IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent of Jingyue Ju et al.
Patent No.:	7,713,698
Application No.:	11/894,690
Title:	MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA
Issue Date:	May 11, 2010
Filing Date:	August 20, 2007

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P.O. Box 1450
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MOTION TO WAIVE PETITION PAGE LIMIT UNDER 37 C.F.R. §42.24(a)(2)

Petitioner requests that the 60 page limit set forth in 37 C.F.R. § 42.24(a)(1)(i) for petitions requesting *Inter Partes* review be waived regarding the Petition for *Inter Partes* Review of U.S. Patent No. 7,713,698 ("the '698 patent"). The petition requesting *Inter Partes* review of the '698 patent which meets the 60 page limit ("Page Limited Petition") has been filed concurrently herewith. Attached hereto is a copy of the proposed petition exceeding the 60 page limit as required by 37 C.F.R. § 42.24(a)(2) ("the Proposed Petition").

Substantial, material prior art is available which demonstrates that claims of the '698 patent for which review is sought are invalid. Petitioner has drafted the Page Limited Petition to provide the arguments and analysis as succinctly as possible. However, even with such succinct drafting, the 60 page limit will bar the Petitioner from making any additional grounds for invalidity. Accordingly, Petitioner respectfully submits that in the interests of justice, the 60 page limit must be waived for the present petition due to the number of invalidating and noncumulative prior art references available and due to the length and number of claims challenged. Failure to grant this petition will prevent Petitioner from raising or reasonably raising any additional grounds for invalidity such as those included in the Proposed Petition.

Although Petitioner believes that no fee is required for this Motion, the Commissioner is hereby authorized to charge any additional fees which may be required for this Motion to Deposit Account No. 18-0882.

Therefore, it is respectfully requested that this motion to waive the 60 page limit for a Petition requesting *Inter Partes* review be granted.

Date: September 16, 2012

Respectfully submitted,
By: /Robert A. Lawler/

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PAT. NO. 7,713,698

Inter Partes review of U.S. Patent 7,713,698 ("the '698 patent") pursuant to 35 U.S.C § 311 and 37 C.F.R. §§ 42.1 to 42.123 is respectfully requested by Illumina, Inc. ("Petitioner"). The Petitioner submits that the attached prior art (attached as Exhibits 1002 to 1020) renders claims 1-7, 11-12, 14-15 and 17 of the '698 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 1-7, 11-12, 14-15 and 17 of the '698 patent. Accordingly, it is requested that *inter partes* review be instituted and that claims 1-7, 11-12, 14-15 and 17 of the '698 patent be found invalid.

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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.)

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Exhibit 1007 - Stemple II (PCT Publication WO 00/53805 to Stemple et al.)

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Exhibit 1021 - Declaration of George Weinstock, Ph.D ("Weinstock Decl.")

Exhibit 1022 - Excerpts from the '698 Patent File History

I. INTRODUCTION

Inter partes review of U.S. Patent No. 7,713,698 ("the '698 patent") and cancellation of claims 1-7, 11-12, 14-15 and 17 ("the challenged claims") under 35 U.S.C. §§ 102 and 103 is respectfully requested. A copy of the '698 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 (with the exception of Dower) were substantively considered by the Examiner (although several of the references, including Tsien, Rabani and Stemple II were only provided among an overwhelming number of references submitted to

the Examiner in several IDSes. Accordingly, Petitioner respectfully requests that the *inter partes* review of the '698 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 '698 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 infringed and continues to infringe the '698 patent.

Further, a petition for *inter partes* review of legally related U.S. Patent No. 7,790,869 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, and 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@reinhartlaw.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 '698 patent is eligible for *inter partes* review and that the

Petitioner is not barred or estopped from requesting *inter partes* review of the '698 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 1-7, 11-12, 14-15 and 17 of the '698 patent. The grounds on which the challenges to each claim are based are identified below:

1. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are anticipated under 35 U.S.C. § 102(b) by PCT Publication WO 91/06678 to Tsien published **May 16, 1991** entitled **DNA Sequencing** ("Tsien," Exhibit 1002).

2. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent 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, *Science* 238, 336-341 (1987) published in **1987** ("Prober I"; Exhibit 1003).

3. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent 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).

4. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Dower in view of Prober I.

5. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over 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) in view of Prober I.

6. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are anticipated under 35 U.S.C. § 102(a) by PCT Publication WO 00/53805 to Stemple et al. published **September 14, 2000** entitled **A Method for Direct Nucleic Acid Sequencing** ("Stemple II," Exhibit 1007).

7. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent 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.

8. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Prober I.

9. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent 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**.

10. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Prober I.

11. Claims 5 and 12 of the '698 patent are invalid as obvious under 35 U.S.C § 103(a) over Tsien and Prober in further view of Rabani.

12. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Dower 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).

13. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Tsien in view of Prober II.

14. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Rabani in view of Prober II.

15. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Prober II.

16. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Prober II.

17. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Dower in view of U.S. Patent No. 4,804,748 issued **Feb. 14, 1989** to Seela entitled **7-Deaza-2'Deoxyguanosine Nucleotides** ("Seela I"; Exhibit 1014).

18. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Tsien in view of Seela I.

19. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Rabani in view of Seela I.

20. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Seela I.

21. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Seela I.

22. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Dower in view of U.S. Patent No. 5,047,519 issued **Sept. 10, 1991** to Hobbs, Jr. et al. entitled **Alkynylamino-Nucleotides** ("Hobbs"; Exhibit 1013).

23. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Tsien in view of Hobbs

24. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Rabani in view of Hobbs

25. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Hobbs

26. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Hobbs

27. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Dower in view of U.S. Patent No. 5,844,106 issued December 1, 1998 to Seela et al. entitled **Modified Oligonucleotides, Their Preparation And Their Use** ("Seela II," Exhibit 1015).

28. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Tsien in view of Seela II.

29. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Rabani in view of Seela II.

30. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple II in view of Seela II.

31. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over Stemple III in view of Seela II.

32. Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a) over PCT Publication WO 93/21340 to Rosenthal et al. published **October 28, 1993** entitled **DNA Sequencing Method** ("Rosenthal," Exhibit 1012) in view of Tsien.

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 IV 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 '698 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.

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 '698 PATENT AND SUMMARY OF INVALIDATING PRIOR ART REFERENCES

1. Summary of the '698 Patent and Invalidating Prior Art

The '698 patent issued on May 11, 2010 from U.S. Application No. 11/894,690 filed August 20, 2007. The '698 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 '698 patent is generally directed to a "sequencing by synthesis" method of determining the sequence of a polynucleic acid, such as DNA or RNA. See Abstract. In the sequencing by synthesis method of the '698 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 the addition of further nucleotides, and 6) repeating steps 3-5 to add and

detect additional nucleotides added to the primer extension strand to determine the sequence of the nucleic acid template. See '698 patent, col. 8, ll. 8-52. But see also, Dower, Tsien, Rabani, and Stemple III and III as discussed below. 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 '698 patent, col. 21, ll. 25-39.

A "nucleotide analogue" is defined in the '698 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." '698 patent, col. 7, ll. 48-51. Specific examples provided in the '698 patent of "nucleotide analogues" are nucleotides having 7-deaza-adenine and 7-deaza-guanine as the nucleobase. *Id*. col. 7, ll. 58-63. The cleavable chemical group that caps the -OH group at the 3'-position of the sugar of the nucleotide analogue 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." *Id*. at col. 9, ll. 52-58. Specific examples of cleavable groups are $-CH_2OCH_3$ and $-CH_2CH=CH_2$. *Id*. The labels that are attached to the nucleotide analogues are a fluorescent moiety, a fluorescent semiconductor crystal, a fluorescent energy transfer tag, or a mass tag. *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 cap group can be likewise cleaved by similar means. The label can be attached to the base of the nucleotide via a linker. As recited in the '698 patent specification, "…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 '698 patent claims priority to Pat. No. 6,664,079. However, the '698 patent was not filed until well after Illumina announced and launched the first commercial sequencing by synthesis system. While both the '698 patent and its parent '079 patent are directed to sequencing by synthesis methods, the '698 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 1 of the '698 patent, relates to a sequencing method, and independent claim 11 relates to a nucleotide analog usable in sequencing by synthesis methods. Challenged dependent claims 2-7, 12, 14-15, and 17 add additional limitations to claims 1 and 11. All challenged claims are reproduced in claim chart 1 below.

However, the prior art submitted with this Petition shows that all of the elements of the unjustifiably broadened claims of the '698 patent were both identically disclosed and well known in the prior art. For example, Dower, Tsien, Rabani and Stemple I, II and III all disclose both sequencing by synthesis methods and a plurality of immobilized nucleic acid templates identical to at least independent claim 1 and 11 of the '698 patent. For example, the prior art shows that it was known to use 3'-OH capped (e.g., chain terminating) and labeled nucleotide analogues mixed with primed, nucleic acid templates attached to a solid surface. Further, in the prior art sequencing processes, a single nucleotide analogue is added to the primer or primer extension strand complementary to the opposite nucleotide of the DNA template. The label (e.g., a fluorescent label attached to the base) is then detected to identify the type of nucleotide (e.g., A, G, C or T) that was added to the strand. Following removal of the 3'-OH capping group, the process is repeated to identify the sequence of the DNA template. Both independent claims 1 and 11 of the '698 patent recite that at least one of the nucleotide analogues is "deaza-substituted." However, as shown below, recitation of a "deaza-substituted " nucleotide analogue does not render the claims patentable.

In fact, the Background of the Invention section of the '698 patent itself confirms the teachings of the prior art submitted herewith. For example, the '698 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 '698 patent, col. 2, ll. 7-9 (emphasis added). The '698 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 '698 patent, col. 2, ll. 11-17 (emphasis added).

Further, the '698 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 '698 patent, col. 2, ll. 43-49 (emphasis added). The '698 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 '698

patent, col. 3, ll. 25-28 (emphasis added). In fact, the MOM and allyl groups identified as prior art in the background section of the '698 patent are the very 3'-OH capping groups that the '698 patent identifies as "embodiments of the invention." See '698 patent, col. 12, ll. 47-50, and FIG. 7.

Given the '698 applicant's understanding of the prior art as set forth in the Applicant's own Background section and the art of which they were aware, it is unclear how the broadened claims of the '698 patent could be patentable.

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

Both independent claims 1 and 11 of the '698 patent recite that at least one of the nucleotide analogues is "deaza-substituted." As background, a "deaza-substituted" nucleotide analogue is one that includes a deazabase. A "deazabase" is a nucleobase in which one of the natural nitrogen atoms in the base ring is substituted with a carbon atom. Specifically, in a "7-deazapurine," the natural 7-position nitrogen atom is replaced with a carbon atom. For reference, the nucleobase adenine is shown below with standard position numbers shown in red:

However, recitation of a "deaza-substituted " nucleotide analogue does not render claims 1 or 11 patentable: use of nucleotide analogues including deazapurines was known in the nucleic acid sequencing field at least as early as the mid-1980s. See Weinstock Decl. ¶ 38. 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 I. Seela I states that deazabases 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. Seela I states that deazabases can be used in place of regular bases in any DNA sequencing method that uses a DNA polymerase. Id. Additionally, Seela I observes that the deazabases can be used without changing the other conditions of the sequencing reaction. See Seela I, col. 4, lines 11-13. See also Seela II, Hobbs, Prober I, and Prober II. Further, it was widely known to use deazapurine-based nucleotides in the sequencing by synthesis methods at least 10 years prior to the '698 patent's earliest claimed filing date. See Dower, Tsien, and Stemple II and the citations therein, including Prober I and Anazawa.

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. 4, lines 31-33. Similarly, Prober I demonstrated 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. Hobbs teaches that the base can be a deoxy or a dideoxy nucleotide, and can have a blocked 3' position. See, e.g., Hobbs, col. 7, line 24 to col. 8, line 12 (particularly col. 8, line 8), col. 9, line 24 to col. 10, line 58. Hobbs also teaches that a linker may be used to connect the label to the 7 position of the deaza-purine and that the linker can include cleavable groups. Id., col. 7, lines 29-35; col. 11,

lines 59-66; and col. 43, lines 34-62. Hobbs also teaches that four different labels can be used to uniquely identify the each of the four bases. See id., col. 5, ll. 1-4, col. 8, ll. 11-12, and 16-27, col. 12, ll. 3-58.

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 '698 patent Background section. See '698 patent, col. 2, lines 45-51. In fact, the work described in Hobbs was recognized as instructive for attaching labels by those in the field of next generation sequencing. See, e.g., J. Williams at col. 9, line 9, et seq., referenced below.

Other references similarly demonstrate that the use of 7-deaza-substituted nucleotide analogs was known in the field of DNA sequencing. Prober II states that the 7-deaza modification is necessary for the stability of the nucleotide. See, e.g., col. 18, line 58 to col. 19, line 12. Prober II likewise teaches that the linker attaching the label can include cleavable groups. See Prober II, col. 19, lines 18-42. Prober II also teaches that the 7-position is an ideal location to attach a fluorescent label. Id.

Third, nucleotides having deaza bases were also known to include benefits applicable to sequencing DNA using a DNA polymerase extension, as in the

sequencing by synthesis references, discussed below. For example, deaza bases were known to simplify polymerase extension with a DNA polymerase when the target DNA was susceptible to forming secondary structure. See, e.g., WO 89/11548 to Saiki ("Saiki," Exhibit 1016) at p. 5, lines 1-5.

