</u> " <u>Rabani</u> , p. 39, lines 7-12 (emphasis added).
Claim 21. The nucleotide of claim 12, wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine.	<u>Rabani</u> discloses using analogues of the "four standard deoxyribonucleotides,," <u>i.e.</u> analogs of adenosine, guanosine, cytosine, and thymidine. <u>Rabani</u> , p. 11, lines 26-29.
Claim 22. The nucleotide of claim 21, wherein said nucleotide analog is incorporated in a primer.	<u>Rabani</u> discloses "polymerizing one or less nucleotides ... onto each sample at the primer." <u>Rabani</u> , p. 6, lines 28-35; <u>see also</u> p. 39, ll. 13-23 and p. 40, ll. 20-35.
Claim 23. The nucleotide of claim 22, wherein said primer is in a complex with a nucleic acid template.	<u>Rabani</u> discloses "polymerizing one or less nucleotides ... onto each sample <u>molecule at the primer ... and in opposition to ... the template polynucleotide strand.</u> " <u>Rabani</u> , p. 6, ll. 28-35 (emphasis added).
Claim 24. The nucleotide of claim 23, wherein said template	<u>Rabani</u> discloses "immobilization of a library" of polynucleotides on to a surface for detection. <u>Rabani</u> , p. 6, ll. 14-17; <u>see also</u> detailed discussion of

is immobilized on a solid surface.	immobilization methods at p. 17, l. 29 to p. 23, l. 13.
Claim 25. The nucleotide of claim 23, wherein said template is part of array.	<u>Rabani</u> teaches detection of " <u>multiple probes (i.e. in arrays ...)</u> " <u>Rabani</u> , p. 11, ll. 3-15 (emphasis added).
Claim 26. The nucleotide of claim 23, wherein said nucleic acid template is derived from genomic nucleic acid.	<u>Rabani</u> discloses that the invention may be applied to "genome sequencing applications." and that samples may be prepared from " <u>total genomic material.</u> " <u>Rabani</u> , p. 38, ll. 6-8 (emphasis added).
Claim 28. The nucleotide of claim 12, wherein said cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase.	" Enzymological evidence concerning binding of <u>3' acetate esterified nucleotides</u> ... to the triphosphate binding site of <i>E. coli</i> Polymerase I <u>supports the acceptability of 3' modified nucleotides as substrates for this enzyme. Such protecting groups should therefore be compatible with either naturally occurring or genetically modified polymerases.</u> " <u>Rabani</u> , p. 39, lines 7-12 (emphasis added).
Claim 29. The nucleotide of claim 23, wherein said complex further comprises a polymerase.	<u>Rabani</u> discloses "polymerizing one or less nucleotides ... onto each sample <u>molecule at the primer ... and in opposition to ... the template polynucleotide strand.</u> " <u>Rabani</u> , p. 6, ll. 28-35 (emphasis added). The disclosed process uses a "DNA polymerase or analogs thereof." <u>Id.</u> , p. 6, line 27. <u>See also</u> p. 39, ll. 13-23 and p. 40, ll. 20-35.
Claim 31. The nucleotide of claim 12, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.	" Enzymological evidence concerning binding of <u>3' acetate esterified nucleotides</u> ... to the triphosphate binding site of <i>E. coli</i> Polymerase I <u>supports the acceptability of 3' modified nucleotides as substrates for this enzyme. Such protecting groups should therefore be compatible with either naturally occurring or genetically modified polymerases.</u> " <u>Rabani</u> , p. 39, lines 7-12 (emphasis added).
Claim 33. The nucleotide of claim 24, wherein the template is attached to the solid surface via an	<u>Rabani</u> discloses that "[s]equencing of polynucleotides may be effected by ... immobilization of a library of such molecules to a surface.... Several methods capable of effecting such immobilization will be obvious to those skilled in the arts...." <u>Rabani</u> , p. 6, ll. 14-21. <u>Rabani</u>

attachment group.	discloses exemplary methods for immobilizing molecules to a surface, including "thiol modified ... DNA molecules to a gold coated surface" and "end-wise attachment to an antibody coated glass surface." <u>Id.</u> , p. 17, l. 31 - p. 18, l. 2.
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8. Ground for Challenge 8 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Rabani and Prober I

