

Filed on behalf of: COLUMBIA

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.
Petitioner,
v.
Patent of THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF
NEW YORK
Patent Owner.

Case IPR2012-00006
U.S. Patent 7,713,698

DECLARATION OF GEORGE L. TRAINOR, PH.D.

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A. INTRODUCTION AND QUALIFICATIONS

1. I have been retained on behalf of The Trustees of Columbia University in the City of New York (“Columbia”) in connection with the challenges by Illumina, Inc. to certain claims of U.S. Patent No. 7,713,698 (the “‘698 Patent”). I am informed and understand the U.S. Patent and Trademark Office Patent Trial and Appeal Board has authorized *inter partes* review of the ‘698 Patent based on the following patentability challenges:

- I. Claims 1-7, 11, 12, 14, 15 and 17 under 35 U.S.C. §103(a) as obvious in view of Tsien et al., PCT Publication WO 91/06678 (Exhibit 1002) (“Tsien”) and Prober et al., *Science* 238, 336-341 (1987) (Exhibit 1003) (“Prober I”);
- II. Claims 5 and 12 under 35 U.S.C. §103(a) as obvious in view of Tsien, Prober I, and Rabani PCT Publication WO 96/27025 (Exhibit 1006) (“Rabani”);
- III. Claims 1-7, 11, 12, 14, 15 and 17 under 35 U.S.C. §103(a) as obvious in view of Tsien and Seela et al. U.S. Patent No. 4,804,748 (Exhibit 1014) (“Seela I”); and

IV. Claims 1-7, 11, 12, 14, 15 and 17 under 35 U.S.C. §102(b) as anticipated by Dower et al., U.S. Patent No. 5,547,839 (Exhibit 1005) (“Dower”).

2. I am being compensated for my time consulting in this matter at the rate of \$450 per hour. I have no financial interest in the outcome of this proceeding and my compensation is in no way contingent upon my opinions or the outcome of the proceeding.
3. I received a Bachelor of Science degree from Stevens Institute of Technology in 1974, a Master of Arts degree and a Doctorate in Organic Chemistry from Harvard University in 1979 and was a NIH Postdoctoral Fellow in the Department of Chemistry of Columbia University from 1979-1981.
4. I am the founder and partner of Trainor Consulting LLC, which provides consulting services for pharmaceutical discovery and development.
5. I have attached to this Declaration as Appendix A a copy of my *curriculum vitae* including a list of all publications on which I am listed as an author. I am also listed as an inventor on 18 issued U.S. patents.

6. Between 1981 and 1991 I was employed by E.I. du Pont de Nemours and Company, Inc., Wilmington, Delaware, and related companies (“DuPont”) working on various projects relating to the design, synthesis and commercial development of novel compounds including the development of novel nucleotide analogues incorporating novel fluorescent labels and linkers for use as irreversible chain terminators in Sanger “dideoxy” DNA sequencing methods. These novel nucleotide analogues include the fluorescently labeled dideoxynucleotide analogues described in Prober I on which I am an author. During my tenure at DuPont I received several promotions, ultimately rising to the position of an Associate Director.
7. My research at DuPont focused on the field of DNA sequencing. During my time at DuPont, I co-invented the Genesis 2000™ DNA Sequencing System. I am also the lead researcher in the invention of fluorescently-labeled, chain terminating nucleotides for automated DNA sequencing, for which I received the American Chemical Society Heroes of Chemistry Award in 2011.
8. In 1991 DuPont I was transferred to a joint venture with Merck called DuPont Merck Pharmaceutical Company (“DuPont Merck Pharmaceutical”) later DuPont Pharmaceuticals, Company. After the

joint venture was formed my responsibilities expanded to include executive roles in managing research in several areas including nucleic acids, cancer, and medicinal chemistry.

9. During my tenure at DuPont, DuPont Merck Pharmaceutical and DuPont Pharmaceutical Company, I closely followed developments relating to DNA sequencing including the development of sequencing by synthesis methods while also working on the development of new chemical compounds for use as pharmaceuticals, including nucleotide analogues useful as inhibitors of viral reverse transcriptases such as human immunodeficiency virus-1 (HIV-1) reverse transcriptase and nucleoside analogues for use as antisense therapeutics.
10. In 2002 I joined Bristol-Myers Squibb Co as Executive Director of Oncology and Early Discovery Chemistry. (Appendix A (CV), page 2.) In 2008, I was promoted to Vice President of Oncology and Early Discovery Chemistry, a position I held until I left Bristol-Myers Squibb in 2010. (Appendix A (CV), page 1, l. 17.)
11. I served as an Editor of the scientific journal Annual Reports of Medicinal Chemistry from 1996 to 2002. (Appendix A (CV), page 2.)

12. Throughout my scientific career I have frequently been an invited lecturer for many different academic and industry groups. (Appendix A (CV), pages 3, 4, 17, 19, 21.)
13. I have also been invited to serve on several Study Sections as a Grant Reviewer assessing applications for funding on behalf of the Department of Energy, The National Institutes of Health, the Office of Technology Assessment. Many of these grant applications related to the field of DNA sequencing.
14. I have also organized a number of scientific conferences including the Gordon Research Conference on Bioorganic Chemistry; and the American Chemical Society's Middle Atlantic Regional Conference (MARM) between 1991 and 2000. I was also on the Pacificchem Organizing Committee from 1996-2005. Various aspects of nucleotide chemistry were discussed at these conferences.

B. DOCUMENTS REVIEWED

15. In connection with the preparation of this Declaration I have read the following documents:
 - a. U.S. Patent No. 7,713,698 (Exhibit 1001)
 - b. The documents referenced in ¶1 as the basis for challenges I-IV (PCT Publication WO 91/06678 to Tsien et al. ("Tsien"))

(Exhibit 1002); Prober et al., *Science* 238, 336-341 (1987) (“Prober I”) (Exhibit 1003); PCT Publication WO 96/27025 to Rabani (“Rabani”) (Exhibit 1006); U.S. Patent No. 4,804,748 to Seela et al. (“Seela I”) (Exhibit 1014); U.S. Patent No. 5,547,839 to Dower et al. (“Dower”) (Exhibit 1005))

- c. The Petition for *Inter Partes* Review of U.S. Pat. No. 7,713,698 (Paper 3) (“the ‘698 Petition”) filed by Illumina
- d. The Declaration of George Weinstock Under Rule 37 C.F.R. §1.132 [*sic*] (Exhibit 1021)
- e. The Decision on Petition for Inter Partes Review Under 35 U.S.C. §311 (Paper 28) (“Decision”)
- f. The Decision on Request for Rehearing Under 35 U.S.C. §41.71(c) of Decision to Institute *Inter Partes* Review & Scheduling Order (Paper 43) (“Decision on Rehearing”)
- g. The transcript of the deposition of George Weinstock on June 8, 9 and 10, 2013. (Exhibit 1034) (I also attended this deposition)
- h. The Decision on Petition for Inter Partes Review Under 35 U.S.C. §311 in IPR2012-00007 (Paper 38)

- i. The Decision on Request for Rehearing Under 35 U.S.C. §41.71(c) of Decision to Institute *Inter Partes* Review & Scheduling Order in IPR2012-00007 (Paper 54)
- j. Maxam and Gilbert (1977) *A new method for sequencing DNA*, Proc. Natl. Acad. Sci. USA. 74:560-564 (Exhibit 2024)
- k. Sanger et. al. (1977) *DNA sequencing with chain-terminating inhibitors*, Proc. Natl. Acad. Sci. USA. 74:5463-5467 (Exhibit 2025)
- l. Metzker et al. (1994) *Termination of DNA synthesis by novel 3'-modified-deoxyribonucleoside 5'-triphosphates*. Nucleic Acids Res. 22: 4259-4267 (Exhibit 2015)
- m. PCT Publication WO 93/21340 to Rosenthal et al. ("Rosenthal") (Exhibit 1020)
- n. Pennisi (2000) *DOE Team Sequences Three Chromosomes*, Science. 288:417-419 (Exhibit 2026)
- o. Welch and Burgess (1999) *Synthesis of Fluorescent, Photolabile 3'-O-Protected Nucleoside Triphosphates for the Base Addition Sequencing Scheme*, Nucleosides & Nucleotides.18:197-201 (Exhibit 2027)

- p. Hyman (1998) *A New Method of Sequencing DNA*, Analytical Biochemistry 174:423-436 (Exhibit 2028)
- q. U.S. Pat. No. 6,255,083 to Williams (“J. Williams”) (Exhibit 1018)
- r. U.S. Pat. No. 5,302,509 (filed Feb. 27, 1991) (Exhibit 2029)
- s. Canard and Sarfati (1994) *DNA polymerase fluorescent substrates with reversible 3’-tags*, Gene. 1481-6 (Exhibit 2030)
- t. U.S. Pat. No. 8,399,188 (filed Sept. 4, 2007) (Exhibit 2031)
- u. U.S. Patent No. 7,270,951 to Stemple et al. (“Stemple III”) (Exhibit 1008)
- v. English translation of PCT Publication WO 98/33939 to Anazawa et al. (“Anazawa”) (Exhibit 1011)
- w. U.S. Pat. No. 8,088,575 (filed July 19, 2010) (Exhibit 2010)
- x. U.S. Pat. No. 7,790,869 (filed June 5, 2007) (Exhibit 2012)
- y. Sarfati et al. (1987) *Synthesis of Fluorescent or Biotinylated Nucleoside Compounds*, Tetrahedron Letters. 43:3491-3497 (Exhibit 2032)
- z. U.S. Patent No. 4,772,691 (filed June 5, 1985) (“Herman”) (Exhibit 1029)

- aa. Rosenblum et al. (1997) *New Dye-Labeled Terminators for Improved DNA Sequencing Patters*, Nucleic Acids Research, 25:4500-4504 (“Rosenblum”) (Exhibit 1030)
- bb. PCT Publication WO 99/49082 to Short (“Short”) (Exhibit 1031)
- cc. U.S. Patent No. 5,449,767 (filed May 20, 1992) (“Ward”) (Exhibit 1032)
- dd. U.S. Patent No. 5,948,648 (filed May 29, 1998) (“Khan”) (Exhibit 1033)

C. SCOPE OF TESTIMONY

- 16. I understand that this proceeding concerns Columbia University’s patents relating to novel nucleotide analogues for use in DNA sequencing.
- 17. I have been asked to provide opinions on the following general topics:
 - a. The subject matter at issue in the ‘698 Patent as well as in the (‘869 and ‘575) Patents, and the state of the art as of October 6, 2000;
 - b. The qualifications of a person of ordinary skill in the art on October 6, 2000;

- c. The disclosures of the references asserted by Illumina against the '698 Patent in its Petition for *Inter Partes* Review;
- d. The Declaration of Dr. George M. Weinstock submitted in support of Illumina's Petition for Inter Partes Review;
- e. The deposition testimony of Dr. George M. Weinstock given on June 8-10, 2013 during a deposition which I attended.

D. THE STATE OF THE ART AS OF OCTOBER 6, 2000

18. In the 1970s two methods of DNA sequencing were described, a method based on degrading the DNA being sequenced into smaller fragments (Exhibit 2024, Maxam and Gilbert (1977)) and a method based on the terminating irreversible addition of a dideoxynucleotide analogue (ddNTP) by a polymerase to a primer strand hybridized to the DNA being sequenced (Exhibit 2025, Sanger (1977).)

1. The Sanger "Dideoxy" Sequencing Method

19. Of these two methods the Sanger dideoxy method (i.e. the irreversible terminator method) was more widely used. However, this method as originally described had major drawbacks. It was time consuming and labor intensive; was performed using four separate reactions, each reaction involving one dideoxynucleotide (ddNTP) and four deoxynucleotides (dNTPs); and required separation of the resulting

fragments (primer extension products) by electrophoresis, originally gel electrophoresis and subsequently capillary electrophoresis. (*See* Exhibit 1003, Prober I (1987), page 336; Exhibit 1001, Ju '698 Patent, col.1, l. 57 - col. 2, l. 3; Exhibit 2015, Metzker (1994), page 4259; Exhibit 1020, Rosenthal (1993), pages 1-6; Exhibit 1014, Seela I, col. 1, ll. 35-68.) Between the 1970s and the 2000s the Sanger dideoxy sequencing method was the mainstay of DNA sequencing despite its limitations. (Exhibit 1034, Weinstock Dep., 213:6-24).

20. During this period of time improvements in the Sanger dideoxy method were made including replacing the radioactively labeled nucleotides and associated autoradiographic analysis originally used with fluorescently labeled ddNTPs including dideoxy deazapurines. (*See e.g.* Exhibit 1003, Prober I (1987), page 337.)
21. Within these ddNTPs the fluorescent labels were attached to the deazapurine via linkers. Since these labeled ddNTPs, once incorporated by a polymerase onto the 3' end of the primer, had to remain intact to permit subsequent electrophoretic analysis of the resulting fragments, the linkers needed to be highly stable and not cleavable. Also, the presence of the dideoxy sugar portion in these ddNTPs was required to make them irreversible, permanent chain

terminators which did not have a reactive 3'OH group on the sugar. Thus, these ddNTPs irreversibly terminated extension of the primer after the addition of one nucleotide. They were not incorporated onto a growing primer extension strand.

22. Another improvement in the Sanger dideoxy sequencing method involved the replacement of the unlabeled, deoxyguanosine triphosphate with an unlabeled deoxy deazaguanosine triphosphate (deoxy deaza GTP) in the reaction mixtures with the labeled ddNTPs. (*See* Exhibit 1014, Seela I, col. 4, ll. 7-12.) The use of such an unlabeled, deoxy deaza GTP in the Sanger dideoxy method overcame problems associated with the sequencing of cytosine rich DNAs, particularly the electrophoretic separation of resulting synthesized complementary guanosine rich fragments by reducing guanosine aggregation and base stacking (Exhibit 1014, Seela I, col. 4, ll. 25-33; Exhibit 1034, Weinstock Dep., 124:23-125:14, 149:12-25.) This resulted in all of the “Gs” in the primer extension strand being deazaguanosine except for a non-deaza ddGTP which ended up at the end of the strand. Dr. Weinstock also testified that the G:C rich sequencing problems were overcome by placing a label on a non deaza-substituted nucleotide and that the addition of a label had a

much greater effect than change to a deaza-substituted base. (Exhibit 1034, Weinstock Dep., 150:25-151:25.)

23. Yet another improvement in the Sanger dideoxy sequencing method was the use of capillary electrophoresis which as of October 2000 was the state of the art technology used for the Human Genome Project (Exhibit 2026, Pennisi (2000), page 419; Exhibit 1001, Ju '698 Patent, col. 1, ll. 48-53.) Illumina's expert, Dr. Weinstock, agreed. (Weinstock Dep., 30:16-31:5, 32:7-13.)