Fourth, 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 nucleotides that are "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.

The known interchangeability by the earliest claimed priority date of the '698 patent is also reflected in a number of the other prior art, next-generation sequencing patents filed around the same time as the ‘698 patent’s earliest claimed priority date. See, e.g., Anazawa; U.S. Pat. No. 7,037,687 to P. Williams (col. 4, lines 1-11, Exhibit 1017); U.S. Pat. No. 6,255,083 to J. Williams (col. 5, lines 46-53, Exhibit 1018); and U.S. Pat. No. 6,001,566 to Canard (see col. 3, lines 19-41,

Exhibit 1019). Each of these references are directed to next generation sequencing methods based on polymerase extension, and each refers to the use of labeled deazapurine bases as a known alternative to using regular purine bases.

3. Summary of the Prosecution History of the '698 Patent

The '698 patent application was originally filed with 60 claims on August 20, 2007, however, in a preliminary amendment filed January 10, 2008 (Exhibit 1022), those claims were canceled and new claims 61-82 were introduced. After amending the claims, independent claims 61 and 77 eventually lead to issued claims 1 and 11, respectively.

Twice during the prosecution of the '698 patent, the applicant amended the claims to recite deaza-substituted nucleotides. In the first response mailed October 16, 2008 (Exhibit 1022), the applicant added the deaza limitations to overcome anticipation rejections based on U.S. Patent Nos. 5,302,509 ("Cheeseman") and 6,087,095 ("Rosenthal"). In a supplemental response mailed January 16, 2009 (Exhibit 1022), the deaza limitations were removed. However, after removing the deaza limitations in the intervening response, in a later response mailed November 5, 2009 (Exhibit 1022), the applicant added the deaza limitations back to the claims to overcome an anticipation rejection based on Dower. Following this amendment, the Examiner sent a Notice of Allowance on December 14, 2009 (Exhibit 1022) allowing claims 1-17 as issued in the '698 patent.

However, as shown by the references accompanying this petition and the Declaration of George Weinstock, Ph.D. (Exhibit 1021), it was widely known in the prior art to use deaza-substituted nucleotide analogues in nucleic acid sequencing methods and systems, including sequencing by synthesis methods and systems. Further, as shown below, Dower incorporates Prober I by reference, and Prober I teaches the "deaza substituted" nucleotide analogues argued as rendering the claims patentable by the applicant of the '698 patent.

IV. DETAILED EXPLANATION OF PETITIONER'S BASIS FOR CHALLENGING CLAIMS 1-7, 11-12, 14-15 and 17 OF THE '698 PATENT DEMONSTRATING A REASONABLE LIKELIHOOD OF PREVAILING AGAINST THE CLAIMS OF THE '698 PATENT

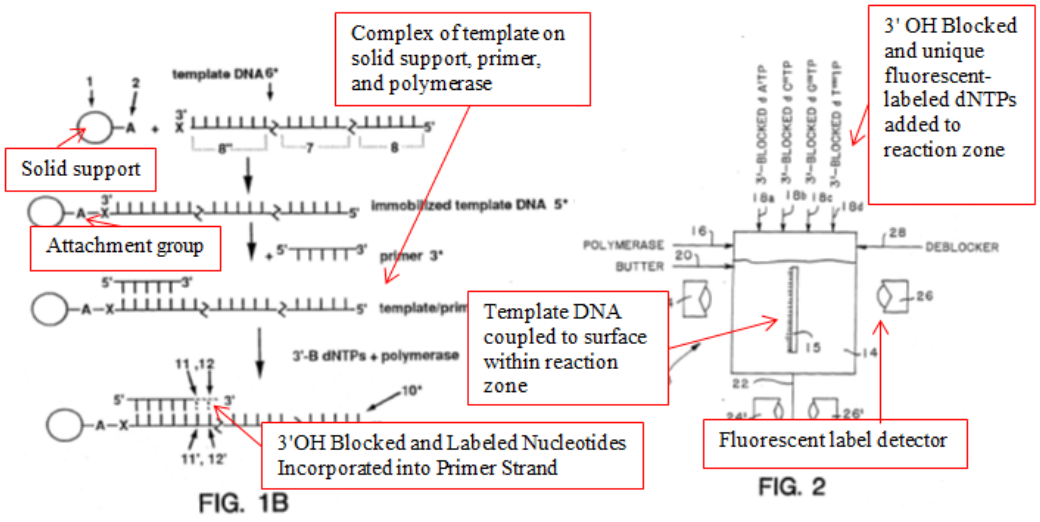
Pursuant to 35 U.S.C. § 312(a)(3) and 37 C.F.R. § 42.104(b), this Petition presents a detailed explanation of the basis of each challenge to claims 1-7, 11-12, 14-15 and 17 of the '698 patent and where each element of each claim can be found in each prior art reference.

1. Ground for Challenge 1 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Tsien

Tsien published **May 16, 1991**. Tsien qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was published more than one year before the earliest claimed filing date of the '698 patent, October 6, 2000 ("the '698 patent's earliest claimed filing date"). *Tsien was submitted to the Patent Office during prosecution of the '698 patent, on page 3 of a 15 page information*

disclosure statement listing 193 separate references. 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. Annotated versions of FIG. 1B and FIG. 2 of Tsien are shown below:



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 use of a deaza-substituted purine in fluorescence-labeled nucleotides.

The analysis and claim charts below demonstrate that claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Tsien:

Claim Chart 1 - Anticipation of Challenged Claims by Tsien

Claim in 7,713,698	**Disclosure and Explanation of Tsien**
1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:	"The present invention relates to an instrument and a method to *determine the nucleotide sequence* in a DNA molecule without the use of a gel electrophoresis step." Tsien, Abstract (emphasis added). "The method employs an unknown *primed* single stranded DNA sequence." Tsien, Abstract (emphasis added).
a) contacting a nucleic acid template attached to a solid surface	"The method employs an unknown primed single stranded DNA sequence which is *immobilized* or entrapped within a chamber." Tsien, Abstract (emphasis added). As shown in FIG. 1B, "template 6* carries the reactive group X which bonds to the *substrate* via the A-X bond to form an *immobilized template 5**" and the substrate identified by reference numeral 1 is identified as a "*solid support 1*." Tsien, page 11, ll. 15-17, page 10, line 27 and FIG. 1B (emphasis added).
with a nucleic acid primer which hybridizes to the template;	"The method employs an unknown *primed* single stranded DNA sequence." Tsien, Abstract (emphasis added). "A primer, which is complementary to the known sequence of the vector is used to start the growth of the unknown complementary chain." Tsien, page 10, ll. 23-25 and FIG. 1B.

	The immobilized template 5* shown in FIG. 1B "*is then hybridized with primer 3** to give the immobilized, primed template 9* upon which the desired adding of dNTPs takes place to add units 11 and 12 and thus identify the sequence and identity of units 11' and 12'." Tsien, page 11, ll. 17-21 and FIG. 1B (emphasis added).
b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU,	As shown in FIG. 2, "In practice, the *polymerase and* the *four labeled dNTPs* are added to the reaction zone 14 under conditions adequate to permit the enzyme to bring about *addition of the one, and only the one*, of the four labeled blocked dNTPs which is complementary to the first available template nucleotide following the primer." Tsien, page 12, ll. 22-27 and FIG. 2 (emphasis added). Tsien discloses use of modified nucleotides having as their nucleoside bases "adenosine, cytidine, guanosine and thymidine." Tsien, p. 9, ll. 30-36
so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand,	The immobilized template 5* shown in FIG. 1B "is then hybridized with primer 3* to give the immobilized, primed template 9* upon *which the desired adding of dNTPs takes place to add units 11 and 12* and thus identify the sequence and identity of units 11' and 12'." Tsien, page 11, ll. 17-21 and FIG. 1B (emphasis added). As shown in FIG. 2 "In practice, the polymerase and the *four labeled dNTPs* are added to the reaction zone 14 under conditions adequate to permit the enzyme to bring about *addition of the one, and only the one*, of the four labeled *blocked dNTPs* which is complementary to the first available template nucleotide following the primer." Tsien, page 12, ll. 22-27 and FIG. 2 (emphasis added).
wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and	FIG. 2 shows the dNTPs as "3'-Blocked d A'TP," "3'-Blocked d C"TP," "3'-Blocked d G'"TP," "3'-Blocked d T""TP," and according to Tsien "When they are each tagged or *labeled with different reporter groups*, such as different fluorescent groups, they are represented as dA'TP, dC"TP, dG'"TP and dT""TP." Tsien, page 10, ll. 7-10 and FIG. 2 (emphasis added).

	"One method involves the use of a fluorescent tag attached to *the base moiety*." Tsien, page, 28, ll. 5-6 (emphasis added).
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, and	FIG. 2 shows the dNTPs as 3'-Blocked dA'TP, 3'-Blocked dC"TP, 3'-Blocked dG'"TP, 3'-Blocked d T""TP. Tsien, FIG. 2. "A deblocking solution is added via line 28 to *remove* the 3' hydroxyl labeled blocking group." Tsien, page 13, ll. 17-19 (emphasis added). "The coupling reaction generally employs *3' hydroxyl-blocked* dNTPs to prevent inadvertent extra additions." Tsien, page 20, ll. 25-26 (emphasis added). "The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications to the 3'-OH position of dNTPs include the introduction of groups such as -F, $-NH_2$, $-OCH_3$, $-N_3$, $-OPO_3^=$, $-NHCOCH_3$, 2-nitrobenzene carbonate, 2,4-dinitrobenzene sulfenyl and tetrahydrofuranyl ether." Tsien, page 21, ll. 12-17.
wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and	In discussing methods utilizing a dNTP in which the fluorescent label group is coupled to the base of the dNTP, Tsien incorporates the disclosure of Prober I , 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™." Tsien, page 28, lines 5-18. The Prober et al. referenced by Tsien is Prober I (1987) Science 238: 336-341, a copy of which accompanies this Petition. See Tsien, page 5, ll. 22-23. Prober et al. 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 *7-deazapurines*." Prober et al., page 337, 1st column (emphasis added).
c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.	"The *identity of this first nucleotide can be determined by detecting and identifying the label attached to it*. This detection and identification can be carried out in the case of a fluorescent label by irradiating the surface with a fluorescence-exciting beam from light source 24 and *detecting the resulting fluorescence with detector 26*. The *detected florescence is then correlated to the fluorescence properties of the four different labels present on the four different deoxynucleotide triphosphates to identify exactly which one of the four materials was incorporated at the first position of the complementary chain*. This identity is then noted." Tsien, page 13, ll. 1-13 (emphasis added).
2. The method of claim 1, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of the incorporated nucleotide analogue, thereby permitting the incorporation of a further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.	"A *deblocking solution is added via line 28 to remove the 3' hydroxyl labeled blocking group*. This then generates *an active 3' hydroxyl position on the first nucleotide present in the complementary chain and makes it available for coupling to the 5' position of the second nucleotide*." Tsien, page 13, ll. 17-22 (emphasis added).
3. The method of claim 1, wherein the unique label is a fluorescent label.	FIG. 2 shows the dNTPs as 3'-Blocked d A'TP, 3'-Blocked d C"TP, 3'-Blocked d G'"TP, 3'-Blocked d T""TP, and according to Tsien "When they are each tagged or labeled with different reporter groups, such as *different fluorescent groups*, they are represented as dA'TP, dC"TP, dG'"TP and dT""TP." Tsien, page 10, ll. 7-10 and FIG. 2 (emphasis added).

4. The method of claim 1, wherein the polymerase is Taq DNA polymerase, T7 DNA polymerase or Vent DNA polymerase.	"One enzyme which can be used is sequenase™ enzyme (an enzyme derived from *bacteriophage T7 DNA polymerase* that is modified to improve its sequencing properties … Other polymerases which can be used instead of sequenase™ include but are not limited to Klenow fragment of DNA polymerase I, AMV reverse transcriptase, and *Taq polymerase*." Tsien, page 19, ll. 7-18 (emphasis added).
5. The method of claim 1, wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface.	As shown in FIG. 2 reproduced above, "A *plurality* of copies of a subject *primed single stranded DNA* are immobilized on this surface 15." Tsien, page 11, ll. 34-36 (emphasis added).
6. The method of claim 1, wherein said nucleic acid template comprises an RNA template.	"DNA and RNA are commonly attached noncovalently through ionic interactions along their length to various types of membranes." Tsien, page 32, ll. 15-17 (emphasis added).
7. The method of claim 6, wherein the polymerase is a reverse transcriptase.	"Other polymerases which can be used instead of sequenase™ include but are not limited to … *AMV reverse transcriptase*." Tsien, page 19, ll. 15-18 (emphasis added).
11. A plurality of nucleic acid templates immobilized on a solid surface,	"The method employs an unknown primed single stranded DNA sequence which is *immobilized* or entrapped within a chamber." Tsien, Abstract (emphasis added). As shown in FIG. 2 reproduced above, "A *plurality of copies of a subject primed single stranded DNA* are immobilized on this surface 15." Tsien, page 11, ll. 34-36 (emphasis added).
wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue,	"The method employs an unknown *primed* single stranded DNA sequence." Tsien, Abstract (emphasis added). "A primer, which is complementary to the known sequence of the vector is used to start the growth of the unknown complementary chain." Tsien, page 10, ll. 23-25 and FIG. 1B.