As previously explained, Rabani teaches systems and methods for sequencing. As shown above, Prober I teaches the advantages of using deazapurine-based nucleotides in sequencing methods. For all the reasons discussed in section V.2. (Tsien and Prober I) above, it would be obvious to use the labeled deazapurines as taught by Prober I in the sequencing process of Rabani to gain the well-known, prior art benefit of the "stable linker arm attachment" as taught by Prober I. The combination of Rabani and Prober I merely utilizes well known prior art components for their intended purpose to obtain the same known, predictable results disclosed in the references. See Weinstock Decl. ¶ 77; see also, reasons in Section **Error! Reference source not found.**, above.

As disclosed above in **Claim Chart 5**, Rabani discloses each element of claim 12. **Claim Chart 2** above demonstrates that Prober I discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Rabani under 35 U.S.C. § 103.

9. Ground for Challenge 9 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Rabani and Prober II

As previously explained, Rabani teaches systems and methods for sequencing. As shown above, Prober II specifically teaches that nucleotide analogues incorporating 7-deazapurines may be used in sequencing reactions. For all the reasons discussed in section V.3. (Tsien and Prober II) above, it would be obvious to use the labeled deazapurines as taught by Prober I in the sequencing process of Rabani to gain the well-known, prior art benefit of increased nucleotide stability as taught by Prober II. As such, the combination of Rabani and Prober II merely utilizes well known prior art components for their intended purpose to obtain the same known, predictable results disclosed in the references. See Weinstock Decl. ¶¶ 78, 79.

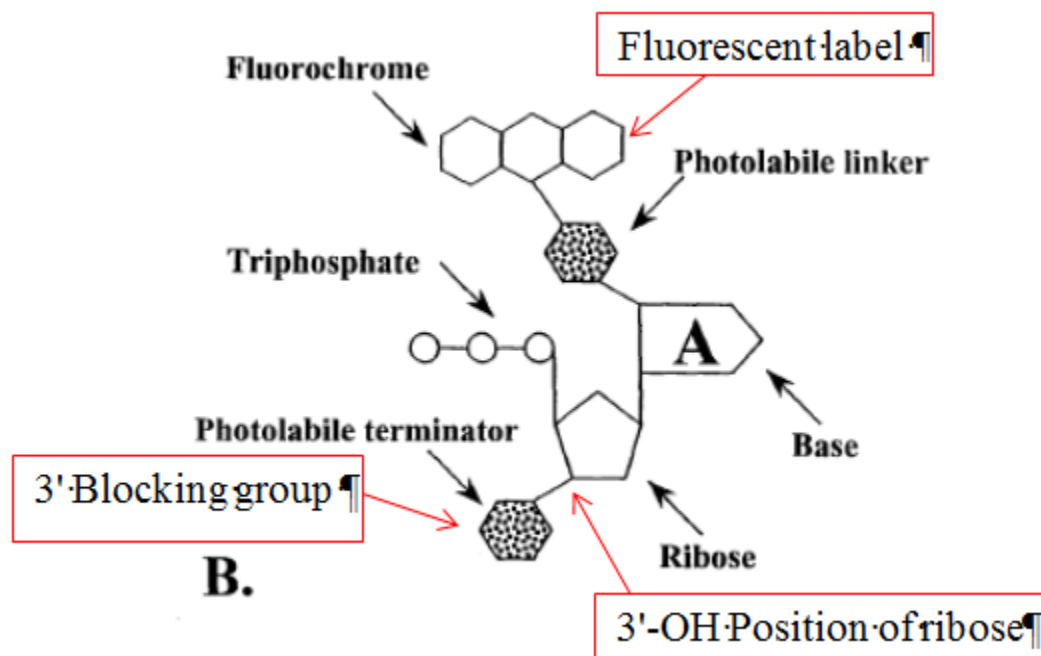
As disclosed above in **Claim Chart 4**, Rabani discloses each element of claim 12. **Claim Chart 3** above demonstrates that Prober II discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Rabani under 35 U.S.C. § 103