2. Sequencing By Synthesis (SBS)

24. Despite the improvements made in the Sanger dideoxy sequencing method between the 1970s and 2000 the requirement to use electrophoresis was still a "bottleneck." (*See* Exhibit 1001, Ju '698 Patent, col. 2, ll. 3-5; Exhibit 2027, Welch and Burgess (1999), page 197.) Dr. Weinstock in commenting on Dr. Ju's statement, agreed it was "a" bottleneck. (Exhibit 1034, Weinstock Dep., 205:2–206:27.) Dr. Burgess, a chemist and colleague of Dr. Weinstock with whom he would have consulted concerning matters involving chemistry, also identified this as a bottleneck in Welch and Burgess. (Exhibit 2027, Welch and Burgess (1999), page 197; Exhibit 1034, Weinstock Dep., 483:14-19.) To address this "bottleneck" and sequence DNA without

the use of electrophoresis, methods for sequencing DNA by synthesis were conceived. Such methods did not use irreversible, labeled dideoxy nucleotide analogues since these were irreversible chain terminators but rather reversible chain terminators were needed. (The one qualification to this statement relates to the hybrid Sanger SBS method described by Dower in column 25 at lines 41-64 (Exhibit 1005), alternative (c) in Step 4, in which four labeled chain terminating dideoxynucleotides are used in concert with four unlabeled deoxynucleotides.)

25. One such method detects the release of pyrophosphate (PPi) during the DNA polymerase reaction (Pyrosequencing). (*See* Exhibit 1001, Ju '698 Patent, col. 2, ll. 18-32; Exhibit 2028, Hyman (1988), pages 423-424; Exhibit 1018, J. Williams (1999), col. 1, ll. 19-24.) Although this method resulted in improved throughput, sequencing of multiple different DNA templates in parallel was limited. (Exhibit 1001, Ju '698 Patent, col. 2, ll. 28-33.)
26. Another method for sequencing by synthesis involved nucleotide analogues that reversibly terminated polymerase-directed DNA sequencing and included distinctly labeled, particularly photocleavably labeled, removable blocking groups attached to the 3'-

OH group of the sugar portion of a deoxynucleotide analogue. This approach is also referred to as the Base Addition Sequencing Scheme (BASS). (See Exhibit 1001, Ju, '698 Patent, col. 2, ll. 33-39; Exhibit 2027, Welch and Burgess (1999), page 197; Exhibit 2015, Metzker (1994), page 4259.) Burgess is a coauthor with Metzker and Richard Gibbs on Metzker (1994) and each of Burgess, Metzker and Gibbs were colleagues of Dr. Weinstock with whom he indicated he would confer concerning questions relating to the design and synthesis of nucleotide analogues. (Exhibit 1034, Weinstock Dep., 15:9-13, 483:6-18, 487:12-20.)

27. Notably, both Metzker (1994) (Exhibit 2015, page 4259) and Welch and Burgess (1999) (Exhibit 2027, page 197), when referring to others that had independently conceived of BASS, list Tsien (1991) (Exhibit 1002); Cheeseman (1994) (Exhibit 2029); and Rosenthal (1993) (Exhibit No. 1020). In addition, Welch lists Canard and Sarfati (Exhibit 2030). All of these methods involve 3'-OH removably capped and labeled nucleotide analogues.
28. Tsien (Exhibit 1002) referred to both by Metzker (1994) (Exhibit 2015, page 4259, n. 15) and by Welch and Burgess (1999) (Exhibit 2027, page 197, n. 2) presents a scheme for sequencing by synthesis

in which he indicates that nucleotide analogues with removable 3'-OH capping groups that include a label are preferred. (Exhibit 1002, page 14, ll. 19-20; Exhibit 1034, Weinstock Dep., 187:17-188:5, 189:7-19.) Tsien also mentions as an alternative, nucleotide analogues which include a label attached to the base (Exhibit 1002, page 28, ll. 5-6) and the possibility of the label being attached to the nucleotide analogue by means of a cleavable tether (Exhibit 1002, page 28, ll. 19-21.) However, Tsien does not describe any base-labeled nucleotide analogue which has the following features in combination: (1) include a deazabase (deazapurine); (2) include a removable 3'-OH capping group; (3) are uniquely labeled; (4) are used as one of four uniquely labeled nucleotide analogues; and (5) are incorporated into a nucleic acid primer extension strand. (Exhibit 1002; Weinstock Dep., 189:20-24, 190:18-21, 193:6-194:3, 194:21-195:8, 271:9-273:11, 287:1-14.)

29. Dower (Exhibit No. 1005) describes four alternative nucleotide analogues ("chain terminators") for use in carrying out sequencing by synthesis, alternatives (a)-(d), at col. 25, l. 25- col. 26, l. 12. Alternative (a) involves 3'-OH labeled BASS-type nucleotide analogues. Alternative (b) involves a nucleotide analogue labeled at a position other than the 3'-OH position. Alternative (c) involves a

hybrid dideoxy Sanger/SBS system using eight nucleotide analogues, a first set of four base-labeled, dideoxy nucleotide analogues as irreversible chain terminators such as the ddNTP described in Prober I (Exhibit 1003) and a second set of four unlabeled deoxynucleotides (dNTPs) with the 3'-OH of the sugar reversibly capped. See also ¶60 below. Alternative (d) involves all four nucleotide analogues labeled with one, non-unique label, with the nucleotide analogues being added sequentially. Dower does not describe any nucleotide analogue which has the following features in combination: (1) includes a deazapurine base; (2) includes a removable 3'-OH capping moiety; and (3) is incorporated into a nucleic acid primer extension strand. (Exhibit 1034, Weinstock Dep., 264:13-267:13, 268:2-9, 277:20-279:5.) In addition, Dower does not describe a label attached to a deazapurine base via a cleavable linker. (Exhibit 1034, Weinstock Dep., 157:19-158:12.)

30. In 1994 Metzker stated “[c]ompared with Sanger sequencing, BASS has two major advantages: base resolution would not require gel electrophoresis and there is a tremendous capacity for simultaneous analyses of multiple samples. The complete scheme demands nucleotide analogs that are tolerated by polymerases,

spectroscopically distinct for each base, stable during the polymerization phase, and deprotected efficiently under mild conditions in aqueous solution. These stringent requirements are formidable obstacles for the design and synthesis of the requisite analogs.” (Exhibit 2015, Metzker (1994), page 4259 (emphasis added).) During his deposition Dr. Weinstock indicated that he agreed with this statement, suggested unnamed companies were working on solutions to these problems, and indicated he did not think that these problems were solved until the mid-2000s, i.e. after the October 6, 2000 filing date of the ‘698 Patent. (Exhibit 1034, Weinstock Dep., 475:24- 477:19).

31. In 1999 Welch and Burgess indicated, “[a] major challenge in development of BASS, however, is that the 3’-blocking group must be removed in an aqueous medium using reagents/conditions that do not denature or modify double strand DNA.” (Exhibit 2027, Welch and Burgess (1999), pages 197-198.) Then, on page 200 Welch concludes, “[p]reliminary tests of compounds 1a and 1b as substrates for polymerases... did not show evidence for incorporation. Further experiments are in progress, including modeling studies... The latter

experiments should highlight bad interactions that must be avoided to advance this work further.” (*Id.* at 200.)

32. Stemple III (Exhibit 1008) provides a depiction of a nucleotide analogue which includes a label which is photolabile (cleavable by light) as part of a removable capping group on the 3'-OH of the sugar. (Exhibit 1008, FIG. 1A, FIG. 1C, col. 10, ll. 36-44.) Stemple III further indicates in a single paragraph in column 22 that if the 3'-OH labeled and capped nucleotide analogue described by him cannot be incorporated by a polymerase, an alternative might be to try a nucleotide analogue which includes a photolabile label attached to the base referring to Anazawa and Metzker. (Exhibit 1008, col. 22, ll. 53-67.)
33. Anazawa purports to describe the synthesis of nucleotide analogues which include photolabile labels attached to a deazapurine base for use in sequencing by synthesis. (Exhibit 1011, page 5, l. 36- page 6, l. 9, Fig. 7.) Anazawa further indicates that these nucleotide analogues (1) are based on using the base-labeled dideoxy nucleotides of Prober I and (2) do not include, or need to include, a removable 3'-OH capping moiety to function as terminators of chain elongation. (Exhibit 1011, Anazawa, page 6, ll. 16-21, 30-33.)

34. Based on my review of the documents referred to above, as of October 6, 2000, there was no description in the art of any of the following:

- a. a nucleotide analogue which had the following features in combination: (1) includes a deazabase to which a removable label is attached by a cleavable linker which is not a photolabile linker; (2) includes a removable 3'-OH chemical capping group; and (3) is capable of being incorporated into a nucleic acid primer extension strand by a polymerase;
- b. a method involving use of four uniquely labeled nucleotide analogues, at least one of which had the following features in combination (1) includes a deaza-substituted base to which a label is attached, particularly via a cleavable linker; (2) includes a removable chemical moiety capping the 3'-OH of the sugar; and (3) is incorporated into a nucleic acid primer extension strand;
- c. a solid surface on which multiple different templates were immobilized, in which a nucleic acid primer is hybridized to each different template and a nucleotide analogue which has the following features in combination (1) is incorporated into a

primer extension strand; (2) includes a deazabase to which a label is attached; and (3) includes a removable chemical moiety capping the 3'-OH of the sugar.

35. Therefore, as of October 6, 2000 there was a need for new labeled nucleotide analogues for use in sequencing DNA that could be incorporated by a polymerase into the end of a primer extension strand.
36. The first stage in the effort to address this need would be to design and synthesize novel labeled nucleotide analogues that could be incorporated by a polymerase onto the end of a primer extension strand and that could be detected when incorporated.
37. Once novel nucleotide analogues had been designed and synthesized and shown to be incorporated, the next stage of development would be to determine whether such nucleotide analogues could be repeatedly incorporated and detected in sequencing DNA.
38. The claims of the patent at issue in this proceeding concern the first stage in this effort, the design and synthesis of novel nucleotide analogues that could be incorporated into a primer extension strand by a polymerase and be detected when incorporated.

39. The challenges confronted in this effort are underscored in a patent application filed in 2006 by Illumina which became U.S. Patent No. 8,399,188 (Exhibit 2031). This Illumina patent filed years after October 6, 2000 describes the formidable obstacles associated with the design and synthesis of nucleotide analogues for use in SBS stating, “[o]ne of the key challenges of sequencing by synthesis (SBS) is to identify a set of modified nucleotides (dATP, dGTP, dTTP, dCTP) as reversible terminators, which can be incorporated by polymerases efficiently and the blocking group removed readily after incorporation.” (Exhibit 2031, col. 3, ll. 32-36.)

E. THE RELEVANT ART AND THE PERSON OF ORDINARY SKILL IN THE ART

40. I have studied the ‘698 Patent at issue in this proceeding as well as the ‘575 and ‘869 Patents at issue in the related proceedings. Based on my study of the patents, the claims relate to novel nucleotide analogues and methods involving detection of these novel nucleotide analogues to identify which nucleotide analogue is incorporated by a polymerase.
41. Based on my experience in, and knowledge of, the field of nucleotide analogues for use in DNA sequencing, the relevant art concerns the

design and synthesis of nucleotide analogues that can be incorporated by a polymerase for use in DNA sequencing.

42. I understand that the claims of the patent at issue must be assessed from the perspective of a hypothetical person of ordinary skill in the relevant art as of the date the invention described in the claims was made. For purposes of this Declaration I have been asked to assume the invention was made by October 6, 2000, when the first application which led to the patent was filed. I further understand this hypothetical person of ordinary skill has knowledge of the relevant art, as described in published and issued patents and in scientific publications and possesses ordinary creativity and a basic skill set. A person of ordinary skill in the art is not an expert in the relevant art.
43. Based on my experience in the field I think the person of ordinary skill in the art relating to the design and synthesis of nucleotide analogues for use in DNA sequencing would have a graduate degree in chemistry or chemical biology or a related discipline. I also think the person of ordinary skill would have knowledge of synthetic nucleotide chemistry and DNA sequencing methods, including the underlying biological principles and several years experience in the design, synthesis and characterization of nucleotide analogues. The

graduate students who worked with the inventor, Dr. Ju, would be examples of persons of ordinary skill and the principal investigator and first named inventor is Dr. Jingyue Ju, a professor in the Department of Chemical Engineering at Columbia University, had such training but far greater experience and expertise.

44. Unless indicated otherwise, the opinions I express in this declaration reflect my understanding of what a person of ordinary skill in the art would have known and would have thought as of October 6, 2000.
45. I note that my opinion of the person of ordinary skill in the relevant art differs from the opinion of Dr. Weinstock in at least the following respects:
 - a. Dr. Weinstock does not think the person of ordinary skill needs to have training and knowledge in synthetic nucleotide chemistry (Exhibit 1034, Weinstock Dep., 21:3-22:19, 111:6-113:19, 114:9-21) and he lacks such training and knowledge (Exhibit 1034, Weinstock Dep., 13:1-13, 26:16-24, 34:19-35:4, 36:7-18, 113:20-114:7.)
 - b. Dr. Weinstock thinks the person of ordinary skill would consult with colleagues knowledgeable concerning issues involving synthetic nucleotide chemistry but he did not do so in

connection with preparing his Declaration. (Exhibit 1034, Weinstock Dep., 113:20-114:7, 162:1-5.)

- c. In my view Dr. Weinstock repeatedly gives opinions from his perspective as an expert and not from the perspective of a person of ordinary skill in the art. (*E.g.*, Exhibit 1021, ¶¶ 67, 70, 80, 81; Exhibit 1034, Weinstock Dep., 307:17-308:6.)

46. Furthermore I note that Dr. Weinstock repeatedly expresses legal conclusions concerning what is “anticipated” and what is or would have been “obvious” but admits he is not familiar with the underlying legal principles and not qualified to give such opinions. (Exhibit 1021, ¶¶ 116, 70, 71, 73, 79, 81, 83, 85, 88, 90, 92, 94, 97, 99, 101, 103, 106, 108, 110, 112.)

F. THE INVENTION CLAIMED IN THE ‘698 PATENT

47. I have been advised that the claims of the ‘698 Patent being challenged in this IPR are being amended to read as set forth in substitute claims 18-29 attached hereto as Appendix B.
48. Based on my review and study of the ‘698 Patent I understand the claimed invention to be (A) a method for identifying an incorporated nucleotide analogue employing a novel nucleotide analogue combining all the features described in substitute claims 18-27; and

(B) a plurality of different nucleic acid templates attached to a solid surface to which a primer extension strand is attached into the end of which such novel nucleotide analogues are incorporated as described in substitute claims 28-29.