	The immobilized template 5* shown in FIG. 1B "*is then hybridized with primer 3** to give the immobilized, primed template 9* upon which the desired adding of dNTPs takes place to add units 11 and 12 and thus identify the sequence and identity of units 11' and 12'." Tsien, page 11, ll. 17-21 and FIG. 1B (emphasis added).
at least one of which is deaza-substituted,	In discussing methods utilizing a dNTP in which the fluorescent label group is coupled to the base of the dNTP, Tsien incorporates the disclosure of Prober I , 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™." Tsien, page 28, lines 5-18. The Prober et al. referenced by Tsien is Prober I (1987) Science 238: 336-341, a copy of which accompanies this Petition. See Tsien, page 5, ll. 22-23. Prober et al. 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 *7-deazapurines*." Prober et al., page 337, 1st column (emphasis added).
wherein each labeled nucleotide analogue comprises a base labeled with a unique label and	FIG. 2 shows the dNTPs as "3'-Blocked d A'TP," "3'-Blocked d C"TP," "3'-Blocked d G'"TP," "3'-Blocked d T""TP," and according to Tsien "When they are each tagged or *labeled with different reporter groups*, such as different fluorescent groups, they are represented as dA'TP, dC"TP, dG'"TP and dT""TP." Tsien, page 10, ll. 7-10 and FIG. 2 (emphasis added). "One method involves the use of a fluorescent tag attached to *the base moiety*." Tsien, page, 28, ll. 5-6

	(emphasis added).
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue.	FIG. 2 shows the dNTPs as 3'-Blocked dA'TP, 3'-Blocked dC"TP, 3'-Blocked dG'"TP, 3'-Blocked d T'""TP. Tsien, FIG. 2. "A deblocking solution is added via line 28 to *remove* the 3' hydroxyl labeled blocking group." Tsien, page 13, ll. 17-19 (emphasis added). "The coupling reaction generally employs *3' hydroxyl-blocked* dNTPs to prevent inadvertent extra additions." Tsien, page 20, ll. 25-26 (emphasis added). "The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications to the 3'-OH position of dNTPs include the introduction of groups such as -F, $-NH_2$, $-OCH_3$, N_3, $-OPO_3^{=}$, $-NHCOCH_3$, 2-nitrobenzene carbonate, 2,4-dinitrobenzene sulfenyl and tetrahydrofuranyl ether." Tsien, page 21, ll. 12-17.
12. The plurality of nucleic acids of claim 11, wherein said plurality are present in a microarray.	"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" Tsien, p. 15, ll. 6-16. Multiple "reaction zones" constitute an array.
14. The method of claim 2, wherein the primer extension strand that results from step b) is the nucleic acid primer onto which the further nucleotide analogue is to be incorporated.	The immobilized template 5* shown in FIG. 1B "is then hybridized with primer 3* to give the immobilized, primed template 9* upon *which the desired adding of dNTPs takes place to add units 11 and 12* and thus identify the sequence and identity of units 11' and 12'." Tsien, page 11, ll. 17-21 and FIG. 1B (emphasis added).
15. The method of claim 1, wherein each of said unique labels is attached to the nucleotide analogue via	"In another type of remote labeling the *fluorescent moiety* or other innocuous label *can be attached to the dNTP through a spacer or tether. The tether can be cleavable* if desired to release the fluorophore or other label on demand. There are *several cleavable tethers that*

a cleavable linker.	*permit removing the fluorescent group before the next successive nucleotide is added*--for example, silyl ethers are suitable tethers which are cleavable by base or fluoride, allyl ethers are cleavable by Hg(II), or 2,4-dinitrophenylsulfenyls are cleavable by thiols or thiosulfate." Tsien, page 28, ll. 19-29 (emphasis added).
17. The method of claim 1, wherein the chemical moiety capping the 3'-OH group is not a fluorescent dye.	Tsien discloses non-fluorescent 3'-OH capping groups stating "The most common 3'-hydroxyl blocking groups are esters and ethers. Other blocking modifications to the 3'-OH position of dNTPs include the introduction of groups such as -F, $-NH_2$, $-OCH_3$, $-N_3$, $-OPO_3^=$, $-NHCOCH_3$, 2-nitrobenzene carbonate, 2,4-dinitrobenzene sulfenyl and tetrahydrofuranyl ether." Tsien, page 21, ll. 12-17.

Regarding the limitation in claims 1 and 11 that at least one of the nucleotide analogs be deaza-substituted, Tsien discloses that "[o]ne method involves the use of a fluorescent tag attached to *the base moiety*." Tsien, page, 28, ll. 5-6 (emphasis added). As a specific example, Tsien incorporates the disclosure of Prober I, *Science* 238, 336-341 (1987) for its teaching of preparing ddNTPs with fluorescent tags that can be successfully incorporated by Tsien's preferred polymerase, Sequenase™. See Tsien et al., page 5, lines 22-23, page 19, lines 4-18; and page 28, lines 5-18; see Weinstock Decl. ¶¶ 63-64. In addition to specifically incorporating the teaching of Prober I in the section regarding attaching the fluorescent label, Tsien et al. generally provides express instruction that the documents identified in the specification are to be 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 (i.e. a base with a carbon rather than a nitrogen at the 7 position). Thus, Tsien et al. 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. As such, Tsien incorporates the teachings of Prober I, and 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" and "material incorporated by reference is effectively part of the host document as if it were explicitly contained therein." (internal quotations and citations omitted)).

2. Ground for Challenge 2 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Tsien and Prober I

Prober I was published in 1987. Prober I is prior art against the '698 patent under 35 U.S.C. § 102(b) because it was published more than one year before the earliest claimed filing date of the '869 patent.

Petitioner has demonstrated that Tsien, through incorporation of Prober I,

anticipates claims 1-7, 11-12, 14-15 and 17 of the '698 patent. In the alternative, claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Tsien combined with Prober I 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, at page 28, lines 5-18. 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. ¶¶ 65-67. 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.

As disclosed above in **Claim Chart 1**, Tsien discloses each element of claims 1-7, 11-12, 14-15 and 17 of the '698 patent. Should it be determined, however, that Tsien does not disclose use of deaza-substituted nucleotide analogs in its method of sequencing by synthesis, Prober I discloses that "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). Thus, Prober I discloses the element of both claims 1 and 11 relating to use of nucleotide analogs having deaza-substituted bases.

In addition, one skilled in the art would be motivated to combine the teachings of Prober I with Tsien because the nucleotide analogues disclosed in Prober I, wherein "a linker is attached to the 5 position in the pyrimidines and to the 7 position in the 7-deazapurines," is shown to be an effective way to attach a fluorescent label to a nucleic acid base while maintaining the ability of the Sequenase™ polymerase used by Tsien to incorporate the associated dNTP into the primer extension strand. See Tsien, page 28, lines 5-18. Combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2. Further, it would have been obvious to combine Tsien and Prober I because the combination of known features with known systems and methods merely produces a predictable result. See Weinstock Decl. ¶¶ 66-67. As such, Tsien combined with Prober et al. renders claims 1-7, 11-12, 14-15 and 17 obvious under 35 U.S.C. § 103.

Further, as shown above, Tsien identically discloses the limitations added by dependent claims 5 and 12. However, in the alternative, claims 5 and 12 are

obvious in view of Tsien in view of Prober I as evidenced by the '698 patent's admitted prior art. Claim 5 recites "wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface, "and claim 12 recites "wherein said plurality are present in a microarray." The background section of the '698 patent admits that "ultra high-throughput" sequencing procedures and the use of "chip format" sequencing are well known in the art. See '698 Background Section, col. 2, ll. 11-16. Thus, dependent claims 5 and 12 are obvious in view of Tsien, Prober I and the '698 patent's admitted prior art.

3. Ground for Challenge 3 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Dower

Dower issued **August 20, 1996**. Dower qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before earliest claimed filing date of the '698 patent.

Dower generally discloses nucleic acid sequencing by synthesis methods, and discloses both a degradative approach and a synthetic approach to sequencing. The synthetic approach is relevant to the ‘698 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. As set forth above in Section III.3, Dower was considered by the Examiner in an office action dated June 5, 2009, and the claims of the '698 patent were amended to

add limitations reciting the use of deaza-substituted nucleotide analogues to overcome rejections based on Dower. However, the Examiner failed to appreciate that Dower does, in fact, disclose the use of deaza-substituted bases in nucleotide analogs. Dower expressly incorporates Prober I by reference for at least its disclosure of deazapurine based, fluorescence-labeled nucleotides. Although Dower was considered by the Examiner, there is no indication that the Examiner recognized that Dower incorporated Prober I by reference.

For example, an annotated version of FIG. 8 of Dower is shown below (the two portions reproduced side by side for clarity):

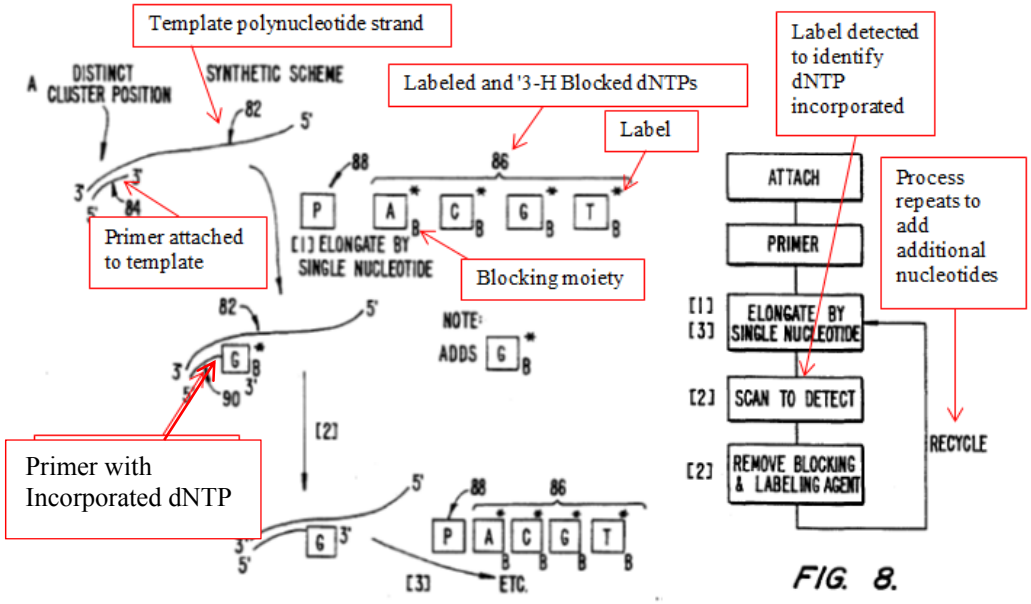
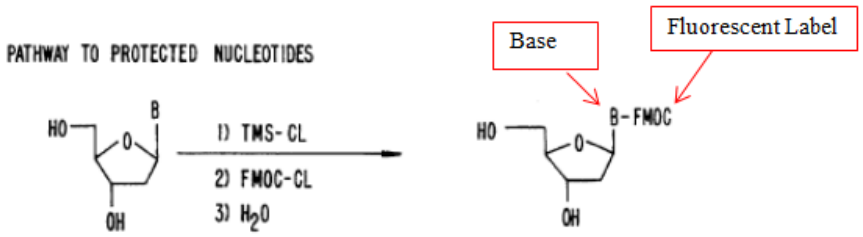


FIG. 8.