10. Ground for Challenge 10 - Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Stemple II

Stemple II is entitled "A Method for Direct Nucleic Acid Sequencing" and published as WO 00/53805 on **September 14, 2000**. Stemple II qualifies as prior art against the '869 patent under 35 U.S.C. § 102(a) because it was published

before the earliest claimed filing date of the '869 patent. *There is no indication that Stemple II was considered in detail by the Examiner.*

Stemple II generally discloses a sequencing by synthesis method in which a nucleic acid template to be sequenced is attached to a solid support via the interaction with a polymerase. Further, the sequencing process taught by Stemple II utilizes chain terminating nucleotides that include a blocking group at the 3'-OH of the ribose and a fluorescent label attached to the nucleotide base. These elements are clearly demonstrated by the annotated versions of FIG. 1B and FIG. 3 reproduced below (FIGs. 1-5 are identical in each of Stemple I, II, and III):



Stemple II discloses every element of at least Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent, and thus anticipates those claims under 35

U.S.C. § 102(b), as set forth in the claim chart provided below:

Claim Chart 6

Claim in 7,790,869	Disclosure and Explanation of <u>Stemple I, II, and III</u>
12. A nucleotide having a base that is attached to a detectable label through a cleavable linker, wherein the nucleotide has a deoxyribose comprising a cleavable chemical group capping the 3' OH group,	Stemple discloses that "<u>[t]he differentially-labeled nucleotides</u> used in the sequencing methods of the present invention have a detachable labeling group and <u>are blocked at the 3' portion with a detachable blocking group</u>.... <u>the labeling group is attached to the base of each nucleotide with a detachable linker</u> rather than to the detachable 3' blocking group." <u>Stemple II</u>, page 4, ll. 1-8 (emphasis added); <u>Stemple III</u>, col. 3, ll. 22-34; <u>Stemple I</u>, page 4, ll. 11-18; <u>see also</u> Fig. 1B (showing sequencing of a deoxyribonucleic acid sample). "The modified 3'-O-(-2-Nitrobenzyl)-<u>dNTP</u> is incorporated into the growing DNA chain." <u>Stemple II</u>, p. 13, ll. 9-10 (emphasis added); <u>see also</u> p. 13, ll. 4-25 and p. 29, ll. 14-17; <u>Stemple III</u>, col. 9, ll. 59-61; <u>see also</u> col. 9, l. 50-col 10, l. 17 and col. 21, ll. 39-41; <u>Stemple I</u>, p. 12, l. 26-27; <u>see also</u> p. 12, l. 20-p. 13, l. 13 and p. 29, ll. 1-3.
wherein the cleavable linker is cleaved by a means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light, and	Stemple discloses that "<u>[t]he labeling group</u> and the 3' blocking group <u>can be removed</u> enzymatically, <u>chemically</u>, or photolytically." <u>Stemple II</u>, page 4, ll. 8-9; <u>Stemple III</u>, col. 3, ll. 34-36; <u>Stemple I</u>, page 4, ll. 18-19 (emphasis added). Stemple further describes a preparation of a dNTP analog wherein "a photolabile group is attached to the 3'-OH ... and a fluorochrome-photolabile linker conjugate is attached directly to the base of the nucleotide as described by Anasawa [<i>sic</i>] <u>et al.</u>, WO 98/33939." <u>Stemple II</u>, p. 31, ll. 10-12; <u>Stemple III</u>, col. 22, ll. 53-57; <u>Stemple I</u>, p. 29, ll. 25-27.
wherein the cleavable chemical group capping the 3' OH group is cleaved by a	Stemple discloses that "<u>[t]he labeling group</u> and <u>the 3' blocking group can be removed</u> enzymatically, <u>chemically</u>, or photolytically." <u>Stemple II</u>, page 4, ll. 8-9; <u>Stemple III</u>, col. 3, ll. 34-36; <u>Stemple I</u>, page 4,