**G. CHALLENGE IV: CLAIMS 1-7, 11, 12, 14, 15 AND 17 UNDER
35 U.S.C. §102(b) AS ANTICIPATED BY DOWER**

1. Claim 15 (Proposed Substituted Claim 18)

49. Proposed substitute claim 18¹ is directed to a method for identifying the identify of an incorporated nucleotide analogue which uses four uniquely labeled nucleotide analogues, wherein at least one nucleotide analogue combines all of the following features: (1) includes a deaza-substituted base labeled with a unique label attached via a cleavable linker; (2) includes a removable chemical moiety capping the 3'-OH

¹ Substitute claims 19-24, 27-29 depend from substitute claim 18, and I understand that these claims add additional features and therefore Dower cannot describe every feature in claims 19-24, 27-29 if Dower does not describe all the features in substitute claim 18.

group of the sugar; and (3) is incorporated into a nucleic acid primer extension strand.

a. No disclosure In Dower Of A Cleavable Linker

50. Even if one of ordinary skill assumed that Dower incorporated by reference a disclosure of a nucleotide analogue which includes a deazabase from Prober I, one of ordinary skill would still not have understood Dower to describe a nucleotide analogue which has feature (a), i.e. includes a deaza-substituted base labeled with a unique label attached via a cleavable linker.
51. There is no description in Dower of a linker attaching a label to a base, and excluding Prober I there is no disclosure of a deaza-substituted base. Thus, the only possible description in Dower relating to a linker attaching a label to a deaza-substituted base is in Prober I. However, the acetylenic linker in Prober I is not cleavable. Illumina in its Petition (Paper 3 at 39) and Dr. Weinstock in his Declaration (Exhibit 1021, ¶69) did not assert that Dower discloses a

cleavable linker². In his Deposition Dr. Weinstock conceded the linker in Prober I is not cleavable. (Exhibit 1034, Weinstock Dep., 157:19-158:12.) Further, as an author of Prober I I know the linker in Prober I is not cleavable.

52. Dower does not disclose a feature of substitute claim 18 (original claim 15.) Therefore, Dower does not disclose each and every feature of substitute claim 18.

b. No Disclosure In Dower Of A Nucleotide Analogue Which Combines The Following Features: (1) Includes A Deaza-Substituted Base To Which A Unique Label Is Attached; (2) Includes A Removable Chemical Moiety Capping The 3'-OH Group Of The Sugar; And (3) Is Incorporated Into A Nucleic Acid Primer Extension Strand

53. Substitute claim 18 recites a nucleotide analogue which combines the following features: (1) includes a deaza-substituted base to which a unique label is attached; (2) includes a removable chemical moiety capping the 3'-OH group of the sugar; and (3) is incorporated into a

² In its March 12 and May 10, 2013 Decisions in related IPR2012-00007 the Board correctly found that Dower does not disclose a nucleotide analogue comprising a label attached to a deazapurine base via a cleavable linker. (Paper 38 at 14-15; Paper 54 at 9-10).

nucleic acid primer extension strand. Dower does not describe such a nucleotide analogue. I understand that the Board in its May 10, 2013 Decision found that Dower incorporated by reference Prober I for a disclosure of dNTPs and ddNTPs useful in DNA sequencing. (Paper 43 at 3-7.) I have been informed that the legal consequence of such an “incorporation by reference” would be that Dower would be considered to include any material incorporated by reference as if it were written out in Dower. I have also been advised that the question of what material is being referenced is to be assessed from the perspective of one of ordinary skill in the art.

54. In its Petition Illumina asserted that Dower at col. 23, l. 18-24, incorporated by reference Prober I for teaching the use of deaza-substituted nucleotide analogue in sequencing by synthesis. (Paper 3 at 39). Inconsistently, Illumina also cited col. 23, ll. 18-22 of Dower as being incorporated for teaching the feature “simultaneously contacting the product of step a).” (Paper 3 at 33). Dr. Weinstock referred to claim chart 2 of Illumina’s Petition in ¶69 of his Declaration but provided no reasoning why claim chart 2 was correct, only a conclusory statement that Dower includes every element of certain claims of the ‘698 Patent including claims 1 and 15.

Specifically, in his Declaration, Dr. Weinstock provided no opinion what material in Prober I a person of ordinary skill in the art would have understood to be referenced.

55. If col. 23, ll. 18-24 is assumed to be an incorporation by reference of material from Prober I, a person of ordinary skill would have understood that the material being referenced in Dower in the phrase “where each of four dNTP analogues is identified by a distinct dye” is only the description of the four distinct dyes used to label four ddNTPs. The only dNTPs described in Prober I are unlabeled nucleotides which are used with four labeled ddNTPs in a Sanger dideoxy sequencing experiment. Since there is no disclosure in Prober I of labeled dNTP analogues, one of ordinary skill would not have understood the referenced material to be dNTP analogues identified by distinct dyes, but only the four dyes used to label the ddNTPs. In his recent deposition Dr. Weinstock agreed that col. 23, ll. 18-24 references the distinct dyes in Prober I. (Exhibit 1034, Weinstock Dep., 171:19-172:1, 172:5-7).
56. In its Petition Illumina also asserted that Dower at col. 25, ll. 4-10, incorporated by reference Prober I for teaching nucleotide analogues which are deaza-substituted. (Paper 3 at 34-35). However, Illumina

provided no evidence to support this conclusion. Dr. Weinstock only referred to claim chart 2 of Illumina's Petition in ¶69 of his Declaration. He provided no reasoning why claim chart 2 was correct, only a conclusory statement that Dower includes every element of certain claims of the '698 Patent including claims 1 and 15. Specifically, in his Declaration, Dr. Weinstock provided no opinion what material in Prober I a person of ordinary skill in the art would have understood to be referenced.

57. If col. 25, ll. 4-10 is assumed to be an incorporation by reference of material in Prober I, a person of ordinary skill would have understood that the material being referenced in Dower by the phrase “[f]luorescent chain terminators (analogues of dATP, dCTP, dGTP, and TP [*sic*]... under suitable reaction conditions (time, temperature, pH, ionic species, etc. See... Prober et al.)....” is only the description of suitable reaction conditions that could be used for a polymerase to incorporate analogues of dATP, dCTP, dGTP, and TP [*sic*] with a polymerase. The only dATP, dCTP, dGTP, and dTP described in Prober I are unlabeled, nucleotide analogues. Moreover, these nucleotide analogues are not chain terminators. No fluorescently labeled chain terminating dNTPs are disclosed in Prober I. Therefore,

one of ordinary skill would have understood that the material referenced in Prober I concerns the reaction conditions for a polymerase to incorporate the fluorescent chain terminating ddNTPs. In his recent deposition Dr. Weinstock agreed that col. 25, ll. 4-10 concerns reaction conditions, not fluorescently labeled dNTP analogs. (Exhibit 1034, Weinstock Dep. 170:23-171:18, 172:8-10).

58. Neither Illumina nor Dr. Weinstock cited Dower col. 25, ll. 41-47 as a disclosure of deaza-substituted dNTPs. However, I am informed that the Trial Board determined that Dower at col. 25, ll. 41-47 refers to Prober I's disclosure of nucleotide analogues (dNTP and dideoxynucleotide triphosphates) in DNA sequencing (Paper 43 at 4) and dNTP analogues in DNA sequencing (Paper 43 at 6).
59. If col. 25, ll. 41-47 is assumed to be an incorporation by reference of some material described in Prober I, one of ordinary skill would have understood that the material being referenced only concerns the four fluorescently labeled, irreversible ddNTP chain terminators described in Prober I. Prober I does not describe use of incorporated labeled dNTP analogues in sequencing only use of unlabeled dNTPs. Therefore, one of ordinary skill would not have understood Dower to be referencing Prober I for a description of the use of labeled dNTP

analogues in DNA sequencing. A person of ordinary skill in the art would have understood Dower in col. 25, ll. 41-47 to be referencing the disclosure in Prober I of the four fluorescently labeled, irreversible ddNTP chain terminators and the four unlabeled dNTPs for use in the specific variation of SBS described by Dower at col. 25, ll. 41-64.

60. At col. 25, ll. 41-64 Dower describes an alternative (c). Alternative (c) is a hybrid variation of SBS in which some primer extension strands are irreversibly terminated by labeled ddNTP chain terminators and the remaining primer extension strands grow by addition of unlabeled dNTPs. This hybrid Sanger/SBS method neither requires nor implies the use of labeled dNTPs. This hybrid SBS method uses a first set of four labeled chain terminating nucleotide analogues (ddNTPs) and a second set of four unlabeled dNTP analogues. Dr. Weinstock testified that alternative (c) of Dower is not an example of the method recited in the claims of the '698 Patent. (Exhibit 1034, Weinstock Dep., 166:2-170:21, 172:11-15, 265:15-23). I agree.

61. Furthermore, in its Petition, Illumina misquoted col. 15, ll. 37-40 of Dower (Paper 3 at 34). Dower at col. 15, ll. 37-40 actually states “[i]n contrast to a dideoxynucleotide, typically the blocking agent will be a

reversible blocking agent thereby allowing for deblocking and subsequent elongation.”(emphasis added). Dr. Weinstock testified that Dower was drawing a contrast between a dideoxynucleotide which would be an irreversible blocking agent and a blocking agent at the 3’-hydroxyl that could be reversible. (Exhibit 1034, Weinstock Dep., 175:13-24). I agree that Dower is clearly indicating ddNTPs would not have removable 3’-OH capping groups.

62. Further, contrary to the Board’s May 10, 2013 Decision rejecting Columbia’s argument that “[t]he deaza-substituted dideoxynucleotides of Prober I do not contain a removable chemical moiety capping the 3’-OH group of the sugar as required by the claims” because Dower taught these ddNTPs “should” be blocked at the 3’-OH with removable capping moieties. (Paper 43 at 7), Dr. Weinstock testified that he is unaware of any chemistry for adding a 3’-OH to a ddNTP, let alone a 3’-OH with a removable moiety capping a 3’-OH. (Exhibit 1034, Weinstock Dep., 156:19-157:10, 462:10-463:16, 466:15-467:8). A person of ordinary skill would have understood that a ddNTP could not be modified to be a dNTP with a removable chemical cap.

63. I agree with Dr. Weinstock's testimony referred to in preceding paragraphs 55, 57, 60 and 61. A person of ordinary skill in the art would not have understood that Dower described a nucleotide analogue that had all of the features: (1) includes a deaza-substituted base labeled with a unique label; (2) includes a removable chemical moiety capping the 3'-OH of the sugar; and (3) is incorporated into a nucleic acid primer extension strand. Further, a person of ordinary skill in the art would have known of no chemistry in October 2000 for modifying the ddNTPs described in Prober I to obtain such a nucleotide analogue.
64. Thus, Dower does not describe a nucleotide analogue with all the features combined such as the nucleotide analogue described in substitute claim 18 (original claim 15 rewritten), namely a nucleotide analogue having all three features combined discussed in this Section, G(1)(b). Further, I do not find in Dower any description that suggests including some of the features of the labeled ddNTPs of Prober I with the feature of a removable 3'-OH capping group in the same nucleotide analogue. To the contrary, Dower makes clear to the person of ordinary skill in the art that the labeled ddNTPs of Prober I are to be used without modification. Therefore, Dower does not

describe, either generally or by way of example, a nucleotide analogue which combines all the features described as present in substitute claim 18, combined as described in the claim. (Exhibit 1034, Weinstock Dep., 264:13-267:13, 268:2-9, 277:20-279:5.) Dower also does not include any discussion suggesting or linking different and disparate parts of his description where Illumina asserts the features appear.

c. No disclosure In Dower Of Simultaneously Contacting

65. Substitute claim 18 recites “simultaneously contacting” the product of step a) with a polymerase and four nucleotide analogues. The product of step a) is a nucleic acid template attached to a solid support to which a primer is hybridized.
66. On cross examination Dr. Weinstock, testified that his interpretation of “simultaneously contacting” was not that each of the four nucleotide analogues and the polymerase necessarily touch the template/primer at exactly the same moment. (Exhibit 1034, Weinstock Dep., 46:16-19; 47:11-12). Instead, Dr. Weinstock indicated that his interpretation is that they are added in a mixture as opposed to other sequencing by synthesis methods where they might

be added separately, or where the nucleotides might be added separately. (Exhibit 1034, Weinstock Dep., 46:14-16, 46:20-23, 47:10-16).

67. On redirect examination Dr. Weinstock testified that the meaning of “simultaneously contacting” is that everything is present in the reaction chamber at the same time. (Exhibit 1034, Weinstock Dep., 374:6-8). This interpretation does not involve any affirmative steps and would be inconsistent with the words “simultaneously contacting.”
68. On cross examination Dr. Weinstock testified that the description of SBS in Dower begins at col. 24, l. 48. (Exhibit 1034, Weinstock Dep., 179:19-180:2). However, when questioned about Step 1 (placing the polymerase in the incubation chamber) col. 24, l. 61- col. 25, l. 3 and then Step 2 (adding the nucleotide analogues) col. 25, ll. 4-6, Dr. Weinstock responded to the question whether Dower was describing the nucleotides being added after adding the polymerase, testified “[i]t [Dower] doesn’t explicitly say they’re added after or sequentially. It just says Step 1 and Step 2.” (Exhibit 1034, Weinstock Dep., 180:19-23). In response to the question whether Dower says they are added in one mixture, Dr. Weinstock testified, “it [Dower] does not say

anything about the mixture.” (Exhibit 1034, Weinstock Dep., 181:5-6).

69. In my view a person of ordinary skill in the art would have understood that when at col. 24, l. 61-col. 25, l. 6 Dower describes Step 1 and then Step 2, Dower is not describing simultaneously contacting the template to which the primer is hybridized with the polymerase and the four nucleotide analogues.
70. Therefore, one of ordinary skill in the art would have understood that Dower does not describe the feature “simultaneously contacting” in Substitute claim 18.

2. Claim 11 (Proposed Substituted Claim 25)

71. Substitute claim 25 corresponds to original independent claim 11 except that it has been amended for clarity and internal consistency to recite “A plurality of different nucleic acid templates....” My understanding of this claim is consistent with Dr. Weinstock’s understanding. He testified that he understood that claim 11 (now substitute claim 25) describes the product of original claim 5, i.e. the product of attaching a plurality of different nucleic acid templates to a solid surface. (Exhibit 1034, Weinstock Dep., 79:22-80:19). There is

no description in either Dower or Prober I of a plurality of different nucleic acids.

72. Substitute claim 25 also indicates that each nucleic acid primer comprises a nucleotide analogue has the following features combined: (1) is incorporated into the primer extension strand; (2) includes a deazabase to which a label is attached; and (3) includes a removable chemical moiety capping the 3'-OH of the sugar.
73. As discussed above in Section G(1)(b), there is no description in Dower either generally or by way of example of a nucleotide analogue which has all the features as described in substitute claim 25 combined in the same way as in substitute claim 25. (*See also* Exhibit 1034, Weinstock Dep., 264:13-267:13, 268:2-9, 277:20-279:5.)

H. CHALLENGE I: CLAIMS 1-7, 11, 12, 14, 15 AND 17³ UNDER 35 U.S.C. §103(a) AS OBVIOUS IN VIEW OF TSIEN AND PROBER I

1. Illumina Did Not Identify In Tsien's Description A Starting Point For Making Novel Nucleotide Analogues

³ As noted in paragraph 49 claims 1-7, 11, 12 and 14-17 are being replaced by substitute claims 18-29.