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:



The analysis and claim charts below demonstrate that claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Dower:

Claim Chart 2 - Anticipation of Challenged Claims by Dower

Claim in 7,713,698	Disclosure and Explanation of Dower
1. A method of determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:	"The invention also embraces methods for *sequencing* a plurality of distinctly positioned polynucleotides attached to a solid substrate comprising the steps of: hybridizing complementary primers to said plurality of polynucleotides; *elongating a complementary primer* hybridized to a polynucleotide by adding a single nucleotide; and *identifying which of said complementary primers have incorporated said nucleotide*." Dower, col. 4, ll. 44-53 (emphasis added). "The synthetic mode, as illustrated in FIG. 1 is easily applied to the *sequencing of nucleic acids* … The synthetic scheme depends, in part, on the stepwise elongation by small and identifiable units. A polymerase is used to extend *a primer complementary to a target template*. *The primer is elongated one nucleotide* at a time by use of a particular modified nucleotide analog to which a blocking agent is added and which prevents further elongation." Dower, col. 14, ll. 38- 53 (emphasis added); see FIG. 8.
a) contacting a nucleic acid template attached to a solid surface	"The invention also embraces methods for sequencing a plurality of distinctly positioned *polynucleotides attached to a solid substrate*." Dower, col. 4, ll. 44-46 (emphasis added); see also FIG. 8 (showing "ATTACH"

	step at beginning of sequencing method). In a section entitled "Attachment to a surface," Dower states "Both degradative and synthetic sequencing methods begin by obtaining and *immobilizing* the target fragments of unknown sequence to be determined at specific locations on *the surface*." Dower, col. 23, ll. 34-37 (emphasis added).
with a nucleic acid primer which hybridizes to the template;	"*hybridizing* complementary *primers* to said plurality of polynucleotides." Dower, col. 4, ll. 47-48 (emphasis added). The synthetic method "involves *annealing a primer* … near to the 3' end of the unknown target sequences." Dower, col. 23, ll. 16-18 (emphasis added).
b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU,	"A *polymerase* is used to *extend a primer complementary to a target template*. The primer is elongated one nucleotide at a time." Dower, col. 14, ll. 48-50 (emphasis added). FIG. 8 of Dower (reproduced above) shows A, C, G, T nucleotides as "labeled and blocked monomers 86" (the "B" stands for blocked and the "*" represents the label in FIG. 8) that are added to the primed template polynucleotide strand." Dower, col. 15, line 1, and FIG. 8. "DNA polymerase, or a similar polymerase, is used to extend the chains by one base by *incubation in the presence of dNTP analogs* which function as both chain terminators and fluorescent labels. This is done in a *one-step process* where *each of the four dNTP analogs* is identified by a distinct dye." Dower, col. 23, ll. 18-22 (emphasis added). See FIG 9 of Dower for nucleotide analogs.
so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and	"The primer is elongated one nucleotide at a time." Dower, col. 14, line 50-51, and FIG. 8. As shown in the example of FIG. 8, "a labeled blocked

form a nucleic acid primer extension strand,	guanosine monomer has been incorporated into the elongated primer 90." Dower, col. 15, line 8-10, and FIG. 8.
wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and	As shown in FIG. 8 reproduced above, "Labeled and blocked monomers 86 are shown, the label depicted by the asterisk … the separate *labeled monomers can be distinguished from one another by the wavelength of fluorescent emission*." Dower, col. 15, line 1-7, and FIG. 8 (emphasis added). "FIG. 9 schematically illustrates the synthesis of a generic protected nucleotide. A suitable nucleotide is labeled with the *FMOC fluorescently detectable label* … FIG. 9 also outlines various reactions which lead to useful nucleotides." Dower, col. 18, line 64 - col. 19, line 10 (emphasis added). An annotated portion of FIG. 9 is reproduced above, where B is the nucleic acid base and FMOC is the fluorescently detectable label. FIG. 9 shows the label attached to the base.
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, and	"The primer is elongated one nucleotide at a time by use of a particular *modified nucleotide analog to which a blocking agent is added and which prevents further elongation*." Dower, col. 14, ll. 50-53 (emphasis added). "To prevent elongation by a unit length greater than one monomer, the nucleotide *should be blocked at the position of 3′ elongation*." Dower, col. 15, ll. 33-35 (emphasis added). "[T]ypically, the blocking agent will be *a reversible blocking agent* thereby allowing for deblocking and subsequent elongation" and "Blocking groups are preferably sensitive to mild acidic conditions, mild basic conditions, or light." Dower, col. 15, ll. 38-40 and 52-56 (emphasis added); see also col. 18, ll. 52-57 (listing "appropriate blocking agents").
wherein at least one of the four nucleotide	"Fluorescent chain terminators (*analogs of dATP, dCTP, dGTP, and TP, each labeled with fluorophore preferably*

analogues within (i) or (ii) is deaza-substituted; and	*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 Sambrook et al. (1989) Molecular Cloning, vols. 1-3, and *Prober et al.*)." Dower, col. 25, ll. 4-10 (emphasis added). Prober et al. referenced by Dower is Prober I (1987) Science 238: 336-341, a copy of which accompanies this Petition. See Dower, col. 17, ll. 33-36. Dower incorporates all documents listed in the specification by reference stating "All publications and patent applications are herein incorporated by reference." Dower, col. 28, ll. 38-39. Prober I 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 7-deazapurines*." Prober I, page 337, 1st column (emphasis added).
c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.	As shown in FIG. 8 "Step 2 is a scan, where the signal at the position corresponding to template 82 indicates that the guanosine analog was incorporated." Dower, col. 15, ll. 11-13. "The process for sequencing may be summarized as follows for enzymatic polymerization … 3) The matrix is *scanned to determine which base was added to each location*. This step correlates the added base with a position on the matrix." Dower, col. 27, ll. 14-25 (emphasis added).
2. The method of claim 1, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of	As shown in FIG. 8, "Reaction 2 is performed, *which removes both the label and blocking group ... Reaction 3 is equivalent to reaction 1*, though the substrate primer has been elongated by one monomer." Dower, col. 15, ll. 13-15 (emphasis added).

the incorporated nucleotide analogue, thereby permitting the incorporation of a further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.	"The process for sequencing may be summarized as follows for enzymatic polymerization … 6) The terminators are activated for further chain extension, *usually by removal of a blocking group*. 7) Steps 2 through 6 are repeated to obtain the base-by-base sequence of many different positionally separated DNA fragments simultaneously." Dower, col. 27, ll. 14-33 (emphasis added).
3. The method of claim 1, wherein the unique label is a fluorescent label.	As shown in FIG. 8 reproduced above, Dower discloses "Labeled and blocked monomers 86 are shown, the label depicted by the asterisk … the separate *labeled monomers can be distinguished from one another by the wavelength of fluorescent emission*." Dower, col. 15, line 1-7, and FIG. 8 (emphasis added). "FIG. 9 schematically illustrates the synthesis of a generic protected nucleotide. A suitable nucleotide is labeled with the *FMOC fluorescently detectable label* … FIG. 9 also outlines various reactions which lead to useful nucleotides." Dower, col. 18, line 64 - col. 19, line 10 (emphasis added).
4. The method of claim 1, wherein the polymerase is Taq DNA polymerase, T7 DNA polymerase or Vent DNA polymerase.	"Polymerases useful in connection with the invention include … modified and cloned versions of *T7 DNA polymerase* … *Taq DNA polymerase* from thermostable Thermus aquaticus." Dower, col. 17, ll. 48-57 (emphasis added).
5. The method of claim 1, wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface.	"The present invention relates to the determination of the sequences of *polymers* immobilized to a substrate. In particular, one embodiment of the invention provides a method and apparatus for sequencing *many nucleic acid sequences immobilized at distinct locations on a matrix* surface." Dower, col. 1, ll. 21-25 (emphasis added).
6. The method of claim 1, wherein said nucleic acid template comprises an RNA template.	"The synthetic mode … is easily applied to the sequencing of nucleic acids, since one target strand may serve as the *template* to synthesize the complementary strand. The nucleic acid can be DNA, *RNA* or mixed polymers." Dower, col. 14, ll. 38-42 (emphasis added).
7. The method of	"Polymerases useful in connection with the invention

claim 6, wherein the polymerase is a reverse transcriptase.	include … various reverse transcriptases." Dower, col. 17, ll. 48-62.
11. A plurality of nucleic acid templates immobilized on a solid surface,	"The present invention relates to the determination of the sequences of *polymers* immobilized to a substrate. In particular, one embodiment of the invention provides a method and apparatus for sequencing *many nucleic acid sequences immobilized at distinct locations on a matrix* surface." Dower, col. 1, ll. 21-25 (emphasis added).
wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue,	"*hybridizing* complementary *primers* to said plurality of polynucleotides." Dower, col. 4, ll. 47-48 (emphasis added). The synthetic method "involves *annealing a primer* … near to the 3' end of the unknown target sequences." Dower, col. 23, ll. 16-18 (emphasis added). "The synthetic mode, as illustrated in FIG. 1 is easily applied to the *sequencing of nucleic acids* … The synthetic scheme depends, in part, on the stepwise elongation by small and identifiable units. A polymerase is used to extend *a primer complementary to a target template*. *The primer is elongated one nucleotide* at a time by use of a particular modified nucleotide analog to which a blocking agent is added and which prevents further elongation." Dower, col. 14, ll. 38- 53 (emphasis added)); see also FIG. 8 (showing "PRIMER" step at beginning of sequencing method)
at least one of which is deaza-substituted,	"Fluorescent chain terminators (*analogs of dATP, dCTP, dGTP, and TP, 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 Sambrook et al. (1989) Molecular Cloning, vols. 1-3, and *Prober et al.*)." Dower, col. 25, ll. 4-10 (emphasis added). Prober et al. referenced by Dower is Prober I (1987) Science 238: 336-341, a copy of which accompanies this Petition. See Dower, col. 17, ll. 33-36.

	Dower incorporates all documents listed in the specification by reference stating "All publications and patent applications are herein incorporated by reference." Dower, col. 28, ll. 38-39. Prober I 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 7-deazapurines*." Prober I, page 337, 1st column (emphasis added).
wherein each labeled nucleotide analogue comprises a base labeled with a unique label and	As shown in FIG. 8 reproduced above, "Labeled and blocked monomers 86 are shown, the label depicted by the asterisk … the separate *labeled monomers can be distinguished from one another by the wavelength of fluorescent emission*." Dower, col. 15, line 1-7, and FIG. 8 (emphasis added).
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue.	"The primer is elongated one nucleotide at a time by use of a particular *modified nucleotide analog to which a blocking agent is added and which prevents further elongation*." Dower, col. 14, ll. 50-53 (emphasis added). "To prevent elongation by a unit length greater than one monomer, the nucleotide *should be blocked at the position of 3′ elongation*." Dower, col. 15, ll. 33-35 (emphasis added).
12. The plurality of nucleic acids of claim 11, wherein said plurality are present in a microarray.	"[A] whole *matrix array* of different polymers targeted for sequencing may be exposed to a series of chemical manipulations in a batch format. *A large array* of hundreds, thousands, or even millions of *spatially separated homogeneous regions may be simultaneously treated by defined sequencing chemistry*." Dower, col. 9, ll. 1-8 (emphasis added).
14. The method of claim 2, wherein the primer extension strand that results from step b)	"The synthetic mode, as illustrated in FIG. 1 is easily applied to the *sequencing of nucleic acids* … The synthetic scheme depends, in part, on the stepwise elongation by small and identifiable units. A polymerase

is the nucleic acid primer onto which the further nucleotide analogue is to be incorporated.	is used to extend *a primer complementary to a target template*. *The primer is elongated one nucleotide* at a time by use of a particular modified nucleotide analog to which a blocking agent is added and which prevents further elongation." Dower, col. 14, ll. 38- 53 (emphasis added); see also FIG. 8. "typically the blocking agent will be a reversible blocking agent thereby allowing for deblocking and *subsequent elongation*" Dower, col. 15, ll. 38-40 (emphasis added).
15. The method of claim 1, wherein each of said unique labels is attached to the nucleotide analogue via a cleavable linker.	Dower discloses that "One important functional property of the monomers is that the *label be removable*. The removal reaction will preferably be achieved using mild conditions. Blocking groups sensitive to mild *acidic conditions, mild basic conditions, or light* are preferred." Dower, col. 15, ll. 52-56 (emphasis added).
17. The method of claim 1, wherein the chemical moiety capping the 3'-OH group is not a fluorescent dye.	Dower discloses that the fluorescent label is not the 3'-OH capping group stating "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 dNTPs to function as a chain terminator. " Dower col. 25, ll. 35-37 (emphasis added).

Regarding claims 1 and 11, as shown above, Dower identically discloses methods of sequencing by synthesis including use of a deaza-substituted nucleotide analogue via the incorporation of the disclosure of Prober I. 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 in the sequencing method of Dower. See Weinstock Decl. ¶ 69. 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).

Dower expressly incorporates by reference Prober I stating "All publications and patent applications are herein incorporated by reference." Dower, col. 28, ll. 38-39. As such, Dower incorporates the teachings of Prober I, and 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).

4. Ground for Challenge 4 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Dower and Prober I

Petitioner has demonstrated that Dower, through incorporation of Prober I, anticipates claims 1-7, 11-12, 14-15 and 17 of the '698 patent. In the alternative, claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Dower combined with Prober I under 35 U.S.C. § 103. Although Dower was considered by the Examiner, there is no indication that the Examiner considered the combination of Dower with Prober I. Thus, the Examiner failed to appreciate that Dower provides an express teaching, suggestion, and motivation to combine the disclosure of Dower with Prober I, thereby teaching the use of use of deaza-substituted bases in nucleotide analogs in the system and method of Dower.

As disclosed above in **Claim Chart 2**, Dower discloses each element of claims 1-7, 11-12, 14-15 and 17 of the '698 patent. Should it be determined,

however, that Dower does not disclose use of deaza-substituted nucleotide analogs in its method of sequencing by synthesis, Prober I further discloses "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). Thus, Prober I teaches the limitation of both claims 1 and 11 relating to nucleotides having deaza-substituted bases.

Dower expressly teaches the combination with Prober I to make the labeled nucleotides stating "Fluorescent chain terminators (*analogs 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, ll. 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. ¶ 70. Further, it would have been obvious to combine Dower and Prober I for all the reasons discussed in section IV.2 (Tsien and Prober I) above, including because the combination of known features with known systems and methods merely produces a predictable result. See Weinstock Decl. ¶ 70. 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. ¶ 70.

5. Ground for Challenge 5 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious over Rabani in view of Prober I

Rabani published **September 6, 1996**. Rabani qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before the '698 patent's earliest claimed filing date. *Rabani was submitted to the Patent Office during prosecution of the '698 patent, on page 5 of a 11 page information disclosure statement listing 156 separate references, and 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. Rabani's sequencing by synthesis method is generally discussed, for example, at pages 6-7 of Rabani. As shown in the claim chart below, Rabani and Prober I discloses every element of at least claims 1-7, 11-12, 14-15 and 17 of the '698 patent, and because there are number of prior art reasons to combine Rabani and Prober I, claims 1-7, 11-12, 14-15 and 17 of the '698 patent are obvious under 35 U.S.C. § 103(a).