means selected from the group consisting of one or more of a physical means, a chemical means, a physical chemical means, heat, and light.	ll. 18-19 (emphasis added).
13. The nucleotide of claim 12, wherein the cleavable linker is cleaved by chemical means, and wherein the cleavable chemical group capping the 3' OH group is cleaved by chemical means.	Stemple discloses that " <u>[t]he labeling group and the 3' blocking group can be removed enzymatically, chemically, or photolytically.</u> " <u>Stemple II</u> , page 4, ll. 8-9; <u>Stemple III</u> , col. 3, ll. 34-36; <u>Stemple I</u> , page 4, ll. 18-19 (emphasis added).
15. The nucleotide of claim 12, wherein the base is a deazapurine.	"In an alternative configuration a photolabile group is attached to the 3'-OH ... <u>and a fluorochrome-photolabile linker conjugate is attached directly to the base of the nucleotide as described by Anasawa et al, WO 98/33939.</u>" <u>Stemple II</u>, page 31, lines 10-12; <u>Stemple III</u>, col. 22, lines 53-57; <u>Stemple I</u>, page 30, lines 25-27 (emphasis added). <u>Stemple II</u> specifically incorporates by reference "PCT Patent Application WO 33939." <u>Stemple II</u>, page 27, lines 30-31; <u>Stemple III</u>, col. 12, lines 55-57; <u>Stemple I</u>, page 17, l. 15. <u>Anazawa</u>¹ discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. Fig. 7 and page 5, l. 36 - page 6, line 9 (also citing "Science 238, 336 – 341, 1987," i.e.

¹ As noted above, a translation of Anazawa WO98/33939 is provided in

Exhibit 1012 . All citations are to Anazawa as translated.

	<u>Prober I).</u>
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.	As set forth above, <u>Stemple I, II, and III</u>, through incorporation of <u>Anazawa</u>, disclose each element of claim 15. As also set forth with respect to claim 15, <u>Anazawa</u> discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. Fig. 7 and page 5, l. 36 - page 6, line 9 (<u>also citing " Science 238, 336 – 341, 1987," i.e. Prober I).</u> "Panel C [of Fig. 1] depicts the four different nucleotides <u>each labeled with a fluorochrome with distinct spectral properties.</u>" <u>Stemple II</u>, page 4, ll. 26-27; <u>Stemple III</u>, col. 3, lines 63-67; <u>Stemple I</u>, page 5, ll. 8-9 (emphasis added).
17. The nucleotide of claim 12, wherein the detectable label is a fluorophore.	Stemple states that "<u>use of fluorescent tags to identify nucleotides in nucleic acid sequencing is well known in the art.</u>" <u>Stemple II</u>, page 14, ll. 2-3; <u>Stemple III</u>, col. 10, ll. 24-27; <u>Stemple I</u>, page 13, ll. 18-19 (emphasis added); see also <u>Stemple I, II, and III</u> Figs. 1B, showing a fluorochrome label and photolabile linker.
20. The nucleotide of claim 12, wherein said cleavable chemical group has a molecular weight of 300 Daltons or less.	Stemple discloses that "<u>the detachable blocking group is a 3'-O-(-2-Nitrobenzyl) group.</u>" <u>Stemple II</u>, page 13, ll. 19-20; <u>Stemple III</u>, col. 10, lines 6-9; <u>Stemple I</u>, page 13, ll. 7-8 (emphasis added). This compound has a molecular weight of less than 300 Daltons.
21. The nucleotide of claim 12, wherein said nucleotide is an analog of adenosine, guanosine, cytosine, or thymidine.	"Panel C [of Fig. 1] depicts <u>the four different nucleotides</u> each labeled with a fluorochrome with distinct spectral properties." <u>Stemple II</u>, page 4, ll. 26-27; <u>Stemple III</u>, col. 3, lines 63-67; <u>Stemple I</u>, page 5, ll. 8-9 (emphasis added). Fig. 1C of <u>Stemple I, II, and III</u> shows "the four different nucleotides" as modified A, C, G, and T nucleotides respectively, <u>i.e. "analog[s] of adenosine, guanosine, cytosine, or thymidine" as claimed.</u>
22. The nucleotide of claim 21, wherein said nucleotide analog is incorporated in a	<u>"A nucleic acid sample and oligonucleotide primers</u> are introduced to the reaction chamber in a buffered solution containing all four labelled-caged nucleoside triphosphate terminators. <u>Template-driven elongation of</u>