74. In October 2000 a person of ordinary skill in the art reading Tsien would have understood that Tsien was presenting various schemes for sequencing DNA by synthesis involving use of four labeled nucleotide analogues. A person of ordinary skill would further have understood that each nucleotide analogue includes a removable blocking or capping group on the 3'-OH of a deoxyribonucleotide (individually analogues of dATP, dCTP, dGTP and dTTP and collectively analogues of dNTP) and that "...preferably, the label [is] incorporated within the blocking group...." (Exhibit 1002, page 14, ll. 19-20). FIG. 2 of Tsien and the accompanying text describe such a method at page 11, l. 28- page 15, l. 5 where the label is included in the removable blocking group present on the 3'-OH. (Exhibit 1002, page 12, ll. 16-18, page 13, ll. 14-19, page 14, ll. 12-20, page 26, l. 1- page 27 l. 32; Exhibit 1034, Weinstock Dep., 189:7-15.)
75. A person of ordinary skill in the art would also have understood that the reason for preferring to include the label in the 3'-OH removable capping group was to accomplish both labeling and removable capping at a single position on the nucleotide in a single series of chemical reactions. If the person of ordinary skill were interested in designing and making new nucleotide analogues this approach would

have been understood to be the approach most likely to create a nucleotide analogue that would be recognized by a polymerase and incorporated into the end of a primer extension strand since it involved the least disruption to the nucleotide structure. The person of ordinary skill also would have understood that as of October 6, 2000 there were no reports of successful incorporation by a polymerase of a nucleotide analogue that had been modified both by placing a removable capping group on the 3'-OH of the sugar and by placing any label, let alone a cleavable label, on the base.

76. In addition to the reason for preferring to include the label in the removable capping group discussed in preceding paragraph 75, the person of ordinary skill in the art interested in designing and making new nucleotide analogues would have understood the likelihood of success of making such a nucleotide analogue with both the label and the removable capping group on the 3'-OH would have been (1) the synthetic approach most likely to succeed from a chemical synthesis perspective and (2) the most economical approach for producing the analogue from a commercial perspective.
77. Therefore, a person of ordinary skill in the art would have understood the 3'-OH labeled nucleotide analogues of Tsien to be the starting

point for any further work to design and synthesize new nucleotide analogues particularly since Examples 1-6 (Exhibit 1002, pages 35-40) the only examples in Tsien that detail the synthesis of 3'-OH labeled nucleotides, of incorporation of such 3'-OH labeled nucleotide analogues into a growing primer extension strand, and removing the 3'-OH blocking group containing the label from the incorporated nucleotide analogue.

a. Tsien's 3'-OH Labeled Nucleotide Analogues As A Starting Point

78. As of October 6, 2000 a person of ordinary skill in the art would have understood that Tsien was focusing on nucleotide analogues in which the label is incorporated into the removable blocking group on the 3'-OH. As discussed in paragraph 30, above. Tsien is cited for this disclosure in Metzker (Exhibit 2015, page 4259) and in Welch and Burgess (Exhibit 2027, page 197), papers authored by Dr. Weinstock's chemistry colleagues with whom he testified he would have consulted on issues involving chemical synthesis of nucleotide analogues. (Exhibit 1034, Weinstock Dep., 483:10-19.)
79. Therefore, in considering the design and synthesis of novel nucleotide analogues in the context of the description in Tsien, the person of ordinary skill in the art would have understood the starting point to be

nucleotide analogues in which the label is incorporated into a removable blocking group on the 3'-OH of the sugar.

80. In its Petition (Paper 3) Illumina did not provide any discussion of what nucleotide analogue in Tsien would be the starting point for making novel nucleotide analogues. Dr. Weinstock in his Declaration (Exhibit 1021) also provided no discussion of what nucleotide analogue in Tsien would be the starting point.⁴

⁴ At his Deposition Dr. Weinstock referenced a “GTP derivative having a carboxyl group as a linker end” as a “starting molecule,” “a 7-deaza dGTP or a derivative of dGTP” as a “starting substance” and “7-deazaguanine” (possibly intended to mean 7-deazaguanosine) as a “starting point.” (Exhibit 1034, Weinstock Dep., 241:15-22, 243:14-17, 249:10-17.) To the extent I understand what specific molecules Dr. Weinstock is referring to, all of them are even further removed from the nucleotide analogue described in the claims of the ‘698 Patent than the starting points I am discussing in this Declaration. Consequently, at least the same lack of a reason to try and the same lack of a basis to reasonably expect success discussed below would apply if any of these molecules were used as a starting point. Moreover, the chemistry required to make a nucleotide analogue

81. In claim chart 1 of its Petition (Paper 3 at 19-26) Illumina in discussing the portion of the description in Tsien applicable to the claims of the '698 Patent cites page 12, ll. 22-27; FIG. 2; page 9; ll. 30-36; page 10, ll. 7-10; page 13, ll. 17-19; page 20; ll. 25-26; page 21; ll. 12-17. These citations concern 3'-OH labeled nucleotide analogues. In addition, Illumina cites page 28, ll. 518. Relying on these citations Illumina asserts that deaza-substituted nucleotide analogues have been disclosed in Tsien by virtue of a reference to Prober I (Exhibit 1003). In his Declaration Dr. Weinstock refers to claim chart 1 (Exhibit 1021, ¶62) and apparently adopts it as his

which included both a removable capping group on the 3'-OH of the sugar and a label, particularly a cleavable label, on the base starting from any of these molecules would be far more complex with far less expectation of success. In the case of the base "7-deazaguanine" or the nucleoside "7-deazaguanosine" as possible starting points, a person of ordinary skill in the art would have had no description of a chemical synthesis available in Tsien or Prober I for using either 7-deazaguanine or 7-deazaguanosine as a starting point in a synthesis to make a nucleotide analogue having the features described in the claims of the '698 Patent.

understanding of the description in Tsien applicable to the nucleotide analogues described in the '698 Patent.

82. I disagree that a person of ordinary skill would have understood that Tsien describes deaza-substituted nucleotide analogues and am advised the Trial Board has also disagreed and found that Tsien does not describe deaza-substituted nucleotide analogues. (Paper 28, 10-14; Paper 43, 7-10.)
83. To the extent claim chart 1 of Illumina's Petition (Paper 3 at 19-26) is understood to be identifying a description of a nucleotide analogue which would be a starting point for the design and synthesis of novel nucleotide analogues, a person of ordinary skill understood that the starting point in Tsien are the 3'-OH labeled nucleotide analogues described since Tsien indicates a preference for such analogues. In addition, a person of ordinary skill in the art would have understood this to be the focus both in Tsien (Exhibit 1002, p. 27, l. 34) and in the art as a whole (See ¶¶ 26, 27 above.)
84. With this starting point, a person of ordinary skill in the art understood that to make a nucleotide analogue described in substitute claims 18-29 of the '698 Patent, the following modifications would

have been needed to address differences between Tsien and the nucleotide analogues in the claims.

(i) With respect to substitute claims 18-24 and 27-29:

1. remove the labels from the 3'-OH capping group of the sugars and place them on the bases;
2. include removable chemical capping groups that did not include labels on the 3'-OH of the sugar;
3. attach four unique labels to the bases via cleavable linkers;
4. change at least one purine base to a deazabase; and
5. retain the property of being incorporated onto a primer extension strand,

(ii) With respect to substitute claims 22, 25 and 26 additionally:

6. incorporate such novel nucleotide analogues onto the ends of multiple, different, growing primer extension strands.

No Reason To Make Changes To Tsien's 3'-OH Labeled Nucleotide Analogues

85. A person of ordinary skill in the art would not have had any reason to make the changes to the 3'-OH labeled nucleotides described in Tsien

and discussed in preceding paragraph 84 for the reasons detailed below.

86. In assessing which new nucleotide analogues to make a person of ordinary skill in the art in October 2000 would not have considered removing the label from the 3'-OH and placing it instead on the base. There would have been no reason to do so. Efforts to make new and improved 3'-OH labeled nucleotide analogues were ongoing and some success had been reported in making 3'-OH labeled nucleotide analogues that were incorporated by a polymerase. (Exhibit 2015, Metzker (1994); Exhibit 2030, Canard and Sarfati (1994))
87. In addition, a person of ordinary skill would not have been aware of any reason to move the label away from the 3'-OH on the sugar, and the art did not suggest any need to do so.
88. Prior to October 6, 2000 neither Tsien nor any other reference discussing DNA sequencing, suggested including a deaza-substituted base in a 3'-OH removably capped and labeled nucleotide analogue. Thus, one of ordinary skill in the art would not have considered changing the base from a non-deaza base to a deaza-substituted base in the context of a 3'-OH removably capped nucleotide analogue.

89. A person of ordinary skill would have had to deviate from the literature available at the time showing continued development of 3'-OH labeled nucleotide analogues for SBS and instead embark on a path that involved multiple changes, each of which was associated with unknown and unpredictable outcomes.
90. For the preceding reasons, a person of ordinary skill would not have looked to, or used the description of irreversibly terminating, labeled ddNTPs in Prober I to design new dNTP analogues for use as reversible, labeled chain terminators. The nucleotide analogues of Prober I were ddNTPs, not dNTPs; and ddNTPs could not be modified to obtain dNTPs. (Exhibit 1034, Weinstock Dep., 462:12-463:1.) For example, a 3'-OH, and therefore a removable capping group on a 3'-OH, could not have been introduced into the ddNTPs of Prober I. (Exhibit 1034, Weinstock Dep., 156:19-157:10, 462:10-463:16, 466:15-467:8.)

No Basis For Reasonably Expecting Success In Making Invention

91. A person of ordinary skill would also have had no basis for reasonably expecting that any combination of the disclosures of Tsien and Prober I could have been used successfully to make nucleotide analogues combining the features described in substitute claims 18-29. Given

the differences in features between Tsien and Prober I and the claims and the lack in either Tsien or Prober I of any reasonable basis for arriving at a nucleotide analogue having such features, a person of ordinary skill would have had no basis for reasonably expecting to be successful in obtaining such a nucleotide analogue. For example, neither Tsien nor Prober I disclosed any chemistry for converting labeled ddNTP into reversibly 3'-OH capped nucleotide analogue with the features of the '698 claims. A person of ordinary skill would have had to design new chemical synthetic procedures to attempt to do so and would not have had a reasonable basis for expecting that such procedures would be successful. Neither Illumina nor Dr. Weinstock points to any chemistry known to a person of ordinary skill for accomplishing such new chemical synthesis.

b. Tsien's Base-Labeled Nucleotide Analogues As A Starting Point

92. If, contrary to my view of the understanding of a person of ordinary skill in the art and despite the lack of any such suggestion, let alone rationale, to do so in Illumina's Petition (Paper 3) or in Dr. Weinstock's Declaration (Exhibit 1021), a person of ordinary skill assumed that the starting point for designing new nucleotide analogues were the base-labeled nucleotide analogues described in

Tsien (Exhibit 1002, page 27, l. 33-page 30) the following differences between the base-labeled nucleotide analogue described in Tsien and the nucleotide analogues described in substitute claims 18-29 of the '698 Patent would have needed to be addressed.

(i) with respect to substitute claims 18-24 and 27-29:

1. remove the identical (non-unique) labels from the C-8 positions of the two purines despite the C-8 position being described by Tsien as the “ideal” position for the attachment of the labels to purines;
2. change the purine bases of the purines to deazapurines;
3. change the identical labels on the pyrimidines to unique labels;
4. replace the uncleavable, acetylenic linker (described in Prober I) on the pyrimidines with a cleavable linker;
5. replace the uncleavable alkylamino linker on the purines with a cleavable linker);
6. include removable 3'-OH capping groups on the uncapped 3'-OH groups of the nucleotide analogues; and
7. incorporate such a novel nucleotide analogue into the end of a primer extension strand.

(ii) With respect to substitute claims 25 and 26, additionally:

8. incorporate such novel nucleotide analogues onto the ends of multiple, different, growing extension strands.

No Reason To Make Changes To Tsien's Base-Labeled Nucleotide Analogues

93. In my opinion a person of ordinary skill in the art would not have had any reason to make the changes to Tsien's base-labeled nucleotide analogues described in preceding paragraph 92 for the reasons detailed below.
94. Neither Tsien nor any prior art reference including any reference cited in Illumina's Petition (Paper 3) or discussed in Dr. Weinstock's Declaration (Exhibit 1021) suggests any problem with the base-labeled nucleotide analogues disclosed in Tsien at pages 27-30.
95. In assessing what new base-labeled nucleotide analogues to make , a person of ordinary skill in the art in October 2000 would not have considered removing the labels from the C-8 positions of the purines since Tsien described the C-8 position as "ideal." (Exhibit 1002, page 29, ll. 3-4, page 30; Exhibit 1034, Weinstock Dep., 190:1-8.)
96. Further, there was no suggestion in Tsien to use deaza-substituted purines such as those described in Prober I at all, let alone labeled at the 7-position. To the contrary, Tsien refers to Prober I for teaching

an approach to producing fluorescently labeled derivatives of pyrimidines and provides the pyrimidine structures on page 30 to illustrate this approach (Exhibit 1002, page 29, ll. 10-16; Exhibit 1034, Weinstock Dep., 190:1-193:15.) In addition, Tsien ignores Prober I's teaching of producing base-labeled deazapurines, instead indicating that "[t]he C-8 position of the purine structure is an ideal position for attachment of a label." (Exhibit 1002, page 29, ll. 3-7.) In support of this statement Tsien cites Sarfati et al. (1987) (Exhibit 2032 which describes derivatization of a purine at C-8 to prepare a purine labeled at the C-8 position. A person of ordinary skill understood that Dr. Tsien was one of the world's leading authorities in the field of fluorescent labels and would have had no reason to disregard his discussion that the C-8 position was "ideal" for attaching a fluorescent label to the base in a nucleotide analogue. (Exhibit 1034, Weinstock Dep., 190:1-8.)

97. Dr. Weinstock testified that a person of ordinary skill might also consider using the 7-position (Exhibit 1034, Weinstock Dep., 346:7-9). Dr. Weinstock stated that "[b]oth 7 and 8 would work" and did not remember whether "technically, 8 was a little better and you might have gotten more efficient synthesis, or it was cheaper, ... but [he

knew] that 7 was widely used.” (Exhibit 1034, Weinstock Dep., 347:5, 347:12-16.) In my opinion a person of ordinary skill would not have deviated from Tsien’s guidance to use the “ideal” 8-position because 1) the 7-position not even mentioned by Tsien; 2) Sarfati reported that nucleotide analogues labeled at the 8-position were incorporated in a primer extension strand (Exhibit 2032, page 3493); 3) Sarfati provided a synthetic route for making the 8-position base-labeled nucleotide analogues, whereas no synthesis was provided in Prober I; and 4) the 8-position base-labeled nucleotide analogues of Sarfati had an intact 3’-OH group which could have been used for adding a removable capping group, whereas Prober I described ddNTPs which did not have a 3’-OH group. Thus, it is my opinion a person of ordinary skill would have followed the explicit teaching of Tsien to place the label on the 8-position of a purine using the synthetic approach of Sarfati. (Exhibit 2032.)

98. Still further, none of the approaches to attaching labels to non-deazabases discussed by Tsien on page 29 at lines 3-18 and illustrated in the structures on page 30 involve use of a cleavable linker. Dr. Weinstock acknowledged the acetylenic linker from Prober I is not cleavable (Exhibit 1034, Weinstock Dep., 157:19-158:12) and that he

would need to check with somebody who would have the necessary expertise to say whether the linkers on page 30 were cleavable (Exhibit 1034, Weinstock Dep., 194:21-195:8.) A person of ordinary skill would have understood the labels on page 30 are not cleavable.