Claim Chart 3 - Disclosure of Rabani and Prober I

Claim in 7,713,698	**Disclosure and Explanation of Rabani + Prober I**
1. A method of determining the	"The present invention has applications in the area of polynucleotide sequence determination, *including DNA*

identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:	*sequencing*." Rabani, page 1, ll. 16-17 (emphasis added). "A sequencing cycle comprises the steps of: (1.) polymerizing one or less nucleotide, … onto each sample molecule *at the primer or at subsequent extensions thereof* and in opposition to (and pairing with) a single unique, base of the template polynucleotide strand." Rabani, page 6, ll. 29-35 (emphasis added). "Various methods may be used to accomplish the controlled addition of monomers, *including nucleotides and especially labeled or protected nucleotides*, to the *daughter strand of a sample template molecule*." Rabani, page 35, ll. 10-12 (emphasis added).
a) contacting a nucleic acid template attached to a solid surface	"Sequencing of polynucleotide molecules may be effected by the (preferably end-wise) *immobilization of a library of such molecules to a surface* at a density convenient for detection, which will vary according to the detection methodology availed." Rabani, page 6, ll. 14-17 (emphasis added).
with a nucleic acid primer which hybridizes to the template;	"*Priming*, which may be random or non-random, is effected by any of a variety of methods, most of which are obvious to those skilled in the relevant arts." Rabani, page 6, ll. 19-21 (emphasis added). "*Priming means* required by any particular enzyme must then be provided, *usually by hybridization of a complementary oligo- or polynucleotide to the sample template molecules*." Rabani, page 10, ll. 6-8 (emphasis added). "For example, the four nucleotides, each respectively labeled with unique, removable or neutralizable fluorescent labels, may be added to appropriately *primed sample template* molecules in the presence of polymerases, at low concentrations." Rabani, page 35, ll. 19-24 (emphasis added).
b) simultaneously contacting the product	"For example, *the four nucleotides*, each respectively labeled with unique, removable or neutralizable

of step a) with a polymerase and four nucleotide analogues which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU,	fluorescent labels, may be added to appropriately primed sample template molecules *in the presence of polymerases*, at low concentrations." Rabani, page 35, ll. 19-24 (emphasis added). "*Nucleotide analogs* comprising such removable protecting groups preferably further comprise labeling moieties." Rabani, page 38, ll. 39-40. See also, Rabani, page 6, lines 22-29.
so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand,	"A sequencing cycle comprises the steps of: (1.) polymerizing one or less nucleotide, … onto each sample molecule *at the primer or at subsequent extensions thereof* and in opposition to (and pairing with) a single unique, base of the template polynucleotide strand." Rabani, page 6, ll. 29-35 (emphasis added); see also, page 35, ll. 15-34.
wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and	"For example, the four nucleotides, *each respectively labeled with unique, removable or neutralizable fluorescent labels*, may be added to appropriately primed sample template molecules in the presence of polymerases, at low concentrations." Rabani, page 35, ll. 19-24 (emphasis added). "Labeling moieties are favorably in communication with or *coupled to nucleotides via a linker* of sufficient length to ensure that the presence of said labeling moieties on said nucleotides will not interfere with the action of a polymerase enzyme on said nucleotides." Rabani, page 32, ll. 10-11 (emphasis added). "A sequencing cycle comprises the steps of: … (5.) optionally removing (by appropriate means) any 3' protecting groups … from the nucleotide added during the present cycle, *if these are distinct from any cleavably linked labeling moieties*." Rabani, page 6, line 29 and page 7, lines 14-18 (emphasis added).
contains a removable chemical moiety capping the 3'-OH	"[P]olymerizing one or less *nucleotides*, which carry some removable or neutralizable molecular label and may optionally be *reversibly 3' protected* (or otherwise

group of the sugar of the nucleotide analogue, and	protected in any manner which modulates polymerization … onto each sample molecule at the primer or at subsequent extensions thereof." Rabani, page 6, ll. 30-33 (emphasis added). Rabani discloses a small, removable chemical moiety stating "[e]nzymological evidence concerning binding of *3' acetate esterified nucleotides* and 5'-triphosphate-3'-(nucleoside-5'-monophosphate) to the triphosphate binding site of E. coli Polymerase I *supports the acceptability of 3' modified nucleotides as substrates for this enzyme*." Rabani, page 39, lines 7-12 (emphasis added)
wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and	Prober I 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 7-deazapurines*." Prober I, page 337, 1st column (emphasis added).
c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer extension strand.	"A sequencing cycle comprises the steps of: … (3.) *detecting*, by either direct or indirect methods said *labeled nucleotides incorporated into said sample molecules*, in a manner which repeatably associates information obtained about the type of label observed with t*he unique identity of the template molecule under observation*." Rabani, page 6, ll. 29-40 (emphasis added); see also, pages 15-17.
2. The method of claim 1, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of the incorporated nucleotide analogue, thereby permitting the incorporation of a	"A sequencing cycle comprises the steps of: … (5.) optionally *removing (by appropriate means) any 3' protecting groups* (or any other protecting groups which may serve to modulate monomer addition rate to the strand being copied from the template molecule) from the nucleotide added during the present cycle, if these are distinct from any cleavably linked labeling moieties." Rabani, page 6, line 29 and page 7, ll. 14-18 (emphasis added).

further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.	"*Removable protecting groups* are particularly advantageous for the genome sequencing applications of the present invention because they may be utilized to permit and ensure that exactly one nucleotide is added to a sample molecule per sequencing cycle." Rabani, page 38, ll. 25-28 (emphasis added).
3. The method of claim 1, wherein the unique label is a fluorescent label.	"A modification of VECFM which is particularly suited for SMD and SMV relies upon *selective fluorescent excitation of an appropriate dye molecule label* (or of molecules within a sample with appropriate fluorescent properties independent of labeling) in some sample by means of some tightly defined beam." Rabani, page 15, ll. 14-18 (emphasis added) "Detection methods for the present invention may favorably exploit *fluorescent labeling techniques*." Rabani, page 29, ll. 26-27.
4. The method of claim 1, wherein the polymerase is Taq DNA polymerase, T7 DNA polymerase or Vent DNA polymerase.	"While *well studied DNA polymerase enzymes*, preferably lacking a 3' to 5' exonuclease activity, or RNA polymerases or reverse transcriptases may be initially preferred for use in sequencing applications of the present invention, use of the term polymerase (as well as the term transcriptase) shall refer to any molecule or complex capable of enforcing fidelity of pairing on single nucleotides at a structurally defined site of a template polynucleotide molecule." Rabani, page 12, ll. 6-12 (emphasis added). "The chain-terminators reported here are incorporated by … *modified T7 DNA polymerase*." Prober I, page 340, col. 1 (emphasis added).
5. The method of claim 1, wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface.	"Sequencing of polynucleotide molecules may be effected by the (preferably end-wise) immobilization of *a library of such molecules* to a surface at a density convenient for detection." Rabani, page 6, ll. 14-16 (emphasis added). "The invention relates to the massively parallel single molecule examination of associations or reactions between *large numbers of first complex molecules, which*

	may be diverse." Rabani, page 1, ll. 4-6 (emphasis added).
6. The method of claim 1, wherein said nucleic acid template comprises an RNA template.	"For purposes of genome sequencing applications of the present invention, … or directly purified genomic DNA or directly purified *RNA* from a particular cell type, etc., may be subjected to fragmentation." Rabani, page 18, ll. 3-9 (emphasis added).
7. The method of claim 6, wherein the polymerase is a reverse transcriptase.	"While well studied DNA polymerase enzymes, preferably lacking a 3' to 5' exonuclease activity, or RNA polymerases or *reverse transcriptases* may be initially preferred for use in sequencing applications of the present invention, use of the term polymerase (as well as the term transcriptase) shall refer to any molecule or complex capable of enforcing fidelity of pairing on single nucleotides at a structurally defined site of a template polynucleotide molecule." Rabani, page 12, ll. 6-12 (emphasis added).
11. A plurality of nucleic acid templates immobilized on a solid surface,	"Sequencing of polynucleotide molecules may be effected by the (preferably end-wise) *immobilization of a library of such molecules to a surface* at a density convenient for detection, which will vary according to the detection methodology availed." Rabani, page 6, ll. 14-17 (emphasis added).
wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue,	"*Priming*, which may be random or non-random, is effected by any of a variety of methods, most of which are obvious to those skilled in the relevant arts." Rabani, page 6, ll. 19-21 (emphasis added). "*Priming means* required by any particular enzyme must then be provided, *usually by hybridization of a complementary oligo- or polynucleotide to the sample template molecules*." Rabani, page 10, ll. 6-8 (emphasis added). "For example, the four nucleotides, each respectively labeled with unique, removable or neutralizable fluorescent labels, may be added to appropriately *primed sample template* molecules in the presence of polymerases, at low concentrations." Rabani, page 35, ll. 19-24 (emphasis added).

	"A sequencing cycle comprises the steps of: (1.) polymerizing one or less nucleotide, … onto each sample molecule *at the primer or at subsequent extensions thereof* and in opposition to (and pairing with) a single unique, base of the template polynucleotide strand." Rabani, page 6, ll. 29-35 (emphasis added).
at least one of which is deaza-substituted,	Prober I 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 7-deazapurines*." Prober I, page 337, 1st column (emphasis added).
wherein each labeled nucleotide analogue comprises a base labeled with a unique label and	"For example, the four nucleotides, *each respectively labeled with unique, removable or neutralizable fluorescent labels*, may be added to appropriately primed sample template molecules in the presence of polymerases, at low concentrations." Rabani, page 35, ll. 19-24 (emphasis added). "Labeling moieties are favorably in communication with or *coupled to nucleotides via a linker* of sufficient length to ensure that the presence of said labeling moieties on said nucleotides will not interfere with the action of a polymerase enzyme on said nucleotides." Rabani, page 32, ll. 10-11 (emphasis added). "A sequencing cycle comprises the steps of: … (5.) optionally removing (by appropriate means) any 3' protecting groups … from the nucleotide added during the present cycle, *if these are distinct from any cleavably linked labeling moieties*." Rabani, page 6, ll 29 and page 7, ll 14-18 (emphasis added).
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue.	"[P]olymerizing one or less *nucleotides*, which carry some removable or neutralizable molecular label and may optionally be *reversibly 3' protected* (or otherwise protected in any manner which modulates polymerization … onto each sample molecule at the primer or at subsequent extensions thereof." Rabani,

	page 6, ll. 30-33 (emphasis added). Rabani discloses a small, removable chemical moiety stating "[e]nzymological evidence concerning binding of *3' acetate esterified nucleotides* and 5'-triphosphate-3'-(nucleoside-5'-monophosphate) to the triphosphate binding site of E. coli Polymerase I *supports the acceptability of 3' modified nucleotides as substrates for this enzyme*." Rabani, page 39, lines 7-12 (emphasis added)
12. The plurality of nucleic acids of claim 11, wherein said plurality are present in a microarray.	Rabani discloses detection of "*multiple probes (i.e. in arrays* …)" Rabani, p. 11, ll. 3-15 (emphasis added).
14. The method of claim 2, wherein the primer extension strand that results from step b) is the nucleic acid primer onto which the further nucleotide analogue is to be incorporated.	"*[P]olymerizing* one or less *nucleotides*, which carry some removable or neutralizable molecular label and may optionally be reversibly 3' protected (or otherwise protected in any manner which modulates polymerization … onto each sample molecule at the primer or *at subsequent extensions thereof*." Rabani, page 6, ll. 30-33 (emphasis added).
15. The method of claim 1, wherein each of said unique labels is attached to the nucleotide analogue via a cleavable linker.	Rabani discloses nucleotides with "*labeling moieties ... coupled to nucleotides via a linker*." Rabani, p. 32, ll. 10-13 (emphasis added). Rabani further discloses removal of moieties attached via a "*photocleavable linker*," and "photocleavable protecting groups." Id. at p. 17, ll. 15-21 (emphasis added).
17. The method of claim 1, wherein the chemical moiety capping the 3'-OH group is not a fluorescent dye.	Rabani teaches an embodiment in which the label group is distinct from the 3'-OH capping group stating "optionally removing (by appropriate means) *any 3' protecting groups* (or any other protecting groups which may serve to modulate monomer addition rate to the strand being copied from the template molecule) from the nucleotide added during the present cycle, *if these are distinct from any cleavably linked labeling moieties*."

	Rabani, page 7, ll. 14-18 (emphasis added). Prober I teaches attachment of the fluorescent label to the 7 position of a deazapurine stating "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 7-deazapurines*." Prober I, page 337, 1st column (emphasis added).

As shown above, Rabani and Prober I disclose every element of claims 1-7, 11-12, 14-15 and 17 of the '698 patent.

As discussed above, Prober I teach the advantages of using deaza-substituted nucleotides in sequencing. For example, Prober I states "[t]he 7-deazapurines were used to facilitate stable linker arm attachment at that site." Prober I, page 337, 1st column. For all the reasons discussed in section IV.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. See Weinstock Decl. ¶ 71. Further, combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2. As such, the combination of Rabani and Prober I merely utilizes well know prior art components for their intended purpose to obtain the same known, predicable results disclosed in the references.