primer.	<i>a nucleic acid is mediated by the attached polymerases using the labeled-caged nucleoside triphosphate terminators."</i> <u>Stemple II</u> , page 3, ll. 15-19; <u>Stemple III</u> , col. 2, l. 62 - col. 3, l. 1; <u>Stemple I</u> , page 3, ll. 22-26 (emphasis added).
23. The nucleotide of claim 22, wherein said primer is in a complex with a nucleic acid template.	" <i>A nucleic acid sample and oligonucleotide primers</i> are introduced to the reaction chamber ... Reaction centers are monitored by the microscope system <i>until a majority of sites contain immobilized polymerase bound to a nucleic acid template with a single incorporated labeled-caged nucleotide terminator.</i> " <u>Stemple II</u> , page 3, ll. 15-21; <u>Stemple III</u> , col. 2, l. 62 - col. 3, l. 5; <u>Stemple I</u> , page 3, ll. 22-28; <u>see also Stemple I, II, and III Fig. 3</u> (showing complex of DNA sample, primer, and polymerase attached to a solid support).
24. The nucleotide of claim 23, wherein said template is immobilized on a solid surface.	" <i>A nucleic acid sample and oligonucleotide primers</i> are introduced to the reaction chamber ... Reaction centers are monitored by the microscope system <i>until a majority of sites contain immobilized polymerase bound to a nucleic acid template with a single incorporated labeled-caged nucleotide terminator.</i> " <u>Stemple II</u> , page 3, ll. 15-21; <u>Stemple III</u> , col. 2, l. 62 - col. 3, l. 5; <u>Stemple I</u> , page 3, ll. 22-28; <u>see also Stemple I, II, and III Fig. 3</u> (showing complex of DNA sample, primer, and polymerase attached to a solid support).
25. The nucleotide of claim 23, wherein said template is part of array.	" <i>A diagram of the DNAs reaction center array is given in FIG. 5...</i> each reaction center is attached to the lower slide of the reaction chamber. Depicted in the left side panel (Microscope Field) is the <i>view of an entire array.</i> " <u>Stemple II</u> , page 7, ll. 26-29; <u>Stemple III</u> , col. 5, l. 65 - col. 6, l. 2; <u>Stemple I</u> , page 8, ll. 2-5 (emphasis added).
26. The nucleotide of claim 23, wherein said nucleic acid template is derived from genomic nucleic acid.	Stemple discloses that "[t]he nucleic acid to be sequenced can be obtained from any source. Example <i>nucleic acid samples to be sequenced include ... total genomic DNA.</i> " <u>Stemple II</u> , page 11, ll. 8-10; <u>Stemple III</u> , col. 8, ll. 28-31; <u>Stemple I</u> , page 10, ll. 21-23 (emphasis added).
28. The nucleotide of claim 12, wherein said cleavable chemical	Stemple discloses that " <i>preferred polymerases are capable of incorporating 3'-modified nucleotides.</i> " <u>Stemple II</u> , page 8, ll. 28-29; <u>Stemple III</u> , col. 6, ll. 52-

group does not interfere with the recognition of the nucleotide by a polymerase.	53; <u>Stemple I</u> , page 8, l. 21 (emphasis added).
29. The nucleotide of claim 23, wherein said complex further comprises a polymerase.	" <u>A nucleic acid sample and oligonucleotide primers</u> are introduced to the reaction chamber ... Reaction centers are monitored by the microscope system <u>until a majority of sites contain immobilized polymerase bound to a nucleic acid template with a single incorporated labeled-caged nucleotide terminator.</u> " <u>Stemple II</u> , page 3, ll. 15-21; <u>Stemple III</u> , col. 2, l. 62 - col. 3, l. 5; <u>Stemple I</u> , page 3, ll. 22-28; <u>see also Stemple I, II, and III Fig. 3</u> (showing complex of DNA sample, primer, and polymerase attached to a solid support).
31. The nucleotide of claim 12, wherein the cleavable chemical group capping the 3' OH group is a small chemical moiety.	Stemple discloses that " <u>the detachable blocking group is a 3'-O-(-2-Nitrobenzyl) group.</u> " <u>Stemple II</u> , page 13, ll. 19-20; <u>Stemple III</u> , col. 10, lines 6-9; <u>Stemple I</u> , page 13, ll. 7-8 (emphasis added).
33. The nucleotide of claim 24, wherein the template is attached to the solid surface via an attachment group.	FIG. 3 of <u>Stemple II</u> , <u>Stemple III</u> and <u>Stemple I</u> shows the DNA sample (template) attached to the lower slide (solid surface) via interaction with the DNA polymerase. "According to the methods of the present invention, a <u>plurality of polymerase molecules is immobilized on a solid support</u> through a covalent or non-covalent interaction." <u>Stemple II</u> , page 3, lines 14-15; <u>Stemple III</u> , col. 2, lines 60-62; <u>Stemple I</u> , page 3, lines 21-22 (emphasis added).