99. In its Petition (Paper 3 at 15) Illumina and in his Declaration (Exhibit 1021, ¶45) Dr. Weinstock suggested a reason for exchanging labeled deaza-substituted purines for the non-deaza purines described in Tsien would be to address problems associated with sequencing DNA involving G:C rich regions. However, the claims of the patent at issue in this proceeding involve incorporation of a single nucleotide analogue having specified features combined in the nucleotide analogue. The method claimed provides the identity of a single incorporated nucleotide. In performing this method, no problem associated with a G:C rich region would have been encountered. Therefore, a person of ordinary skill would not have considered this a problem in the first stage of designing and synthesizing a novel nucleotide analogue. Where the paramount concern was whether the nucleotide analogue would be incorporated by a polymerase.
100. In the first stage of developing a novel nucleotide analogue the person skilled in the art would have been concerned with whether the

required chemical synthesis steps could be devised, whether these synthetic steps would result in synthesis of the desired nucleotide analogue, and whether once synthesized the novel nucleotide analogue would be recognized by a polymerase and incorporated into the end of a primer extension strand. Only if those hurdles were overcome would a person skilled in the art have turned his attention to the issue of repeatedly employing the method described in the claim to sequence a long stretch of DNA and only then would any issue relating to sequencing G:C rich regions have encountered.

101. Thus, a person of ordinary skill in the art would not have perceived any hypothetical future issue involving sequencing of G:C rich regions as relevant to the design and synthesis of novel nucleotide analogues and certainly would not have considered it necessary to take such a hypothetical future problem into account given the major obstacles that first had to be overcome.

102. Illumina's and Dr. Weinstock's reliance on Seela I for a motivation to use deaza-substituted purines is also misplaced. The deaza nucleotide analogues described in Seela I are neither base-labeled nor removably capped. Moreover, they are intended for use without a base label in sequencing methods such as Sanger dideoxy sequencing. The

problem of sequencing G:C rich regions was recognized in such sequencing methods when they were used to sequence lengthy DNA stretches and the use of Seela I's unlabeled deazaguanosine may have provided an advantage in such a context. However, in the context of designing and synthesizing a novel base-labeled nucleotide analogue which would be incorporated onto the end of a primer extension strand there was no G:C rich problem that needed to be addressed. (Exhibit 1034, Weinstock Dep., 150:25- 151:25.)

No Basis For Reasonably Expecting Success In Making Invention

103. If a person of ordinary skill in the art, despite all the reasons not to do so, were motivated to make a nucleotide analogue that addressed all the differences between the nucleotide analogues described in Tsien and the nucleotide analogues described in the claims of the patent at issue, he or she could not have done so simply by combining the descriptions in Prober I with those in Tsien.
104. The nucleotide analogues described in Prober I involve an acetylenic linker that cannot be cleaved under any conditions that would not destroy the nucleotide analogue. (Exhibit 1034, Weinstock Dep. 158:1-12.) Further, the nucleotide analogues of Prober I are ddNTPs

that do not include, and cannot be modified to include, a 3'-OH group.
(Exhibit 1034, Weinstock Dep. 157:1-10.)

105. Since the nucleotide analogues of Prober I do not have a 3'-OH group and cannot be modified to include a 3'-OH group, there is no possibility to add a removable capping moiety on a 3'-OH. Thus, a person of ordinary skill in the art would not have any reasonable basis for expecting that it would be possible to obtain nucleotide analogues in which the combination of features described in the claims would be present by combining the descriptions in Tsien and in Prober I.
106. Furthermore, given the many differences between the nucleotide analogues described in Tsien and the nucleotide analogue described in the claims, a person of ordinary skill in the art would have to create completely new chemical procedures to obtain a nucleotide analogue having the combination of features described in the claims.
107. At his deposition Dr. Weinstock repeatedly disclaimed any knowledge of chemistry, each time indicating he would need to consult with a chemist having expertise in synthetic chemistry. (Exhibit 1034, Weinstock Dep., 113:20-114:7, 135:25-136:11, 154:18-155:21, 157:1-10, 161:10-12, 162:1-5, 164:11-16, 164:23-25, 174:14-25, 175:7-11, 194:21-195:8, 239:9-240:10, 242:4-10, 245:6-12, 245:23-246:13,

251:12-24, 298:5-16, 462:21-463:16, 466:25-467:8, 481:10-18, 487:4-15.) Creating such new chemical procedures is complex and fraught with difficulties. The result of each step in such a procedure cannot be predicted and unintended intermediates may be formed. Reaction conditions suitable for making one nucleotide analogue may be inapplicable to making another analogue.

108. Despite Dr. Weinstock's disclaimer of any knowledge of nucleotide chemistry and knowledge of any reference which described a nucleotide analogue in which features were combined in the same way as in the claims (Exhibit 1034, Weinstock Dep., 157:7-10, 160:8-161:12, 306:18-307:8), Dr. Weinstock confidently predicted that nucleotide analogues having the features described in the claims could be made and would have been incorporated by a polymerase. (Exhibit 1034, Weinstock Dep., 159:20-162:5).

109. In my opinion any such suggestion by Dr. Weinstock during his deposition that a person of ordinary skill would have been motivated to make, and would have expected to succeed in making, a nucleotide analogue described in the claims and that such a nucleotide analogue would be incorporated into the end of a primer extension strand by a polymerase are totally speculative and unsupported by any scientific

reason or literature. The fact is that as of October 6, 2000 the chemists Dr. Weinstock would have consulted, e.g. Dr. Metzker, Welch, and Burgess, were actively pursuing labeling the 3'-OH position of the sugar and describing the formidable obstacles they were facing. (¶ 30-31.)

110. In my opinion, a person of ordinary skill in the art in October 2000 would not have had any reason to make a nucleotide analogue which combined the following features: (1) includes a deaza-substituted base to which a unique label is attached, particularly a cleavable linker; (2) includes a removable chemical moiety capping the 3'-OH group of the sugar; and (3) is incorporated into a nucleic acid primer extension strand.
111. In my opinion, a person of ordinary skill in the art would also have found no direction how to make such a nucleotide analogue in any combination of the descriptions present in Tsien and in Prober I or in any other reference in the prior art.
112. In my opinion, a person of ordinary skill further have had no basis to reasonably expect that any such nucleotide analogue, however made, would be incorporated by a polymerase into the end of a primer extension strand. It was already known that even when making

modifications solely on the 3'-OH of the sugar, the ability of the resulting nucleotide analogue to be incorporated by a polymerase was unpredictable. Contrast Exhibit 2015, Metzker (1994), page 4263 and Exhibit 2030, Canard and Sarfati (1994), page 3 with Exhibit 2027, Welch and Burgess (1999), page 200. Clearly the effect of making an additional modification by placing the label on the base on the incorporation of a nucleotide analogue by a polymerase could not have been predicted with any reasonable certainty.

2. Additional Reasons Why Substitute Claims 25 And 26 Would Not Have Been Obvious Over Tsien And Prober I

113. In addition to the reasons why all the substitute claims would not have been obvious from any combination of the descriptions in Tsien and Prober I discussed in preceding paragraphs 74-112, substitute claims 25 and 26 could not have been derived from any combination of Tsien and Prober I for the additional reason that these claims require multiple different templates immobilized on a solid surface. Neither Tsien nor Prober I describe multiple different templates immobilized on a solid surface. (Exhibit 1034, Weinstock Dep.,263: 1-8, 294:3-8) Therefore, no combination of the descriptions in Tsien and Prober I

can result in multiple different templates immobilized on a solid surface.

**I. CHALLENGE II: CLAIMS 5 AND 12⁵ UNDER 35 U.S.C. §103(a)
AS OBVIOUS IN VIEW OF TSIEN, PROBER I AND RABANI**

114. I understand that the Trial Board has instituted this proceeding by adding Rabani to Tsien and Prober I in relation to claims 5 and 12 on the basis of a description in Rabani of a purported description in Rabani of a plurality of different nucleic acids and of such a plurality of different nucleotide analogues being present in a microarray. A person of ordinary skill in the art understood that Rabani is describing examination of associations or reactions between large numbers of complex molecules. A person of ordinary skill would further have understood that all nucleotide analogues described in Rabani involve a label attached at the 3'-OH position of the sugar.

115. In relation to claims 5 and 12 Rabani does not provide the description missing from the combined descriptions of Tsien and Prober I discussed in preceding Section H.

⁵ As noted in paragraph 49 claims 5 and 12 are being replaced by substitute claims 22 and 26, respectively.

116. I have been informed that the only purported evidence of a motivation to combine the description of Rabani with those of Tsien and Prober I and Rabani is the statement “[m]odifying 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.” (Exhibit 1021 at ¶77). Even if the section of Rabani asserted against claims 5 and 12 was a description of a microarray of nucleic acids (which it is not), that statement would not have provided a person of ordinary skill in the art any motivation to combine any teaching in Rabani with the descriptions in Tsien and Prober I because the passages cited in Rabani do not add anything in terms of the features missing after combining the description in Tsien and Prober I.
117. Importantly, the only disclosure of an array in Rabani cited by Illumina in its Petition (Paper 3 at 52) or by Dr. Weinstock in his Declaration (Exhibit 1021, ¶77) is an array of detection instrumentation, not a DNA microarray. Therefore, the description in Rabani being cited in combination with the descriptions in Tsien and

Prober I, would describe not the features in claim 26. Rabani states that “[d]etection will have constraints entailed by the particular instrumentation and method used, but many degrees of freedom exist with regard to means of providing parallelism in detection instrumentation... multiple probes [i.e. in arrays will parallel detection provided]....” (Exhibit 1006, page 11, ll. 6-13). This is a disclosure of an array for detection purposes. It is not a description of a plurality of different nucleic acid templates or a microarray involving a plurality of different nucleic acids templates.

J. CHALLENGE III: CLAIMS 1-7, 11, 12, 14, 15 AND 17⁶ UNDER 35 U.S.C. §103(a) AS OBVIOUS IN VIEW OF TSIEN AND SEELA I

1. Illumina Did Not Identify In Tsien’s Description A Starting Point For Making Novel Nucleotide Analogues

118. For the reasons discussed above in paragraphs 74-77 a person of ordinary skill would have understood the 3’-OH labeled nucleotide analogues of Tsien to be the starting point for any further work to design and synthesize new nucleotide analogues in SBS particularly

⁶ As noted in paragraph 49 claims 1-7, 11, 12 and 14-17 are being replaced by substitute claims 18-29.

since Examples 1-6 (Exhibit 1002, pages 35-40) the only examples in Tsien describe the synthesis of 3'-OH labeled nucleotides, incorporation of such 3'-OH labeled nucleotide analogues into a growing primer strand, and removing the 3'-OH blocking group containing the label from the incorporated nucleotide analogue.

a. Tsien's 3'-OH Labeled Nucleotide Analogues As A Starting Point

119. As of October 6, 2000 a person of ordinary skill in the art would have understood that Tsien was focusing on nucleotide analogues in which the label is incorporated into the removable blocking group on the 3'-OH, as discussed in paragraphs 74-77 and 80, above. Therefore, in considering the design and synthesis of novel nucleotide analogues in the context of the description in Tsien, the person of ordinary skill would have understood the starting point to be nucleotide analogues in which the label is incorporated into a removable blocking group on the 3'-OH of the sugar.

120. In its Petition (Paper 3) Illumina did not provide any discussion of what nucleotide analogue in Tsien would be the starting point for making novel nucleotide analogues. Dr. Weinstock in his Declaration (Exhibit 1021) also provided no discussion of what nucleotide analogue in Tsien would be the starting point.

121. In claim chart 1 of its Petition (Paper 3 at 19-26) Illumina in discussing the portion of the description in Tsien applicable to the claims of the '698 Patent cites page 12, ll. 22-27; FIG. 2; page 9; ll. 30-36; page 10, ll. 7-10; page 13, ll. 17-19; page 20; ll. 25-26; page 21; ll. 12-27. These citations concern 3'-OH labeled nucleotide analogues. In addition, Illumina cites page 28, ll. 518. Relying on these citations Illumina asserts that deaza-substituted nucleotide analogues have been disclosed in Tsien by virtue of a reference to Prober I (Exhibit 1003). In his Declaration Dr. Weinstock refers to claim chart 1 (Exhibit 1021, ¶62) and apparently adopts it as his understanding of the description in Tsien applicable to the nucleotide analogues described in the '698 Patent.
122. I disagree that a person of ordinary skill would have understood that Tsien describes deaza-substituted nucleotide analogues and am advised the Trial Board has also disagreed and found that Tsien does not describe deaza-substituted nucleotide analogues. (Paper 28, 10-14; Paper 43, 7-10.)
123. To the extent claim chart 1 of Illumina's Petition (Paper 3 at 19-26) is understood to be identifying a description of a nucleotide analogue which would be a starting point for the design and synthesis of novel

nucleotide analogues, a person of ordinary skill understood that the starting point in Tsien are the 3'-OH labeled nucleotide analogues described since Tsien indicates a preference for such analogues. In addition, a person of ordinary skill in the art would have understood this to be the focus both in Tsien (Exhibit 1002, p. 27, l. 34) and in the art as a whole (*See* ¶¶ 26, 27 above.)

124. With this starting point, a person of ordinary skill in the art understood that to make a nucleotide analogue described in substitute claims 18-29 of the '698 Patent, the following modifications would have been needed to address differences between Tsien and the nucleotide analogues in the claims.

(i) With respect to substitute claims 18-24 and 27-29:

1. remove the labels from the 3'-OH capping group of the sugars and place them on the bases;
2. include removable chemical capping groups that did not include labels on the 3'-OH of the sugar;
3. attach four unique labels to the bases via cleavable linkers;
4. change at least one purine base to a deazabase; and

5. retain the property of being incorporated onto a primer extension strand,

(ii) With respect to substitute claims 22, 25 and 26 additionally:

6. incorporate such novel nucleotide analogues onto the ends of multiple, different, growing primer extension strands.

No Reason To Make Changes To Tsien's 3'-OH Labeled Nucleotide Analogues

125. For the reasons detailed in paragraphs 85-90 above, a person of ordinary skill in the art would not have had any reason to make the changes to the 3'-OH labeled nucleotides described in Tsien and discussed in preceding paragraph 124.