6. Ground for Challenge 6 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Stemple II

Stemple II published as WO 00/53805 on **September 14, 2000**. Stemple II qualifies as prior art against the '698 patent under 35 U.S.C. § 102(a) because it was published before the '698 patent's earliest claimed filing date. *Stemple II was submitted to the Patent Office during prosecution of the '698 patent, on page 3 of a 15 page information disclosure statement listing 193 separate references, and 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 (identical in Stemple I, II and III) reproduced below.

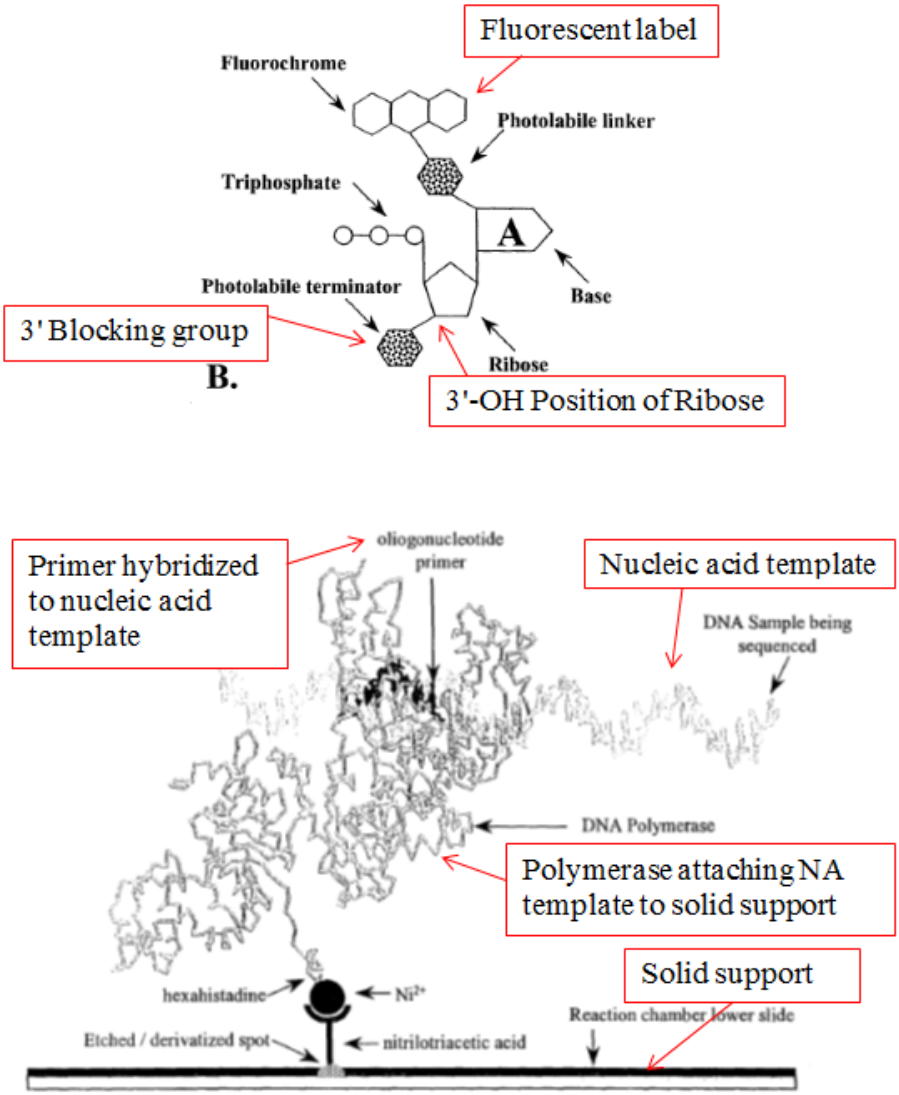


FIG. 3 Example of a DNAS Reaction Center

The analysis and claim chart below demonstrate that claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Stemple II (cites to Stemple I and Stemple III are provided as discussed below in Section IV.9).

Claim Chart 4 - Anticipation of Challenged Claims by Stemple I, II, and III.

Claim in 7,713,698	Disclosure and Explanation of Stemple I, II, and III
1. A method of determining the	"The present invention relates to methods for sequencing nucleic acid samples." Stemple II, page 1, line 3;

identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:	Stemple III, col. 1, ll. 11-12; Stemple I, page 1, line 6; see also Stemple II, page 3, ll. 9-10; Stemple III, col. 2, ll. 52-54; Stemple I, page 3, ll. 16-17. "The present invention provides rapid, cost effective, high throughput methods for sequencing unknown nucleic acid samples." Stemple II, page 3, lines 9-10; Stemple III, col. 2, lines 52-54; Stemple I, page 3, lines 16-17.
a) contacting a nucleic acid template attached to a solid surface	"According to the methods of the present invention, a *plurality of polymerase molecules is immobilized on a solid support* through a covalent or non-covalent interaction." Stemple II, page 3, ll. 14-15; Stemple III, col. 2, ll. 60-62; Stemple I, page 3, ll. 21-22 (emphasis added). "*Template*-driven elongation of a nucleic acid is mediated by *the attached polymerases* using the labeled-caged nucleoside triphosphate terminators." Stemple II, page 3, ll. 17-19; Stemple III, col. 2, ll. 66-67 thru col. 3, line 1; Stemple I, page 3, ll. 24-26 (emphasis added). As shown above, FIG. 3 of Stemple I, II, and III shows the DNA sample (i.e., the template) attached to the lower slide (i.e., the solid surface) via the interaction with the DNA polymerase.
with a nucleic acid primer which hybridizes to the template;	As shown above, FIG. 3 of Stemple I, II, and III shows a primer hybridized to the DNA sample (i.e., the template). "A nucleic acid sample and *oligonucleotide primers* are introduced to the reaction chamber in a buffered solution containing all four labeled-caged nucleoside triphosphate terminators." Stemple II, page 3, ll. 15-17; Stemple III, col. 2, ll. 62-66; Stemple I, page 3, ll. 22-24 (emphasis added).
b) simultaneously contacting the product of step a) with a polymerase and four nucleotide analogues	As shown above, FIG. 3 of Stemple I, II, and III show the DNA sample (i.e., the template) attached to the lower slide (i.e., the solid surface) via the interaction with the DNA polymerase.

which are either (i) aA, aC, aG, and aT, or (ii) aA, aC, aG, and aU,	"A nucleic acid sample and oligonucleotide primers are introduced to the reaction chamber in a buffered solution containing *all four labeled-caged nucleoside triphosphate terminators*." Stemple II, page 3, ll. 15-17; Stemple III, col. 2, ll. 62-66; Stemple I, page 3, ll. 22-24 (emphasis added). "Panel C [of Fig. 1] depicts *the four different nucleotides* each labeled with a fluorochrome with distinct spectral properties." Stemple II, page 4, ll. 26-27; Stemple III, col. 3, ll. 63-67; Stemple I, page 5, ll. 8-9 (emphasis added). "During each sequencing cycle, four images of the entire array are produced, and each image corresponds to excitation of one of the four fluorescently labeled *nucleotide bases A, C, G, or T (U)*." Stemple II, page 21, ll. 17-19; Stemple III, col. 15, ll. 53-56; Stemple I, page 20, ll. 22-24 (emphasis added).
so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand,	"*Template-driven elongation of a nucleic acid* is mediated by the attached polymerases using the labeled-caged nucleoside triphosphate terminators." Stemple II, page 3, ll. 17-19; Stemple III, col. 2, ll. 66-67 thru col. 3, line 1; Stemple I, page 3, ll. 24-26 (emphasis added). "Reaction centers are monitored by the microscope system until a majority of sites contain immobilized polymerase bound to a nucleic acid template *with a single incorporated labeled-caged nucleotide terminator*." Stemple II, page 3, ll. 19-21; Stemple III, col. 3, ll. 1-5; Stemple I, page 3, ll. 26-28 (emphasis added). "The modified 3'-0-(-2-Nitrobenzyl)-*dNTP* is incorporated into the growing DNA chain." Stemple II, p. 13, ll. 9-10 (emphasis added); see also p. 13, ll. 4-25 and p. 29, ll. 14-17; Stemple III, col. 9, ll. 59-61; see also col. 9, l. 50-col 10, l. 17 and col. 21, ll. 39-41; Stemple I, p. 12, l. 26-27; see also p. 12, l. 20-p. 13, l. 13 and p. 29, ll. 1-3.

wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and	"Four fluorochromes with *distinct spectral properties allow the four nucleotides to be distinguished* during the detection phase of the DNAS reaction cycle." Stemple II, page 14, ll. 21-23; Stemple III, col. 10, ll. 53-56; Stemple I, page 14, ll. 9-10 (emphasis added). FIG. 1B of Stemple I, II, and III shows a 3'-OH blocked and base-labeled nucleotide.
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, and	"The differentially-labeled nucleotides used in the sequencing methods of the present invention have a detachable labeling group and *are blocked at the 3' portion with a detachable blocking group*." Stemple II, page 4, ll. 1-3; Stemple III, col. 3, ll. 22-25; Stemple I, page 4, ll. 11-13 (emphasis added).
wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and	"In an alternative configuration 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 et al, WO 98/33939*." Stemple II, page 31, ll. 10-12; Stemple III, col. 22, ll. 53-57; Stemple I, page 30, ll. 25-27 (emphasis added). Stemple II specifically incorporates by reference "PCT Patent Application WO 33939." Stemple II, page 27, ll. 30-31; Stemple III, col. 12, ll. 55-57; Stemple I, page 17, l. 15. Anazawa discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. See Anazawa, Fig. 7 and page 5, l. 36 - page 6, line 9 (also citing " Science 238, 336 – 341, 1987," i.e. Prober I).
c) detecting the unique label of the incorporated nucleotide analogue, so as to thereby determine the identity of the nucleotide analogue incorporated into the nucleic acid primer	"*Specific nucleotide incorporation is then determined* for each active reaction center. Following *detection* … ." Stemple II, page 3, ll. 22-23; Stemple III, col. 15, ll. 23-24; Stemple I, page 4, ll. 1-2 (emphasis added). "Four fluorochromes with *distinct spectral properties allow the four nucleotides to be distinguished* during the *detection phase* of the DNAS reaction cycle." Stemple II, page 14, ll. 21-23; Stemple III, col. 10, ll. 53-56;

extension strand.	Stemple I, page 14, ll. 9-10 (emphasis added).
2. The method of claim 1, further comprising removing the chemical moiety capping the 3'-OH group of the sugar of the incorporated nucleotide analogue, thereby permitting the incorporation of a further nucleotide analogue so as to create a growing annealed nucleic acid primer extension strand.	"Following detection, the reaction chamber is irradiated to *uncage the incorporated nucleotide* and flushed with wash buffer once again … The *sequencing cycle* outlined above is *repeated* until a large proportion of reaction centers fail." Stemple II, page 3, ll. 23-31; Stemple III, col. 15, ll. 24-39; Stemple I, page 4, ll. 2-10 (emphasis added); see also Fig. 2 (showing cycle).
3. The method of claim 1, wherein the unique label is a fluorescent label.	"Four fluorochromes with *distinct spectral properties allow the four nucleotides to be distinguished* during the detection phase of the DNAS reaction cycle." Stemple II, page 14, ll. 21-23; Stemple III, col. 10, ll. 53-56; Stemple I, page 14, ll. 9-10 (emphasis added).
4. The method of claim 1, wherein the polymerase is Taq DNA polymerase, T7 DNA polymerase or Vent DNA polymerase.	"In a preferred embodiment, sequencing is done with a DNA-dependent DNA polymerase …. Examples of DNA-dependent DNA polymerases include … the bacteriophage T4 and *T7* DNA polymerases, and those from *Thermus aquaticus* (*Taq*), ... and *Thermococcus litoralis* (*Vent*) Stemple II, page 9, ll. 2-8; Stemple III, col. 6 ll. 59 - col. 7, line 2; Stemple I, page 8, ll. 25 - page 9, line 3(emphasis added).
5. The method of claim 1, wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface.	"The present invention provides a novel sequencing apparatus and the methods employed to determine the nucleotide sequence of *many single nucleic acid molecules simultaneously, in parallel*." Stemple I, II, and III, Abstract.
6. The method of claim 1, wherein said nucleic acid template comprises an RNA template.	"In an alternative preferred *embodiment where RNA is used as template* the selected DNA-dependent DNA polymerase functions as an RNA-dependent DNA polymerase, or reverse transcriptase" Stemple II, page 9, ll. 15-17; Stemple III, col. 7, ll. 12-15; Stemple I, page 8,

	ll. 25 - page 9, ll. 8-10 (emphasis added).
7. The method of claim 6, wherein the polymerase is a reverse transcriptase.	"In an alternative preferred embodiment where RNA is used as template the selected DNA-dependent DNA polymerase functions as an RNA-dependent DNA polymerase, or *reverse transcriptase*" Stemple II, page 9, ll. 15-17; Stemple III, col. 7, ll. 12-15; Stemple I, page 8, ll. 25 - page 9, ll. 8-10 (emphasis added).
11. A plurality of nucleic acid templates immobilized on a solid surface,	"The present invention provides a novel sequencing apparatus and the methods employed to determine the nucleotide sequence of *many single nucleic acid molecules simultaneously, in parallel*." Stemple I, II, and III, Abstract.
wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue,	"Depicted in FIG. 2 is a single round of the reaction cycle, i.e., (1) the incorporation of a labeled-caged nucleotide; (2) the detection of the labeled nucleotide; and (3) the unblocking of the caged nucleotide.… As a *result the primer is extended by one base ... and the 3'-OH is restored so that another nucleotide can be incorporated on the next cycle*." Stemple II, page 15, line 31 - page 16, line 10; Stemple III, col. 11, ll. 1-18; Stemple I, page 14, ll. 18-29 (emphasis added); see also Fig. 2 (showing cycle).
at least one of which is deaza-substituted,	"In an alternative configuration 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 et al, WO 98/33939*." Stemple II, page 31, ll. 10-12; Stemple III, col. 22, ll. 53-57; Stemple I, page 30, ll. 25-27 (emphasis added). Anazawa et al. discloses attachment of fluorescent labels to the 7 position of the 7-deaza-guanine base of the nucleotide analog. Anazawa, Fig. 7 and page 5, l. 36 - page 6, line 9 (also citing " Science 238, 336 – 341, 1987," i.e. Prober I).
wherein each labeled nucleotide analogue comprises a base labeled with a unique label and	"Four fluorochromes with *distinct spectral properties allow the four nucleotides to be distinguished* during the detection phase of the DNAS reaction cycle." Stemple II, page 14, ll. 21-23; Stemple III, col. 10, ll. 53-56; Stemple I, page 14, ll. 9-10 (emphasis added).