Regarding claims 15 and 16, as discussed above, Stemple II's citation and incorporation by reference of Anazawa satisfies the "all elements rule" of anticipation. In particular, Stemple II states that labels should be attached to the base using the method disclosed in Anazawa. The method of Anazawa converts

the 7 position of purines to a carbon (making them “deaza”) to increase the stability of the nucleotide. Thus, following the method of Anazawa as instructed by Stemple II necessarily requires the use of deaza bases. The same is true when following the teachings of Prober I. See Weinstock Decl., ¶ 80.

11. Ground for Challenge 11 - Claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated by Stemple III

Stemple III is entitled "A Method for Direct Nucleic Acid Sequencing", and issued as U.S. Patent No. 7,270,951 on September 18, 2007, as the national stage application of the PCT application that published as Stemple II. Stemple III also claims priority under 35 U.S.C. § 120 to U.S. application serial no. 09/266,187 ("Stemple I"), filed **March 10, 1999**, as a continuation-in-part application.

Because the March 10, 1999 filing date of Stemple I is before the earliest claimed filing date of the '869 patent, October 6, 2000, Stemple III also qualifies as prior art under 35 U.S.C. § 102(e). **Claim Chart 6**, provided in Section V.10. above, provides citations to the relevant portions of the Stemple III reference and corresponding support in Stemple I for the priority date of March 10, 1999.

Accordingly, claims 12-13, 15-17, 20-26, 28-29, 31, and 33 of the '869 patent are invalid as anticipated under 35 U.S.C § 102(e) by Stemple III.

12. Ground for Challenge 12 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Stemple II and Anazawa

Anazawa is entitled "Method for Determining Nucleic Acids Base Sequence

and Apparatus Therefor," and was published on Aug. 6, 1998, and is therefore prior art under 35 U.S.C. § 102(b).

Petitioner has demonstrated that Stemple II, through direct reference to Anazawa, anticipates claims 15 and 16. In the alternative, Stemple II in view of Anazawa renders claims 15 and 16 of the '869 invalid for obviousness under 35 U.S.C. § 103. Stemple II states that a fluorescent label and linker "is attached directly to the base of the nucleotide as described by Anasawa [*sic*], WO 98/33939." Stemple II, col. 22, ll. 53-57. Stemple II thus provides an express teaching, suggestion, and motivation to combine Stemple II with the disclosures of Anazawa with respect use of 7-deazapurine nucleotide analogues in methods for sequencing by synthesis. See, e.g., Anazawa, Figs. 3-7 (also citing Prober I) and page 5, l. 36 - page 6, line 9; see also Weinstock Decl., ¶ 83. The combination of Stemple II and Anazawa thus renders claims 15 and 16 obvious under 35 U.S.C. § 103, as set forth in **Claim Chart 6** at claims 15 and 16.

13. Ground for Challenge 13 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Stemple III and Anazawa et al.

For the same reasons given with respect to Stemple II in Section V.12. above, a person of skill in the art would also be motivated to combine Stemple III with Anazawa. The combination of Stemple III and Anazawa renders claims 15 and 16 obvious under 35 U.S.C. § 103, as set forth in **Claim Chart 6** above.