No Basis For Reasonably Expecting Success in Making Invention

126. A person of ordinary skill would also have had no basis for reasonably expecting that any combination of the disclosures of Tsien and Seela I could have been used successfully to make nucleotide analogues combining the features described in substitute claims 18-29. Given the differences in features between Tsien and Seela I and the claims and the lack in either Tsien or Seela I of any reasonable basis for

arriving at a nucleotide analogue having such features, a person of ordinary skill would have had no basis for reasonably expecting to be successful in obtaining such a nucleotide analogue.

b. Tsien's Base-Labeled Nucleotide Analogues As A Starting Point

127. If, contrary to my view of the understanding of a person of ordinary skill in the art and despite the lack of any such suggestion, let alone rationale, to do so in Illumina's Petition (Paper 3) or in Dr. Weinstock's Declaration (Exhibit 1021), a person of ordinary skill in the art assumed that the starting point for designing new nucleotide analogues were the base-labeled nucleotide analogues described in Tsien (Exhibit 1002, page 27, l. 33-page 30) the following differences between the base-labeled nucleotide analogue described in Tsien and the nucleotide analogues described in substitute claims 18-29 of the '698 Patent would have needed to be addressed:

(i) with respect to substitute claims 18-24 and 27-29:

1. remove the identical (non-unique) labels from the C-8 positions of the two purines despite the C-8 position being described by Tsien as the "ideal" position for the attachment of the labels to purines;
2. change the purine bases of the purines to deazapurines;

3. change the identical labels on the pyrimidines to unique labels;
4. replace the uncleavable, acetylenic linker on the pyrimidines with a cleavable linker;
5. replace the uncleavable alkylamino linker on the purines with a cleavable linker;
6. include removable 3'-OH capping groups on the uncapped 3'-OH groups of the nucleotide analogues; and
7. incorporate such novel nucleotide analogues into the ends of multiple, growing primer extension strands.

(ii) With respect to substitute claims 25 and 26, additionally:

8. incorporate such novel nucleotide analogues onto the ends of multiple, different, growing extension strands.

No Reason To Make Changes To Tsien's Base-Labeled Nucleotide Analogues

128. For reasons detailed in paragraphs 93-102 above, a person of ordinary skill in the art would not have had any reason to make the changes to Tsien's base-labeled nucleotide analogues described in preceding paragraph 127.
129. Further, there was no suggestion in Tsien to use deaza-substituted purines such as those described in Seela I at all, let alone labeled at

the 7-position. Tsien does not refer to Seela I or to labeling a substitute nucleotide at all. Instead Tsien indicates that “[t]he C-8 position of the purine structure is an ideal position for attachment of a label.” (Exhibit 1002, page 29, ll. 3-7.) In support of this statement Tsien cites Sarfati et al. (1987) (Exhibit 2032 which describes derivatization of a purine at C-8 to prepare a purine labeled at the C-8 position. A person of ordinary skill understood that Dr. Tsien was one of the world’s leading authorities in the field of fluorescent labels and would have had no reason to disregard his discussion that the C-8 position was “ideal” for attaching a fluorescent label to the base in a nucleotide analogue.

130. In its Petition (Paper 3 at 15) Illumina and in his Declaration (Exhibit 1021, ¶45) Dr. Weinstock suggested a reason for exchanging labeled deaza-substituted purines for the non-deaza purines described in Tsien would be to address problems associated with sequencing DNA involving G:C rich regions. However, the claims of the patent at issue in this proceeding involve incorporation of a single nucleotide analogue having specified features combined in the nucleotide analogue. The method claimed provides the identity of a single incorporated nucleotide. In performing this method, no problem

associated with a G:C rich region would have been encountered.

Therefore, a person of ordinary skill would not have considered this a problem in the first stage of designing and synthesizing a novel nucleotide analogue where the paramount concern was whether the nucleotide analogue would be incorporated by a polymerase.

131. In the first stage of developing a novel nucleotide analogue the person skilled in the art would have been concerned with whether the required chemical synthesis steps could be devised, whether these synthetic steps would result in synthesis of the desired nucleotide analogue, and whether once synthesized the novel nucleotide analogue would be recognized by a polymerase and incorporated into the end of a primer extension strand. Only if those hurdles were overcome would a person skilled in the art have turned his attention to the issue of repeatedly employing the method described in the claim to sequence a long stretch of DNA and only then would any issue relating to sequencing G:C rich regions have encountered.

132. Thus, a person of ordinary skill in the art would not have perceived any hypothetical future issue involving sequencing of G:C rich regions as relevant to the design and synthesis of novel nucleotide analogues and certainly would not have considered it necessary to

take such a hypothetical future problem into account given the major obstacles that first had to be overcome.

133. Illumina's and Dr. Weinstock's reliance on Seela I for a motivation to use deaza-substituted purines is also misplaced. The deaza nucleotide analogues described in Seela I are neither base-labeled nor removably capped. Moreover, they are intended for use without a base label in sequencing methods such as Sanger dideoxy sequencing. The problem of sequencing G:C rich regions was recognized in such sequencing methods when they were used to sequence lengthy DNA stretches and the use of Seela I's unlabeled deazaguanosine might have provided an advantage in such a context. However, in the context of designing and synthesizing a novel base-labeled nucleotide analogue which would be incorporated onto the end of a primer extension strand there was no G:C rich problem that needed to be addressed. (Exhibit 1034, Weinstock Dep., 150:25- 151:25.)

No Basis For Reasonably Expecting Success in Making Invention

134. If a person of ordinary skill in the art, despite all the reasons not to do so, were motivated to make a nucleotide analogue that addressed all the differences between the nucleotide analogues described in Tsien

and the nucleotide analogues described in the claims of the patent at issue, he or she could not have done so simply by combining the descriptions in Seela I with those in Tsien.

135. The nucleotide analogue described in Seela I involve an unlabeled base. (Exhibit 1034, Weinstock Dep., 122:7-18.) Further, the nucleotide analogue does not include a removable 3'-OH capping group. In fact, for the use for which the nucleotide analogues are intended neither would be desired. Still further the nucleotide analogues described in Seela I cannot be modified to include both a label on the base and a 3'-OH removable capping group without developing chemistry for modifying Seela I's structure. (Exhibit 1034, Weinstock Dep., 122:18-21, 135:5-136:11.)
136. Because the nucleotide analogue of Seela I do not include a label on the base and no chemistry was available to modify it to include a label on the base and a removable capping group on the 3'-OH, there also would have been no basis for successfully adding a cleavable linker between the label and the base. Thus, a person of ordinary skill in the art would not have any basis for reasonably expecting that it would be possible to obtain nucleotide analogues which included the

combination of features described in the claims would be present by combining the descriptions in Tsien and in Seela I.

137. Furthermore, given the many differences between the nucleotide analogues described in Tsien and the nucleotide analogue described in the claims, a person of ordinary skill in the art would have to create completely new chemical procedures to obtain a nucleotide analogue having the combination of features described in the claims.
138. At his deposition Dr. Weinstock repeatedly disclaimed any knowledge of chemistry, each time indicating he would need to consult with a chemist having expertise in synthetic chemistry. (Exhibit 1034, Weinstock Dep. 113:20-114:7, 135:25-136:11, 154:18-155:21, 157:1-10, 161:10-12, 162:1-5, 164:11-16, 164:23-25, 174:14-25, 175:7-11, 194:21-195:8, 239:9-240:10, 242:4-10, 245:6-12, 245:23-246:13, 251:12-24, 298:5-16, 462:21-463:16, 466:25-467:8, 481:10-18, 487:4-15.) Creating such new chemical procedures is complex and fraught with difficulties. The result of each step in such a procedure cannot be predicted and unintended intermediates may be formed. Reaction conditions suitable for making one nucleotide analogue may be inapplicable to making another nucleotide analogue.

139. Despite Dr. Weinstock's disclaimer of any knowledge of nucleotide chemistry and knowledge of any reference which described a nucleotide analogue in which the features were combined in the same way as in the claims (Exhibit 1034, Weinstock Dep., 157:7-10, 160:8-161:12, 306:18-307:8), Dr. Weinstock confidently predicted that nucleotide analogues having the features described in the claims could be made and would have been incorporated by a polymerase. (Exhibit 1034, Weinstock Dep., 159:20-162:5).
140. In my opinion the suggestion by Dr. Weinstock during his deposition that a person of ordinary skill would have been motivated to make, and would have expected to succeed in making, a nucleotide analogue described in the claims that such a nucleotide analogue would be incorporated into the end of a primer extension strand by a polymerase is totally speculative and unsupported by any scientific reason or literature. The fact is that as of October 6, 2000 the chemists Dr. Weinstock would have consulted, e.g. Dr. Metzker, Welch, and Burgess, were actively pursuing labeling the 3'-OH position of the sugar of purines that had a natural base, not a deazabase, and describing the formidable obstacles they were facing (§30.)

141. In my opinion, a person of ordinary skill in the art in October 2000 would not have had any reason to make a nucleotide analogue which combined the features: (1) includes a deaza-substituted base to which a unique label is attached, particularly a cleavable linker; (2) includes a removable chemical moiety capping the 3'-OH group of the sugar; and (3) is incorporated into a nucleic acid primer extension strand.
142. In my opinion, a person of ordinary skill in the art would also have found no direction how to make such a nucleotide analogue in any combination of the descriptions present in Tsien and in Seela I or in any other reference in the prior art.
143. In my opinion, a person of ordinary skill further have had no basis to reasonably expect that any such nucleotide analogue however made, would be incorporated by a polymerase into the end of a primer extension strand. It was already known that even when making modifications solely on the 3'-OH of the sugar, the ability of the resulting nucleotide analogue to be incorporated by a polymerase was unpredictable. Contrast Exhibit 2015, Metzker (1994), page 4263 and Exhibit 2027, Welch and Burgess (1999), page 200. Clearly, the effect of making an additional modification by placing the label on the

base on the incorporation of a nucleotide analogue by a polymerase could not have been predicted with any reasonable certainty.

2. Additional Reasons Why Substitute Claims 25 And 26 Would Not Have Been Obvious Over Tsien And Seela I

144. In addition to the reasons why all the substitute claims would not have been obvious from any combination of the descriptions in Tsien and Seela I discussed in preceding paragraphs 118-143, substitute claims 25 and 26 could not have been derived from any combination of Tsien and Seela I for the additional reason that these claims require multiple different templates immobilized on a solid surface. Neither Tsien nor Seela I describe multiple different templates immobilized on a solid surface. (Exhibit 1034, Weinstock Dep., 263: 1-8, 294:3-8) Therefore, no combination of the descriptions in Tsien and Seela I can result in multiple different templates immobilized on a solid surface.

K. COMMENTS ON PARAGRAPHS IN THE WEINSTOCK DECLARATION NOT OTHERWISE ADDRESSED

'698 Weinstock Declaration Paragraph	Comment
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34	This paragraph is being addressed in detail elsewhere in this Declaration. (see above)
38	This statement would be correct only if limited to sequencing methods other than SBS.
39-45	This paragraph is being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶99-102, 130-133.)
46-53	I understand that the Board has determined that Hobbs and Prober II are similar to Prober I, which is being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶51, 55-59, 62-63, 90-92, 96-98.)
54	This paragraph is being addressed in detail elsewhere in this Declaration. (see above)
55	I understand that the Board has determined that the Saiki reference is no more relevant to the issues in this case than Seela I, which is being addressed in detail elsewhere in this Declaration.
56	This statement is very general and cites nothing in support. (see above)
57-67	To the extent relevant to the issues in this case, these paragraphs are being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶ 71-110.)
68	This statement is unclear, and cites nothing in support.
69-70	These paragraphs are being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶ 46-60.)

71-103	These paragraphs are being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶ 115-141.)
104-113	These paragraphs are being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶ 115-141.)
114-116	These paragraphs are being addressed in detail elsewhere in this Declaration. (Exhibit 2033, ¶¶ 71-110.)

**L. COMMENTS ON REFERENCES FIRST SUBMITTED AS
EXHIBITS DURING DR. WEINSTOCK'S RE-DIRECT
TESTIMONY ON JUNE 10, 2013**

1. Herman (Exhibit 1029)

145. Herman discloses nucleotide analogues for use as molecular probes for labeling or isolating DNA or DNA/protein complexes. (Exhibit 1029, Herman, field [57], abstract, col. 2, ll. 7-47.)
146. The claimed nucleotide analogues and methods do not relate to molecular probes for labeling or isolating DNA or DNA/protein complexes.
147. The nucleotide analogues in Herman contain biotin labels that are attached through a cleavable chemical linker (e.g., disulfide linker) to a nucleobase.
148. Herman describes a large genus of potential nucleobases, including deazapurines. (Exhibit 1029, Herman, col. 2, ll. 7-47).
149. There are no suggestions in Herman that the disclosed nucleotide analogues are useful in DNA sequencing. The Herman nucleotide analogues do not (1) contain a deazapurine-substituted base to which a label is attached through a cleavable linker, (2) include a removable chemical moiety capping the 3'-OH group of the sugar, as required for the nucleotide analogues and methods, and (3) there is no disclosures

demonstrating that the nucleotide analogues are incorporated into the end of a primer extension strand, as required by the claims.

150. To the extent that Illumina is relying on Herman because of Herman's disclosure of a large genus of potential nucleobases, including deazapurines, as evidence a person of ordinary skill would have been motivated to combine the references identified in the obviousness challenges to arrive at the nucleotide analogues and methods in the claims, I disagree there would be any such motivation.
151. In my opinion Herman provides no motivation to combine the references at issue in the challenge because the claimed nucleotide analogues and methods require incorporation of a single nucleotide analogue into the end of the primer extension strand.
152. Because the nucleotide analogues and methods do are not described for sequencing regions of DNA such as G-C rich regions, any purported advantage of a deazapurine nucleotide analogue for solving any problem of sequencing G-C rich regions is inapplicable to the claimed nucleotide analogues and methods.
153. Therefore, Herman does not provide a person of ordinary skill with any motivation to make the claimed deaza-substituted nucleotide analogues or methods using such nucleotide analogues.

154. There is also no disclosure in Herman of a synthetic process for converting the disclosed biotin-labeled nucleotide analogues into the claimed deaza-substituted base-labeled and reversibly terminated 3-OH nucleotide analogues, either with or without a cleavable linker.
155. Even if a person of ordinary skill would have been motivated to combine Herman with other references because of Herman's disclosure of a large genus of potential nucleobases, including deazapurines, he or she would not have any reasonable expectation any nucleotide analogue could be used successfully in the claimed methods, for the reasons stated above and throughout my Declaration.

2. Rosenblum (Exhibit 1030)

156. Rosenblum discloses fluorescently labeled, irreversible chain-terminating nucleotide analogues for Sanger sequencing, including deazapurine-labeled nucleotide analogues. (Exhibit 1030, Rosenblum, page 4500, abstract, ll. 16-22.)
157. Rosenblum discloses fluorescent dyes that purportedly improved signal to noise ratios and nucleotide detection accuracy for the Sanger sequencing method.

158. Rosenblum offers no information over and above that in Prober I of any possible relevance to the reversibly terminated fluorescently-labeled nucleotide analogues for use in sequencing.
159. Rosenblum's disclosed fluorescently labeled nucleotide analogues are dideoxynucleotide analogues and cannot be converted into deoxynucleotides removably capped on their 3'OH.
160. There are no suggestions in Rosenblum that the disclosed nucleotide analogues are useful for any purpose other than in irreversibly terminating Sanger dideoxy sequencing. The Rosenblum nucleotide analogues do not (1) contain a deazapurine-substituted base to which a label is attached through, particularly attached through a cleavable linker, and (2) include a removable chemical moiety capping the 3'-OH group of the sugar, as required for the claimed nucleotides and methods, nor (3) is there any disclosure demonstrating that the Rosenblum nucleotide analogues are incorporated into the end of a nucleic acid primer extension strand, as required in the claims.
161. To the extent that Illumina is relying on Rosenblum because of Rosenblum's disclosure of labeled deazapurine nucleotide analogues, as evidence a person of ordinary skill would have been motivated to combine Rosenblum with the disclosures of the other references cited

in respect to obviousness to arrive at the claimed nucleotide analogues and methods, I disagree there would be any such motivation.