	FIG. 1B of Stemple I, II, and III shows a 3'-OH blocked and base-labeled nucleotide.
contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue.	"The differentially-labeled nucleotides used in the sequencing methods of the present invention have a detachable labeling group and *are blocked at the 3' portion with a detachable blocking group*." Stemple II, page 4, ll. 1-3; Stemple III, col. 3, ll. 22-25; Stemple I, page 4, ll. 11-13 (emphasis added).
12. The plurality of nucleic acids of claim 11, wherein said plurality are present in a microarray.	"*A diagram of the DNAS reaction center array is given in FIG. 5*…. each reaction center is attached to the lower slide of the reaction chamber. Depicted in the left side panel (Microscope Field) is the *view of an entire array*." Stemple II, page 7, ll. 26-29; Stemple III, col. 5, l. 65 - col. 6, l. 2; Stemple I, page 8, ll. 2-5 (emphasis added).
14. The method of claim 2, wherein the primer extension strand that results from step b) is the nucleic acid primer onto which the further nucleotide analogue is to be incorporated.	"Depicted in FIG. 2 is a single round of the reaction cycle, i.e., (1) the incorporation of a labeled-caged nucleotide; (2) the detection of the labeled nucleotide; and (3) the unblocking of the caged nucleotide.… As a *result the primer is extended by one base ... and the 3'-OH is restored so that another nucleotide can be incorporated on the next cycle*." Stemple II, page 15, line 31 - page 16, line 10; Stemple III, col. 11, ll. 1-18; Stemple I, page 14, ll. 18-29 (emphasis added); see also Fig. 2 (showing cycle).
15. The method of claim 1, wherein each of said unique labels is attached to the nucleotide analogue via a cleavable linker.	"In another preferred embodiment, *the labeling group is attached to the base of each nucleotide* with a detachable linker rather than to the detachable 3' blocking group." Stemple II, page 4, ll. 7-8; Stemple III, col. 3, ll. 31-33; Stemple I, page 4, ll. 17-18 (emphasis added).
17. The method of claim 1, wherein the chemical moiety capping the 3'-OH group is not a fluorescent dye.	"In another preferred embodiment, *the labeling group is attached to the base of each nucleotide* with a detachable linker rather than to the detachable 3' blocking group." Stemple II, page 4, ll. 7-8; Stemple III, col. 3, ll. 31-33; Stemple I, page 4, ll. 17-18 (emphasis added).

As shown above, Stemple II identically discloses every element of claims 1-7, 11-12, 14-15 and 17 of the '698 patent, and therefore Stemple II anticipates claims 1-7, 11-12, 14-15 and 17 of the '698 patent under 35 U.S.C. § 102(a).

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. See Weinstock Decl. ¶ 72. The same is true when following the teachings of Prober I.

7. Ground for Challenge 7 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Anazawa

Petitioner has demonstrated that Stemple II, through direct reference to Anazawa, anticipates claims 1-7, 11-12, 14-15 and 17 of the '698 patent. Independent claims 1 and 11, and claims 2-7, 12, 14-15 and 17 depending therefrom, are also obvious in view of Stemple II combined with Anazawa under 35 U.S.C. § 103. Anazawa was published on Aug. 6, 1998, and thus qualifies as prior art under 35 U.S.C. § 102(b).

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 Fig. 7 and page 5, l. 36 - page 6, line 9; see Weinstock Decl. ¶ 73. Thus, it would have been obvious for one of ordinary skill in the art to combine the teachings of Stemple II with the 7-deazapurine base feature, and attachment of the label to the 7 position of that deazapurine base, as disclosed in Anazawa

8. Ground for Challenge 8 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Prober I

Independent claims 1 and 11, and claims 2-7, 12, 14-15 and 17 depending therefrom, are also obvious in view of Stemple II combined with Prober I under 35 U.S.C. § 103. As shown above in Claim Charts 4 and i, Stemple II and Prober I disclose every element of claims 1 and 11, and Stemple II discloses each limitation of dependent claims 2-7, 12, 14-15 and 17 of the '698 patent.

As shown above, Prober I teaches the advantages of using deazapurine-based nucleotides in sequencing methods. For all the reasons discussed in section IV.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. ¶ 74. Further, combining references teaching

sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2. As such, the combination of Stemple II and Prober I merely utilizes well know prior art components for their intended purpose to obtain the same known, predicable results disclosed in the references.

9. Ground for Challenge 9 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated by Stemple III

Stemple III 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 '698 patent's earliest claimed filing date, Stemple III also qualifies as prior art under 35 U.S.C. § 102(e).[1] **Claim Chart 4** 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. See Weinstock Decl. ¶ 75. Accordingly, claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as anticipated under 35 U.S.C § 102(e) by Stemple III.

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[1] The priority claim under 35 U.S.C. § 120 is shown on the front page of Stemple III.

10. Ground for Challenge 10 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple III and Prober I

Independent claims 1 and 11, and claims 2-7, 12, 14-15 and 17 depending therefrom, are also obvious in view of Stemple III combined with Prober I under 35 U.S.C. § 103. As shown above in Claim Charts 4 and 1, Stemple III and Prober I disclose every element of claims 1 and 11, and Stemple III discloses each limitation of dependent claims 2-7, 12, 14-15 and 17 of the '698 patent. For the reasons discussed above in Section IV.8, one of ordinary skill in the art would be motivated to combine the teachings of Stemple III and Prober I. See Weinstock Decl. ¶ 76.

11. Ground for Challenge 11 - Claims 5 and 12 of the '698 patent are invalid as obvious in view of Tsien and Prober I in further view of Rabani

As shown above in Section IV.1, Tsien identically discloses the limitations added in dependent claims 5 and 12. However, in the alternative, claims 5 and 12 of the '698 patent are also obvious in view of Tsien Prober I, and Rabani under 35 U.S.C. § 103. Claim 5 recites "wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface," and claim 12 recites "wherein said plurality are present in a microarray." Rabani identifies that "[t]he invention relates to the massively parallel single molecule examination of associations or reactions between *large numbers of first complex molecules, which may be diverse*." Rabani, page 1, ll. 4-6 (emphasis added). Rabani also discloses detection

of "*multiple probes (i.e. in arrays …)*" Rabani, p. 11, ll. 3-15 (emphasis added). Modifying the sequencing process taught by Tsien to either sequence a large number of diverse molecules or to use an array format as taught by Rabani would be obvious because it is merely the use of known techniques to improve the similar Tsien systems and methods in the same way that the known features improve the methods and reagents of Rabani. See Weinstock Decl. ¶ 77.

12. Ground for Challenge 12 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Dower and Prober II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Dower combined with Prober II under 35 U.S.C. § 103. Prober II issued September 7, 1993. Prober II qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before the '698 patent's earliest claimed filing date.

As previously explained, Dower 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 use of "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 disclosed in Prober II 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, as disclosed by Prober II, to enhance the capability of the Dower systems and methods in the same way they enhance the capability of the Prober II methods and reagents. Additionally, it would have been obvious to combine Dower and Prober II because the combination of known features with known systems and methods merely produces a predictable result. Further, combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2. Furthermore, Prober II discloses the synthesis scheme underlying Prober I, and as discussed in Section IV.3 Dower expressly identifies Prober I as providing additional details about the fluorescent labeled

dNTPs that may be used in the sequencing method of Dower. See Dower, col. 17, ll. 33-36. See Weinstock Decl. ¶¶ 78, 79.

13. Ground for Challenge 13 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Tsien and Prober II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Tsien combined with Prober II under 35 U.S.C. § 103. The disclosure of Tsien is shown above in Claim Chart 1, and the disclosure of Prober II is shown above in Section IV.12. Both Tsien and Prober II relate to polymerase-based DNA sequencing methods, and it would be obvious to modify the sequencing method of Tsien to include the deazapurine taught by Prober II for the same reasons discussed above in Section IV.12. See Weinstock Decl. ¶¶ 80, 81.

14. Ground for Challenge 14 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Rabani and Prober II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Rabani combined with Prober II under 35 U.S.C. § 103. The disclosure of Rabani is shown above in Claim Chart 3, and the disclosure of Prober II is shown above in Section IV.12. Both Rabani and Prober II relate to polymerase-based DNA sequencing methods, and it would be obvious to modify the sequencing method of Rabani to include the deazapurine taught by Prober II for the same reasons as discussed above in Section IV.12. See Weinstock Decl. ¶¶ 82, 83.

15. Ground for Challenge 15 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Prober II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple II combined with Prober II under 35 U.S.C. § 103. The disclosure of Stemple II is shown above in Claim Chart 4, and the disclosure of Prober II is shown above in Section IV.12. Both Stemple II and Prober II relate to polymerase-based DNA sequencing methods, and it would be obvious to modify the sequencing method of Stemple II to include the deazapurine taught by Prober II for the same reasons as discussed above in Section IV.12. See Weinstock Decl. ¶¶ 84, 85.

16. Ground for Challenge 16 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple III and Prober II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple III combined with Prober II under 35 U.S.C. § 103. The disclosure of Stemple III is shown above in Claim Chart 4, and the disclosure of Prober II is shown above in Section IV.12. Both Stemple III and Prober II relate to sequencing methods, and it would be obvious to modify the sequencing method of Stemple III to include the deazapurine taught by Prober II for the same reasons as discussed above in Section IV.12. See Weinstock Decl. ¶ 86.

17. Ground for Challenge 17 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Dower and Seela I

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Dower combined with Seela I under 35 U.S.C. § 103. Seela I issued February 14, 1989. Seela I qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before the '698 patent's earliest claimed filing date.

Seela I is directed toward nucleotide analogues to be used for sequencing methods. Seela I discloses use of a deazapurine for sequencing, for example, stating "The present invention provides 7-deaza-2'-deoxyguanosine nucleotides … The present invention … is also concerned with the use thereof in the sequencing of DNA." Seela I, Abstract. Seela I specifically teaches the use of 7-deaza-2'-deoxyguanosine nucleotides in any polymerase-mediated DNA sequencing method. See Seela I, col. 4, lines 4-7. Seela I expressly teaches an advantage of using the 7-deaza-2'-deoxyguanosine stating "by using the compounds according to the present invention, a disturbance-free sequencing of cytosine-guanine-rich nucleic acids is possible." Seela I, col. 4, ll. 31-33. Thus, it would have been obvious for one of ordinary skill in the art to use the deaza nucleotides of Seela I with the polymerase medicated DNA sequencing method of Dower as expressly stated in Seela I. In addition, it would be obvious to combine the teachings of Dower with the 7-deaza-2'-deoxyguanosine disclosed in Seela I 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 Seela I. Furthermore, it would have been obvious to use the features taught by Seela I for their intended purpose, as disclosed by Seela I, to enhance the capability of the Dower systems and methods in the same way they enhance the capability of the Seela I methods and reagents. Additionally, it would have been obvious to combine Dower and Seela I because the combination of known features with known systems and methods merely produces a predictable result. See Weinstock Decl. ¶¶ 87, 88. Further, combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2.

18. Ground for Challenge 18 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Tsien and Seela I

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Tsien combined with Seela I under 35 U.S.C. § 103. The disclosure of Tsien is shown above in Claim Chart 1, and the disclosure of Seela I is shown above in Section IV.17. Both Tsien and Seela I relate to polymerase-mediated DNA sequencing methods, and it would be obvious to modify the sequencing method of Tsien to include the deazapurine taught by Seela I for the same reasons as discussed above in Section IV.17. See Weinstock Decl. ¶¶ 89, 90.

19. Ground for Challenge 19 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Rabani and Seela I

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Rabani combined with Seela I under 35 U.S.C. § 103. The disclosure of Rabani is shown above in Claim Chart 3, and the disclosure of Seela I is shown in Section IV.17. Both Rabani and Seela I relate to polymerase-mediated sequencing methods, and it would be obvious to modify the polymerase-mediated DNA sequencing method of Rabani to include the deazapurine taught by Seela I for the same reasons as discussed above in Section IV.17. See Weinstock Decl. ¶¶ 91-92.