14. Ground for Challenge 14 - Claims 15 and 16 of the '869 patent are

invalid as obvious in view of Stemple II and Prober I

Claims 15 and 16 are also obvious in view of Stemple II combined with Prober I under 35 U.S.C. § 103. As shown above, Prober I teaches the advantages of using deazapurine-based nucleotides in sequencing methods. For all the reasons discussed in section V.2. (Tsien and Prober I) above, it would be obvious to use the labeled deazapurines as taught by Prober I in the sequencing process of Stemple II to gain the well-known, prior art benefit of the "stable linker arm attachment" as taught by Prober I. See Weinstock Decl., ¶ 85; see also, reasons in Section **Error! Reference source not found.**, above. As such, the combination of Stemple II and Prober I merely utilizes well known prior art components for their intended purpose to obtain the same known, predictable results disclosed in the references. As disclosed above in **Claim Chart 6**, Stemple II discloses each element of claim 12. **Claim Chart 2** above demonstrates that Prober I discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Stemple II under 35 U.S.C. § 103.

15. Ground for Challenge 15 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Stemple III and Prober I

For the same reasons given with respect to Stemple II in Section V.14. above, a person of skill in the art would also be motivated to combine Stemple III with Prober I. As disclosed above in **Claim Chart 6**, Stemple III discloses each element of claim 12. **Claim Chart 2** above demonstrates that Prober I discloses

the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Stemple III under 35 U.S.C. § 103.

16. Ground for Challenge 16 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Tsien and Hobbs

Claims 15 and 16 are also obvious in view of Tsien combined with Hobbs under 35 U.S.C. § 103. Hobbs is entitled "Alkynylamino-Nuclotides," and issued September 10, 1991, and is therefore prior art under 35 U.S.C. § 102(b). As disclosed above in **Claim Chart 1**, Tsien discloses each element of claim 12. The claim chart below demonstrates that Hobbs discloses the elements of both claims 15 and 16, and thereby renders claims 15 and 16 obvious in combination with Tsien.

Claim Chart 7

Claim in 7,790,869	Disclosure and Explanation of <u>Hobbs et al.</u>
15. The nucleotide of claim 12, wherein the base is a deazapurine.	"This invention pertains to alkynylaminonucleotides and especially to their use in preparing <i>fluorescently-labeled nucleotides as chain-terminating substrates for a fluorescence-based DNA sequencing method</i> ." <u>Hobbs</u> , col. 1, lines 14-17 (emphasis added).
16. The nucleotide of claim 15, wherein the deazapurine is selected from the group consisting of deaza-adenine and deaza-guanine, each comprising a unique label attached through a cleavable linker to a 7-position of deaza-adenine or deaza-guanine.	<u>Hobbs</u> discloses that the nucleotides include a heterocyclic base and that "[p]referred heterocyclic bases include: ... <i>7-deazaadenine</i> [and] (j), <i>7-deazaguanine</i>... The <i>unnatural 7-deazapurines</i> can be employed to attach the linker without adding a net charge to the base portion and thereby destabilizing the glycosidic linkage." <u>Hobbs</u> col. 10, line 67 - col. 11, line 4 (emphasis added). <u>Hobbs</u> also discloses that "the <i>7-position of the purine nucleotides provide labeled chain-terminating substrates that do not interfere excessively with the degree or</i>

	<i>fidelity of substrate incorporation."</i> <u>Hobbs</u>, col. 8, lines 57-60 (emphasis added). Hobbs discloses that "[t]he linker is an alkynylamino group in which one end of the triple bond is attached to an amine ... the other end of the triple bond is <i>covalently attached to the heterocyclic base at ... the 7-position (purine numbering) for the 7-deazapurines.</i>" <u>Hobbs</u>, col. 11, ll. 51-57 (emphasis added). Finally, Hobbs discloses that "[i]t is desirable to have <i>unique, distinguishable fluorescent reporters for each DNA base</i> encountered in sequencing applications." <u>Hobbs</u>, col. 12, ll. 6-9 (emphasis added).
--	--

Hobbs is directed toward nucleotide analogues to be used for sequencing methods. Hobbs specifically teaches the use of "unnatural 7-deazapurines" including "7-deazaadenine" and "7-deazaguanine" in fluorescence-based sequencing methods. See Weinstock Decl., ¶ 90. Thus, it would have been obvious for one of ordinary skill in the art to combine the teachings of Tsien with the "unnatural 7-deazapurines" disclosed in Hobbs because it is merely the use of known techniques to improve the sequencing methods and nucleotides of Tsien and merely produces a predictable result. See Weinstock Decl., ¶ 91; see also, reasons in Section **Error! Reference source not found.**, above.