162. In my opinion there is no motivation based on Rosenblum to combine the references at issue the claimed nucleotide analogues and methods require incorporation of a single nucleotide analogue into the end of a primer extension strand.
163. Because the claimed nucleotide analogues and methods do not require sequencing of G-C rich regions of DNA, any purported advantage of using labeled deazapurine nucleotide analogue for solving a problem of sequencing G-C rich regions is inapplicable to the claimed nucleotide analogues and methods.
164. Therefore, Rosenblum does not provide a person of ordinary skill with any motivation to make the claimed nucleotide analogues or methods.
165. Even if a person of ordinary skill were motivated to combine the description of Rosenblum with those of the references at issue because of Rosenblum's disclosure of labeled deazapurine nucleotide analogues, he or she would not have any reasonable expectation that using a Rosenblum nucleotide analogue could be successfully used in the claimed methods, for the reasons stated above and throughout my Declaration.

3. Short (Exhibit 1031)

166. Short discloses labeled nucleotide analogues useful for Sanger sequencing. (Exhibit 1031, Short, page 7, ll. 12-18.)
167. Short describes historical essential criteria for a nucleotide analogue to be used in DNA sequencing methods an irreversibly terminated nucleotide analogue, including deazapurine nucleotide analogues.
168. To the extent that Illumina is relying on Short because of Short's disclosure of a large genus of potential nucleobases, including deazapurines, as evidence of a person of ordinary skill's motivation to combine the other references at issue to arrive at the claimed nucleotide analogues and methods, I disagree there would be any such motivation.
169. In my opinion there is no motivation to combine any of the references at issue and Shorts adds nothing because the claimed nucleotide analogues and methods require incorporation of a single nucleotide analogue into the end of a primer extension strand.
170. Because the claimed nucleotide analogues and methods do not require sequencing G-C rich regions of DNA, any purported advantage of a deazapurine nucleotide analogue for solving a problem of sequencing

G-C rich regions is inapplicable to the nucleotide analogues and methods in the claim.

171. Therefore, Short does not provide to a person of ordinary skill any motivation to make any of the claimed deazapurine nucleotide analogues or methods.
172. There are no express disclosures in Short of essential criteria for nucleotide analogues used in reversibly terminating DNA sequencing methods, such as the nucleotide analogues and methods in the claim.
173. There are no suggestions in Short that the disclosed nucleotide analogues would be useful in the methods claimed. Further, the Short nucleotide analogues do not (1) contain a deazapurine-substituted base to which a label is attached through a cleavable linker, and (2) include a removable chemical moiety capping the 3'-OH group of the sugar, as required for the claimed nucleotides and methods, nor are (3) there any disclosures demonstrating that the Short nucleotide analogues are incorporated into the end of a nucleic acid primer extension strand, as required for the claimed methods.
174. There is also no disclosure in Short of a synthetic process for converting the disclosed reversibly terminated labeled nucleotide

analogues into the claimed cleavable deazapurine base-labeled and reversibly capped 3-OH nucleotide analogues.

175. Therefore, Short does not provide a person of ordinary skill any motivation to make any of the claimed nucleotide analogues. Nor would he or she have any reasonable expectation that using a Short nucleotide analogue could be successfully used in the claimed methods, for the reasons stated above and throughout my Declaration.

4. Ward (Exhibit 1032)

176. Ward described the use of nucleotide analogues in molecular probes for labeling or isolating DNA or DNA/protein complexes. (Exhibit 1032, Ward, col. 3, ll. 17-23). The nucleotide analogues in Ward contain biotin labels that are attached through a non-cleavable chemical linker to a nucleobase. Ward describes a large genus of potential nucleobases, including deazapurines. (Exhibit 1032, Ward, field [57], abstract).

177. The claimed nucleotide analogues and methods do not relate to molecular probes for labeling or isolating DNA or DNA/protein complexes.

178. There are no suggestions in Ward that the disclosed nucleotide analogues are useful in DNA sequencing. The Ward nucleotide

analogues do not (1) contain a deazapurine-substituted base to which a label is attached through a cleavable linker, and (2) include a removable chemical moiety capping the 3'-OH group of the sugar, as required for the claimed nucleotides and methods, nor are (3) there any disclosures demonstrating that the Ward nucleotide analogues are incorporated into the end of a nucleic acid primer extension strand, as required for the claimed nucleotide analogues and methods.

179. To the extent that Illumina is relying on Ward because of Ward's disclosure of a large genus of potential nucleobases, including deazapurines, as evidence of a person of ordinary skill's motivation to combine the references at issue to obviously arrive at the claimed nucleotide analogues and methods, I disagree there would be any such motivation.
180. In my opinion there is no motivation to combine the references at issue obtained from Ward because the claimed nucleotide analogues and methods only require incorporation of a single nucleotide analogue into the end of a primer extension strand.
181. Because the claimed nucleotide analogues and methods do not require sequencing G-C rich regions of DNA, any purported advantage of a deazapurine nucleotide analogue for solving a problem of sequencing

G-C rich regions is inapplicable to the nucleotide analogues and methods in the claim.

182. Therefore, Ward does not provide a person of ordinary skill with any motivation to make any of the claimed deazapurine nucleotide analogues or methods.

183. There is also no disclosure in Ward of a synthetic process for converting the disclosed biotin-labeled nucleotide analogues into the claimed cleavable deazapurine base-labeled and reversibly terminated 3-OH nucleotide analogues.

184. Therefore, Ward does not provide a person of ordinary skill with any motivation to make any of the claimed deazapurine nucleotide analogues. Nor would he or she have any reasonable expectation that a nucleotide analogue described in Ward could be successfully used in the claimed methods, for the reasons stated above and throughout my Declaration.

185. After being referred to Ward by his attorney during his redirect deposition examination, Dr. Weinstock stated that Ward may be suggesting that the 7-deazapurine may be preferred for the purposes of Ward. (Exhibit 1034, Weinstock Dep., 351:10-23.)

186. In my opinion, Ward would not have been understood by a person of ordinary skill to supersede the disclosure in Tsien because Ward did not relate to nucleotide analogues for sequencing DNA, whereas Tsien's nucleotide analogues were disclosed as being for that purpose.

5. Khan (Exhibit 1033)

187. Khan discloses labeled nucleotide analogues that are useful for Sanger sequencing. (Exhibit 1033, Khan, col. 2, ll. 54-63, col. 10, l. 66 - col. 11, l. 24.)

188. There are no suggestions in Khan that the disclosed nucleotide analogues are useful in other types of DNA sequencing. The Khan nucleotide analogues do not (1) contain a deazapurine-substituted base to which a label is attached through a cleavable linker, and (2) include a removable chemical moiety capping the 3'-OH group of the sugar, as required for the claimed nucleotides and methods, nor are (3) there any disclosures demonstrating that the Khan nucleotide analogues are incorporated into a nucleic acid primer extension strand, as required for the claimed methods.

189. To the extent that Illumina is relying on Khan because of Khan's disclosure of a large genus of potential nucleobases, including deazapurines, as evidence of a person of ordinary skill's motivation to

combine other references to obviously arrive at the claimed nucleotide analogues and methods, I disagree there would be any such motivation.

190. In my opinion there is no motivation to combine Khan with other references because the claimed nucleotide analogues and methods only require incorporation of a single nucleotide analogue into the primer extension strand.
191. Because the claimed nucleotide analogues and methods do not require sequencing G-C rich regions of DNA, any purported advantage of a deazapurine nucleotide analogue for solving a problem of sequencing G-C rich regions is inapplicable to the claimed nucleotide analogues and methods.
192. Therefore, Khan does not provide a person of ordinary skill with any motivation to make any of the claimed deazapurine nucleotide analogues or methods.
193. There is also no disclosure in Khan of a synthetic process for converting the disclosed reversibly terminated labeled nucleotide analogues into the claimed cleavable deazapurine base-labeled and reversibly capped 3'-OH nucleotide analogues.

194. Therefore, Khan does not provide a person of ordinary skill any motivation to make any of the claimed deazapurine nucleotide analogues or methods. Nor would he or she have any reasonable expectation that a Khan nucleotide analogue could be successfully used in the claimed methods, for the reasons stated above and throughout my Declaration.
195. After being referred to Khan by his attorney during his redirect deposition examination, Dr. Weinstock stated that Khan was discussed for attachment of a label to either the 8-position or the 7-position, and decided to attach at the 7-position. (Exhibit 1034, Weinstock Dep., 354-355).
196. In my opinion, Khan would not have been understood by a person of ordinary skill to supersede the disclosure in Tsien because Khan did not relate to reversibly capped nucleotide analogues, whereas Tsien's nucleotide analogues were disclosed as being used for that method. Moreover, just as Khan was choosing between using the 7-position and the 8-position of a base for attaching a label, so would have a person having ordinary skill also would have to choose between those positions in the context of the guidance provided by Tsien that the 8-position is ideal.

M.OBJECTIVE INDICIA OF NONOBVIOUSNESS

197. Columbia's counsel has informed me that evidence of so-called "objective indicia of nonobviousness" must be considered when evaluating whether a patent claim is obvious in light of the prior art.

198. I have further been informed that these objective indicia include, but are not limited to, "unexpected properties," "praise and awards," "commercial success," "copying," and "skepticism."

199. I address the facts relating to these objective indicia below.

1. Unexpected Properties and Results

200. I have also been asked by Columbia's counsel to consider whether Columbia's claimed inventions have yielded unexpected properties or results not present in the prior art.

201. Based on my knowledge and experience in the field, and on my review of the materials mentioned below, it is my opinion that Columbia's claimed nucleotide analogues and methods of using them have unexpected properties and have yielded unexpected results.

202. Despite the lack of any reasonable expectation, as explained above, that a nucleotide analogue combining all the features arranged as in Columbia patent claims –a cleavable chemical group capping the 3'-

OH position of the sugar and a label attached to the nucleotide base via a cleavable linker – would be incorporated into a primer extension strand by a polymerase, such nucleotide analogues are in fact successfully incorporated.

203. The claimed nucleotide analogues also have advantageous unexpected properties that go beyond incorporation into a primer extension strand of a single labeled nucleotide analogue as recited in the claims, and these properties have revolutionized the DNA sequencing industry.
204. Using the claimed nucleotides and repeatedly using the claimed methods, Ju *et al.* (2006) reported successful sequencing of a 20-nucleotide DNA template – an important threshold in the development of sequencing technology. Ju *et al.* did so using four nucleotide analogues, each having both a unique detectable label attached through a chemically cleavable linker to the base (two pyrimidines and two deazapurines), and a chemically cleavable chemical group capping the 3'-OH group of the sugar, as shown in Fig. 1. (Ex. 2034, Ju 2006 at 19636.)
205. Not only did Dr. Ju's claimed nucleotides and methods allow sequencing of a 20-nucleotide DNA template – it did so better than other next-generation sequencing techniques, a result that was

unexpected. For example, Ju 2006 provides a comparison of the results of SBS using the four nucleotide analogues shown in Fig. 1 with results obtained using “pyrosequencing”. (Ex. 2034, Ju 2006 at 19636, Fig. 1, Fig. 5.)

206. When the four nucleotide analogues shown in Fig. 1 were used, the Ju 2006 SBS method “clearly identified” all 20 nucleotide in the DNA template, including regions of five and ten repeating “A” (adenosine) residues, as shown in Fig 5A. (Ex. 2034, Ju 2006 at Fig. 5.)
207. This accurate identification was made possible by the fact that Dr. Ju’s nucleotide analogues separated the cleavable chemical group at the 3’-OH position of the sugar from the detectable label, which was placed instead on the base. That separation resulted in nucleotide analogues that do not hinder recognition by the polymerase, not only in a single incorporation but also during multiple (*i.e.*, 20 nucleotide) incorporations.
208. In contrast, sequencing the same DNA template sequence using pyrosequencing produced a result from which it was “very difficult to identify the exact sequence from the data,” due to a build-up of signal into large peaks.

209. Thus, not only was it not predictable that the claimed nucleotide analogue would be incorporated *at all* by a polymerase, it was unexpected that multiple incorporations of such nucleotide analogues would produced a clear and accurate signal that significantly improved the readout over the signal obtained by pyrosequencing, over a 20-nucleotide template containing difficult-to-sequence repeat regions.
210. Nucleotide analogues having the features recited as in the claims were reported by others to provide “perfectly matched” readouts when used in SBS. For example, Batista 2008 reported: “[w]e used Solexa sequencing technology (Seo et al., 2004) to generate 29,112,356 small-RNA cDNA reads that perfectly matched the *C. elegans* genome.” (Ex. 2035, Batista 2008 at 2.) It would have been very difficult if not impossible to obtain 29,112,356 “perfectly matched” reads using pyrosequencing.
211. Based on my analysis of the literature, Batista 2008 is one of hundreds that use nucleotide analogues having the features as in the claims (*i.e.*, nucleotide analogues separating the cleavable 3'-OH cap and the cleavably-linked base label) to successfully sequence DNA.

212. In fact, nucleotides configured as in the claims have been used in “massively parallel” systems to sequence entire genomes. (See, e.g. Batista 2008) Such a result would not have been expected in October 2000 given the state of the art at that time.
213. Another unexpected benefit associated with the nucleotide analogues claimed was identified by Illumina’s expert Dr. Weinstock. During his Deposition, at which I was present, Dr. Weinstock testified that nucleotide analogues having a label on the base have the beneficial property of being useable in sequencing methods that require repetitive incorporation of nucleotide analogues, in particularly dGTPs, to sequence DNA having stretches of G:C rich regions. (Exhibit 1034, Weinstock Dep., 150:25-153:15.) Dr. Weinstock testified that placing a label on the base has a much larger effect toward addressing the problem associated with sequencing G:C rich regions than the effect of changing a purine base to a deazapurine base. (*Id.*, 151:13-152:5.)
214. Dr. Weinstock runs one of the largest sequencing centers in the country and has significant experience in sequencing G:C rich regions using various sequencing methods (Ex. 1021, ¶3; Ex 1034, Weinstock Dep. 14:8-12). I was surprised to learn that nucleotide analogues

having a label on the base have solved the problem of sequencing G:C rich regions. Thus, a person of ordinary skill in the art would also be surprised that nucleotide analogues having a label on the base have unexpected properties that solved the problem of sequencing G:C rich regions.