20. Ground for Challenge 20 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Seela I

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple II combined with Seela I under 35 U.S.C. § 103. The disclosure of Stemple II is shown above in Claim Chart 4, and the disclosure of Seela I is shown above in Section IV.17. Both Stemple II and Seela I relate to sequencing methods, and it would be obvious to modify the polymerase-mediated DNA sequencing method of Stemple II to include the deazapurine taught by Seela I for the same reasons as discussed above in Section IV.17. See Weinstock Decl. ¶¶ 93, 94.

21. Ground for Challenge 21 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple III and Seela I

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple III combined with Seela I under 35 U.S.C. § 103. The disclosure of

Stemple III is shown above in Claim Chart 4, and the disclosure of Seela I is shown above in Section IV.17. Both Stemple III and Seela I relate to sequencing methods, and it would be obvious to modify the polymerase-mediated DNA sequencing method of Stemple III to include the deazapurine taught by Seela I for the same reasons as discussed above in Section IV.17. See Weinstock Decl. ¶ 95.

22. Ground for Challenge 22 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Dower and Hobbs

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Dower combined with Hobbs under 35 U.S.C. § 103. Hobbs issued September 10, 1991. Hobbs qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before t the '698 patent's earliest claimed filing date.

Hobbs "pertains to alkynylaminonucleotides and especially to their use in preparing *fluorescently-labeled nucleotides as chain-terminating substrates for a fluorescence-based DNA sequencing method*. " Hobbs, col. 1, ll. 14-17 (emphasis added). Hobbs expressly teaches various advantages of attaching the label group via a linker to the 7-deazapurine. For example, Hobbs teaches that "The *unnatural 7-deazapurines* can be employed to attach the linker *without adding a net charge to the base portion and thereby destabilizing the glycosidic linkage*." See Hobbs, col. 11, ll. 1-4 (emphasis added). Further, Hobbs teaches that "the 7-position of the purine nucleotides provide labeled chain-terminating substrates that do not

interfere excessively with the degree or fidelity of substrate incorporation." Hobbs, col. 8, ll. 57-60.

Thus, it would have been obvious for one of ordinary skill in the art to combine the teachings of Dower with the "unnatural 7-deazapurines" disclosed in Hobbs 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 Hobbs. Furthermore, it would have been obvious to use the features taught by Hobbs for their intended purpose, as disclosed by Hobbs, to enhance the capability of the Dower systems and methods in the same way they enhance the capability of the Hobbs methods and reagents. Additionally, it would have been obvious to combine Dower and Hobbs because the combination of known features with known systems and methods merely produces a predictable result. See Weinstock Decl. ¶¶ 96, 97. Further, combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2.

23. Ground for Challenge 23 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Tsien and Hobbs

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Tsien combined with Hobbs under 35 U.S.C. § 103. The disclosure of Tsien is shown above in Claim Chart 1, and the disclosure of Hobbs is discussed above in

Section IV.22. Both Tsien and Hobbs relate to polymerase mediated sequencing methods, and it would be obvious to modify the sequencing method of Tsien to include the deazapurine nucleotides taught by Hobbs el for the same reasons as discussed above in Section IV.22. See Weinstock Decl. ¶¶ 98, 99.

24. Ground for Challenge 24 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Rabani and Hobbs

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Rabani combined with Hobbs under 35 U.S.C. § 103. The disclosure of Rabani is shown above in Claim Chart 3, and the disclosure of Hobbs is discussed above in Section IV.22. Both Rabani and Hobbs relate to polymerase mediated sequencing methods, and it would be obvious to modify the sequencing method of Rabani to include the deazapurine taught by Hobbs el for the same reasons as discussed above in Section IV.22. See Weinstock Decl. ¶¶ 100, 101.

25. Ground for Challenge 25 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Hobbs

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple II combined with Hobbs under 35 U.S.C. § 103. The disclosure of Stemple II is shown above in Claim Chart 4, and the disclosure of Hobbs discussed above in Section IV.22. Both Stemple II and Hobbs relate to polymerase mediated sequencing methods, and it would be obvious to modify the sequencing method of

Stemple II to include the deazapurine taught by Hobbs el for the same reasons as discussed above in Section IV.22. See Weinstock Decl. ¶¶ 102, 103.

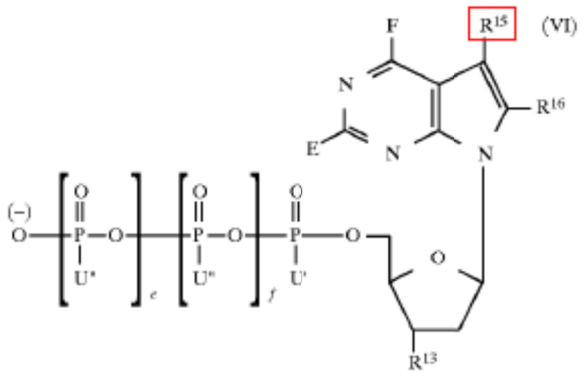
26. Ground for Challenge 26 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple III and Hobbs

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple III combined with Hobbs under 35 U.S.C. § 103. The disclosure of Stemple III is shown above in Claim Chart 4, and the disclosure of Hobbs discussed above in Section IV.22. Both Stemple III and Hobbs relate to polymerase mediated sequencing methods, and it would be obvious to modify the sequencing method of Stemple III to include the deazapurine taught by Hobbs el for the same reasons as discussed above in Section IV.22. See Weinstock Decl. ¶ 104.

27. Ground for Challenge 27 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Dower and Seela II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Dower combined with Seela II under 35 U.S.C. § 103. Seela II issued December 1, 1998. Seela II qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before the '698 patent's earliest claimed filing date.

Seela II discloses multiple uses and formulations for nucleotides having a 7-deazpurine base, as shown in this annotated example:



(VI)

Seela II, col. 15, ll. 19-31. Seela II specifies that "R15 and R16 are, independently of each other … where appropriate *via a further linker*, to one or more groups which … *serve as labeling for a DNA or RNA probe* or, when the oligonucleotide analog hybridizes to the target nucleic acid, attack the latter while binding, crosslinking or cleaving." Id., col. 15, ll. 41-67. Seela II states that the prior art "EP 251 786 *discloses 7-deazapurine nucleotides* … which possess an alkynylamino group at the 7-purine position. The alkynylamino group serves as a *linker by way of which fluorescent labeling molecules can be coupled to the nucleotide*." Seela II, col. 15, ll. 6-11.

Seela II discloses that:

"[t]he use of the novel 7-deazapurine nucleotides for sequencing nucleic acids is advantageous for several reasons. Thus, the band compression which can often be observed in GC-rich nucleotide regions in the Sanger sequencing method (dideoxy technique), and which hinders correct determination of the nucleotide sequence, is either eliminated or at least reduced. In addition, the double stranded

nucleic acids which are synthesized by DNA polymerases or RNA polymerases during the sequencing are stabilized by the incorporation of 7-, 8- or 7,8-substituted 7-deazapurine bases. It is consequently more advantageous to use substituted 7-deazapurine nucleotides than to use unsubstituted 7-deazaguanosine nucleotides, which are customarily employed in nucleic acid sequencing in order to eliminate band compressions in GC-rich DNA stretches (EP 65 212536). A further advantage of using substituted 7-deazapurine nucleotides in the sequencing is that fluorescent residues in the form of reporter groups … can be introduced onto the substituents in a series of subsequent reactions. In addition, the incorporation of self-fluorescent, substituted 7-deazapurine bases into oligonucleotides renders it possible to detect the latter directly by way of the self-fluorescence of the substituted 7-deazapurine bases." Seela II, col. 16, l. 50 - col. 17, l. 8.

Thus, it would have been obvious for one of ordinary skill in the art to modify the polymerase-mediated DNA sequencing method of Dower to utilize the "novel 7-deazapurine nucleotides" disclosed in Seela II 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 Seela II. Furthermore, it would have been obvious to use the features taught by Seela II for their intended purpose, as disclosed by Seela II, to enhance the capability of the Dower systems and methods in the same way they enhance the capability of the

Seela II methods and reagents. Additionally, it would have been obvious to combine Dower and Seela II because the combination of known features with known systems and methods merely produces a predictable result. See Weinstock Decl. ¶¶ 105, 106. Further, combining references teaching sequencing by synthesis methods with references teaching the use of deaza-substituted nucleotide analogues was well known in the art and provided well known advantages. See Section III.2.

28. Ground for Challenge 28 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Tsien and Seela II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Tsien combined with Seela II under 35 U.S.C. § 103. The disclosure of Tsien is shown above in Claim Chart 1, and the disclosure of Seela II is shown above in Section IV.27. Both Tsien and Seela II relate to polymerase-mediated DNA sequencing methods, and it would be obvious to modify the sequencing method of Tsien to include the deazapurine taught by Seela II for the same reasons as discussed above in Section IV.27. See Weinstock Decl. ¶¶ 107, 108.

29. Ground for Challenge 29 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Rabani and Seela II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Rabani combined with Seela II under 35 U.S.C. § 103. The disclosure of Rabani is shown above in Claim Chart 3, and the disclosure of Seela II is shown above in Section IV.27. Both Rabani and Seela II relate to polymerase mediated

DNA sequencing methods, and it would be obvious to modify the method of Rabani to include the deazapurine taught by Seela II for the same reasons as discussed above in Section IV.27. See Weinstock Decl. ¶¶ 109, 110.

30. Ground for Challenge 30 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple II and Seela II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple II combined with Seela II under 35 U.S.C. § 103. The disclosure of Stemple II is shown above in Claim Chart 4, and the disclosure of Seela II is shown above in Section IV.27. Both Stemple II and Seela II relate to polymerase mediated DNA sequencing methods, and it would be obvious to modify the sequencing method of Stemple II to include the deazapurine taught by Seela II for the same reasons as discussed above in Section IV.27. See Weinstock Decl. ¶¶ 111, 112.

31. Ground for Challenge 31 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Stemple III and Seela II

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Stemple III combined with Seela II under 35 U.S.C. § 103. The disclosure of Stemple III is shown above in Claim Chart 4, and the disclosure of Seela II is discussed above in Section IV.27. Both Stemple III and Seela II relate to polymerase mediated DNA sequencing methods, and it would be obvious to modify the sequencing method of Stemple III to include the deazapurine taught by

Seela II for the same reasons as discussed above in Section IV.27. See Weinstock Decl. ¶ 113.

32. Ground for Challenge 32 - Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are invalid as obvious in view of Rosenthal and Tsien

Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are also obvious in view of Rosenthal combined with Tsien under 35 U.S.C. § 103. Rosenthal published October 28, 1993 and, therefore, qualifies as prior art against the '698 patent under 35 U.S.C. § 102(b) because it was patented more than one year before the '698 patent's earliest claimed filing date.

The disclosure of Tsien is shown above in Claim Chart 1. Rosenthal teaches "a method for sequencing DNA" in which "[t]he primer is extended by a DNA polymerase in the presence of a single labeled nucleotide, either A, C, G or T." Rosenthal, page 1, ll. 1-2, page 9, ll. 5-6. Rosenthal teaches a "sequencing method which allows the rapid, unambiguous sequencing of DNA at low cost. The requirements for such a system are that … it should allow several DNA clones to be processed in parallel." Rosenthal, page 6, ll. 15-26. Rosenthal states "[p]referably, the template is bound to a solid-phase support" Rosenthal, page 8, ll. 31-32. Rosenthal teaches a method in which 3'-OH blocked and fluorescent labeled dNTPs include a blocking group on "the 3' moiety of the deoxyribose group of the labeled nucleotide may be used to prevent nonspecific incorporation." Rosenthal, page 11, ll. 3-12.

Rosenthal specifically teaches a sequencing by synthesis method and system identified as "scheme 5" that utilizes 3'-OH blocked and labeled nucleotides and expressly identifies that "scheme 5" may be implemented in a "chip array" format. See Rosenthal, page 20, ll. 6 - page 22, ll. 21. Combined, Rosenthal and Tsien disclose, teach or suggest all of the elements of claims 1-7, 11-12, 14-15 and 17 of the '698 patent. It would be obvious to modify the sequencing system of Rosenthal based on various teachings of Tsien (e.g., to include deazapurine-based dNTPs, dNTPs having a label attached to directly to the nucleotide base, etc.) at least to improve the system and methods of Rosenthal in the same way as they improve the systems and methods of Tsien. See Weinstock Decl. ¶¶ 114, 115.

V. 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 1-7, 11-12, 14-15 and 17 of the '698 patent are as required by as required by 35 U.S.C. § 314(a). At least Claims 1-7, 11-12, 14-15 and 17 of the '698 patent are not patentable over the prior art documents cited herein. 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 '698 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.:	7,713,698
Issue Date:	May 11, 2010
IPR Proceeding No.:	To be determined
IPR Proceeding Filing Date	September 16, 2012
Attorney Docket No.:	048522-0027-698
Customer No.:	22922

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Alexandria, VA 22313-1450

CERTIFICATE OF SERVICE

Copies of the following were sent by United States Postal Service Express Mail® this 16th day of September 2012 to Cooper and Dunham, LLP, 30 Rockefeller Plaza, 20th Floor, New York, NY 10112:

1. Motion to Waive Petition Page Limit Under 37 C.F.R. §42.24(a)(2); and

2. Version of Petition for *Inter Partes* Review of U.S. Patent No. 7,713,698 exceeding 60 page limit.

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.:	7,713,698
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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
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