17. Ground for Challenge 17 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Dower and Hobbs et al.

Claims 15 and 16 are also obvious in view of Dower combined with Hobbs under 35 U.S.C. § 103. Both Dower and Hobbs relate to sequencing methods, and

it would be obvious to modify the sequencing method of Dower to include the deazapurine taught by Hobbs for the reasons as discussed above in Section V.16. See Weinstock Decl., ¶¶ 92, 93.

18. Ground for Challenge 18 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Stemple II and Hobbs et al.

Claims 15 and 16 are also obvious in view of Stemple II combined with Hobbs under 35 U.S.C. § 103. Both Stemple II and Hobbs relate to sequencing methods, and it would be obvious to modify the sequencing method of Stemple II to include the deazapurine taught by Hobbs for the reasons as discussed above in Section V.16. Weinstock Decl., ¶¶ 96, 97.

19. Ground for Challenge 18 - Claims 15 and 16 of the '869 patent are invalid as obvious in view of Stemple III and Hobbs et al.

Claims 15 and 16 are also obvious in view of Stemple III combined with Hobbs under 35 U.S.C. § 103. Both Stemple III and Hobbs relate to sequencing methods, and it would be obvious to modify the sequencing method of Stemple III to include the deazapurine taught by Hobbs for the reasons as discussed above in Section V.16. Weinstock Decl., ¶ 98.

VI. CONCLUSION

The prior art documents presented in the above Petition and the arguments above demonstrate that Petitioner is reasonably likely to prevail regarding at least one of Claims 12-13, 15-17, 20-25, 28-29, 31, and 33 of the '869 patent are as required by as required by 35 U.S.C. § 314(a). Accordingly, the Office is

requested to grant this Petition and to initiate *inter partes* review with special dispatch. Petitioner reserves all rights and defenses available including, without limitation, defenses as to invalidity and unenforceability. By filing this Petition in compliance with applicable statutes, rules, and regulations, Petitioner does not represent, agree, or concur that the '869 patent is enforceable or valid under any other provision of title 35 of the U.S. Code, common law or equitable law not expressly addressed herein.

Date: September 16, 2012 Respectfully submitted,

By: /Robert A. Lawler/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of: Jingyue Ju et al.
Title: MASSIVE PARALLEL METHOD FOR DECODING
 DNA AND RNA
Patent No.: 7,790,869
Issue Date: September 7, 2010
IPR Proceeding No.: To be determined
IPR Proceeding Filing September 16, 2012
Date
Attorney Docket No.: 048522-0027-869
Customer No.: 22922

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Alexandria, VA 22313-1450

CERTIFICATE OF SERVICE

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Rockefeller Plaza, 20th Floor, New York, NY 10112:

1. Petition for *Inter Partes* Review of U.S. Patent No. 7,790,869; and
2. Exhibit Nos. 1001-1022.

Dated this 16th day of September 2012.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of: Jingyue Ju et al.
Title: MASSIVE PARALLEL METHOD FOR DECODING
 DNA AND RNA
Patent No.: 7,790,869
Issue Date: September 7, 2010
IPR Proceeding No.: To be determined
IPR Proceeding Filing September 16, 2012
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of: Jingyue Ju et al.
Title: MASSIVE PARALLEL METHOD FOR DECODING
 DNA AND RNA
Patent No.: 7,790,869
Issue Date: September 7, 2010
IPR Proceeding No.: To be determined
IPR Proceeding Filing September 16, 2012
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1. Petition for *Inter Partes* Review of U.S. Patent No. 7,790,869; and
2. Exhibit Nos. 1001-1022.

Dated this 16th day of September 2012.

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