2. **Praise and Awards**

215. I have also been asked by Columbia's counsel to consider whether the Columbia inventions have received significant praise or awards.
216. Based on my knowledge and experience in the field, and on my review of the materials mentioned below, it is my opinion that the Columbia inventions have received significant praise or awards.
217. Dr. Ju received highly-competitive government grants to support his work in connection with each of the patents-at-issue. The inventive work presented in the '698, '869, and '575 Patents was supported by National Science Foundation ("NSF") award no. BES0097793, as indicated at the beginning of each of the patents.
218. I reviewed the NSF "Form 7" for Dr. Ju's grant funding the inventions of the '698, '869, and '575 Patents. (Ex. 2036, CU0055411-12.) That form summarizes the review process and ratings for Dr. Ju's grant proposal that resulted in NSF award no. BES0097793. (Ex. 2036,

CU0055411-12.) Form 7 indicates that Dr. Ju's grant proposal was ranked as the number two proposal of 38 proposals considered. (*Id.* at CU0055412.) It also indicates that all reviewers rated the proposal "Excellent to Very Good." (*Id.*)

219. The nucleotide and analogues and methods claimed in the patents-at-issue here are also described in several publications by Dr. Ju in the prestigious PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES ("PNAS"). Among those publications is Ju, J. *et al.*, *Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators*, 103 PROC. NAT'L ACAD. SCI. 19635 (Oct. 2006) ("Ju 2006") (Ex. 2034).
220. Reviewer comments for Ju PNAS 2006 indicate that the paper is in the top 10% in its field.
221. Reviewer comments also state that "[Dr. Ju's] manuscript presents a novel approach involving DNA sequencing by synthesis using four fluorescent reversible terminators;" that it "clearly establishes a unique and robust strategy for DNA sequencing by synthesis on a chip;" and that "the general principle shown in the manuscript can be extended to develop a very high throughput DNA sequencing chip

system that can be used routinely for a wide range of applications.”
(Ex. 2037, CU0050552-53.)

222. In addition, I understand that in 2001 Dr. Ju received a Packard Fellowship from the David & Lucile Packard Foundation, a private foundation that provides grants to non-profit organizations. (Ex. 2038, CU0055444-46.) The Packard Fellowship related to Dr. Ju’s inventive work and provided Dr. Ju with \$625,000 of funding for that work over a five-year period.

223. According to the Packard Foundation website, the Packard Foundation “established the Fellowships for Science and Engineering to allow the nation’s most promising professors to pursue science and engineering research early in their careers with few funding restrictions and limited reporting requirements.” (*See* Ex. 2039, “What We Fund” *available at* <http://www.packard.org/what-we-fund/conservation-and-science/packard-fellowships-for-science-and-engineering>, *last visited* June 21, 2013.)

224. All of these facts confirm my own opinion that others with expertise in the field of DNA sequencing have praised Dr. Ju’s work and the inventions recited in the claims of the patents.

[TEXT REDACTED]

I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001.)

Executed on June 25, 2013



George L. Trainor, Ph.D.

GEORGE L. TRAINOR, Ph.D.

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SUMMARY

- Proven drug discovery leader with over 35 development candidates advanced into development across multiple therapeutic areas, including oncology, virology, and neuroscience.
- Experienced in all aspects of oncology drug discovery including therapeutic area strategy, target selection, lead identification, lead optimization, and drug candidate qualification.
- Respected team leader, adept at developing and managing teams of 100+ scientists.
- Extensive expertise in conceptualizing, establishing, and managing research alliances with both internal and external partners.
- Broad capabilities in the in-licensing and out-licensing of assets including due diligence and opportunity analysis.
- Experience in partnering and licensing in the Asian sector (Japan, China, India).
- Expertise in discovery portfolio analysis and sustainability.
- Deep understanding of the development and implementation of transformational research technologies (2011 ACS Heroes of Chemistry Award for fluorescence-tagged terminator DNA sequencing).
- Outstanding communicator in all forums (50 invited symposium and university lectures).
- Demonstrated productivity with over 85 peer-reviewed publications and 18 issued US patents.

EXPERIENCE

BIOMOTIV – The Harrington Project for Discovery and Development 2012-Present
Venture Partner

- Scientific Leadership in medicinal chemistry and in all aspects of drug discovery through to clinical candidate selection.
- Due diligence and portfolio management in a bio-accelerator environment.

TRAINOR CONSULTING, LLC 2011-Present
Partner, Executive Pharmaceutical Consultant

- Consulting services on all aspects of pharmaceutical discovery.
- Experience with large pharma, biotech, and non-profits on a “one off”, periodic, or continuous basis.

Case IPR2012-00006

U.S. Patent 7,713,698

June 25, 2013

- Special expertise in conducting due diligence behind firewalls on programs, lead series, and drug candidates.
- Experience as an expert witness.
- On site consultation provided internationally.

BRISTOL-MYERS SQUIBB CO.

2002-2010

Vice President, Oncology and Early Discovery Chemistry, 2008-2010

Executive Director, Oncology and Early Discovery Chemistry, 2002-2008

- Leadership of a team of 100+ scientists.
- Responsible for all oncology chemistry, hits-to-leads chemistry across all BMS therapeutic areas, chemical synthesis, and radiochemistry.
- Advanced candidates targeted at Her1/2, VEGFR2, met, AR, IGF-1R, etc.
- Initiated and/or supervised alliances with Ambit, Nerviano, Exelixis, et al.
- Led portfolio sustainability and research project team optimization initiatives.
- Active Member of the Drug Discovery and Early Development Senior Leadership Team.

DUPONT-MERCK / DUPONT PHARMAEUTICAL CO.

1991-2002

Executive Director, Chemistry, 1998-2002

Senior Director, Chemistry, 1994-1998

Associate Director, Cancer Research, 1993

Associate Director, Nucleic Acid Technology, 1991-1992

- Candidates advanced: antitumor agents, HIV (NNRTIs, PIs), and neuroscience targets (CRF), etc.
- Preclinical development studies leading to US marketing approval for the NNRTI efavirenz (SustivaTM).
- Seminal studies on antisense oligonucleotide sequence selection and *in vivo* pharmacology.

DUPONT CENTRAL RESEARCH AND DEVELOPMENT

1981-1991

Associate Director, 1991

Research Leader, 1987-1990

Member of the Research Staff, 1981-1986

- Co-inventor of the Genesis 2000TM DNA Sequencing system.
- Lead inventor on the US patent covering the use of fluorescence-tagged, chain-terminating nucleotides for automated DNA sequencing.

EDUCATION

COLUMBIA UNIVERSITY, Department of Chemistry 1979-1981
NIH Postdoctoral Fellow

- Advisor: Prof. Ronald Breslow

HARVARD UNIVERSITY, Department of Chemistry 1979
Ph.D. and M.A. in Organic Chemistry

- Thesis Advisor: Prof. Yoshito Kishi

STEVENS INSTITUTE OF TECHNOLOGY 1974
B. S. Chemistry

- Research Advisor: Prof. Ajay Bose

PROFESSIONAL ACTIVITIES

- | | |
|--|-----------|
| • Study Sections: DOE, NIH, OTA for Genomic Studies | 1988-1990 |
| • Conference Chair: GRC (Bioorg Chem), ACS MARM | 1991-2000 |
| • Pacificchem Organizing Committee | 1996-2005 |
| • Section Editor – Annual Reports in Medicinal Chemistry | 1996-2002 |
| • Member: ACS, AACR | |

AWARDS

- 2011 American Chemical Society Heroes of Chemistry Award for “Dye Terminator DNA Sequencing”.

George L. Trainor

Publications

1. P. Houdewind, U. K. Pandit, A. K. Bose, R. J. Brambilla, and G. L. Trainor, Heterocycles, **1**, 53-57 (1973). *"Influence of the Heterocyclic Base-Component on the Reaction of Enamines with Allylic Halides"*
2. A. K. Bose, P. R. Srinivasan, and G. L. Trainor, Journal of the American Chemical Society, **96**, 3670-3671 (1974). *"Nuclear Magnetic Resonance Spectral Studies. VIII. Titanium Tetrachloride as a Shift Reagent"*
3. G. L. Trainor and R. Breslow, Journal of the American Chemical Society, **103** 154-158 (1981). *"High Acylation Rates and Enantioselectivity with Cyclodextrin Complexes of Rigid Substrates"*
4. R. Breslow, G. L. Trainor, and A. Ueno, Journal of the American Chemical Society, **105**, 2739-2744 (1983). *"Optimization of Metallocene Substrates for β -Cyclodextrin Catalysis"*
5. W. J. le Noble, S. Srivastava, R. Breslow, and G. Trainor, Journal of the American Chemical Society, **105**, 2745-2748 (1983). *"Effect of Pressure on Two Cyclodextrin-Promoted Ester Hydrolyses"*
6. G. L. Trainor and B. E. Smart, Journal of Organic Chemistry, **48**, 2447-2448 (1983). *"Preparation of a Stable Glucopyranosyliron Compound"*
7. R. Breslow, J. Chin, D. Hilvert, and G. Trainor, Proceedings of the National Academy of Science USA, **80**, 4585-4589 (1983). *"Evidence for the General Base Mechanism in Carboxypeptidase A-Catalyzed Reactions: Partitioning Studies on Nucleophiles and $H_2^{18}O$ Kinetic Isotope Effects"*
8. G. L. Trainor, Journal of Organometallic Chemistry, **282**, C43-C45 (1985). *"Chirality Transfer to Iron in a Photochemical Reaction of a Glucopyranosyliron Compound"*
9. P. Deshong, G. A. Slough, V. Elango, and G. L. Trainor, Journal of the American Chemical Society, **107**, 7788-7790 (1985). *"Organo-Transition-Metal-Based Approach to C-Glycosides"*
10. G. L. Trainor, Journal of Carbohydrate Chemistry, **4**, 545-563 (1985). *"The Preparation of O-Trifluoromethyl Carbohydrates"*
11. J. M. Prober, G. L. Trainor, R. J. Dam, F. W. Hobbs, C. W. Robertson, R. J. Zagursky, A. J. Cocuzza, M. A. Jensen, and K. Baumeister, Science, **238**, 336-341 (1987). *"A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides"*
12. G. L. Trainor and M. A. Jensen, Nucleic Acids Research, **16**, 11846 (1988). *"A Procedure for the Preparation of Fluorescence-Labeled DNA with Terminal Deoxynucleotidyl Transferase"*
13. G. L. Trainor, Anal. Chem., **62**, 418-426 (1990). *"DNA Sequencing, Automation, and the Human Genome"*
14. M. A. Jensen, R. J. Zagursky, G. L. Trainor, A. J. Cocuzza, A. Lee, and E. Y Chen, Sequence, **1** (4) 233-239 (1991). *"Improvements in the Chain-Termination Method of DNA Sequencing through the Use of 7-Deaza-2'-deoxyadenosine"*
15. J. A. Zebala, J. Choi, G. L. Trainor, and F. Barany, J. Biol. Chem., **267** (12) 8106-8116 (1992). *"DNA Recognition of Base-Analogue and Chemically Modified Substrates by the TaqI Restriction Endonuclease"*

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The Oak Ridge Conference on Advanced Analytical Concepts for the Clinical Laboratory, Savannah GA, "A Fluorescence-Based Nucleic Acid Analysis System", April 1988.

Workshop on International Cooperation for the Human Genome Project, Valencia, Spain, October 1988.

ATB '88 Advance Technology for the Clinical Laboratory and Biotechnology, Milan, Italy, "A Fluorescence-Based Nucleic Acid Analysis System", November 1988.

Banbury Center Conference on DNA Technology and Forensic Science, Cold Spring Harbor NY, "Fluorescence Detection in Nucleic Acid Analysis", December 1988.

American Chemical Society, Delaware Section Meeting, Wilmington DE, "A Fluorescence-Based System for Nucleic Acid Sequencing", January 1989.

20th NSF Workshop on Organic Synthesis and Natural Products Chemistry, Holderness NH, July 1989.

American Chemical Society National Meeting, *Organic Chemistry in Industry Symposium*, Miami Beach FL, "Chemical Reagents for Molecular Biology", September 1989.

Natural Products Gordon Research Conference, New Hampton NH, "Chemical Reagents for Molecular Biology", July 1990.

Advances in Interpretative Biochemistry, Toronto General Hospital, "Methodologies for Genetic Analysis", September 1990.

Nagoya Conference: Frontier of Organic Synthesis--Rational Creation of Biologically Active Molecules, Nagoya, Japan, "Chemical Reagents for Molecular Biology", December 1990.

Middle Atlantic Regional American Chemical Society Meeting, Newark DE, "Novel Oligonucleotide Analogues with a Sulfur-Based Linkage", May 1991.

Symposium in Honor of Ronald Breslow, Columbia University, NY, "Chemical Reagents for Molecular Biology", August 1991.

Delaware Valley Enzymology Club, King of Prussia, PA, "Progress and Prospects in Nucleic Acid-Based Therapeutics", November 1991.

Banbury Center Conference on Oligonucleotide Manipulation of Gene Expression: Its Therapeutic Potential, Cold Spring Harbor, NY, "Oligonucleotide Analogues with Sulfamate and Sulfamide Internucleotide Linkages", October 1992.

Western Biotech Conference, San Diego, CA, "An Antisense Therapeutic Approach to Multidrug Resistance: Sequence Selection", October 1995.

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Medicinal Chemistry Gordon Research Conference, New London, NH, "Plasma Protein Binding and Drug Action", August 2004.

Drew Residential School on Medicinal Chemistry, Madison, NJ, "Plasma Protein Binding", June 2005.

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American Chemical Society National Meeting, Philadelphia PA, "Preparation, Structure, and Reactivity of a Glucopyranosyliron Compound", August 1984.

Nucleic Acids Gordon Research Conference, New Hampton NH, "A Fluorescence-Based Nucleic Acid Analysis System", June 1987.

Molecular Genetics Gordon Research Conference, Newport RI, "A Fluorescence-Based Nucleic Acid Analysis System" (poster), August 1987.

Genome Mapping and Sequencing, Cold Spring Harbor NY, "An Automated System for Fluorescence-Based Nucleic Acid Analysis", April 1988.

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Nucleic Acid Applications, San Diego CA, "Chemical Reagents for Molecular Biology" (poster), October 1989.

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Villanova University, Department of Chemistry, Villanova PA, "A Fluorescence-Based System for Nucleic Acid Analysis", September 1988.

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State University of New York at Stony Brook, Stony Brook, NY, "Nucleic Acid-Based Therapeutics: Progress and Prospects", December 1991.

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PROPOSED SUBSTITUTE CLAIMS

Claim 18. A method of ~~claim 1~~ determining the identity of a nucleotide analogue incorporated into a nucleic acid primer extension strand, comprising:

a) contacting a nucleic acid template attached to a solid surface with a nucleic acid primer which hybridizes to the template;

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, so as to incorporate one of the nucleotide analogues onto the nucleic acid primer and form a nucleic acid primer extension strand, wherein each nucleotide analogue within (i) or (ii) comprises a base labeled with a unique label and contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue, wherein each of said unique labels is attached to the nucleotide analogue via a cleavable linker and wherein at least one of the four nucleotide analogues within (i) or (ii) is deaza-substituted; and

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.

Claim 19. The method of claim [[1]] 18, 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.

Claim 20. The method of claim [[1]] 18, wherein the unique label is a fluorescent label.

Claim 21. The method of claim [[1]] 18, wherein the polymerase is Taq DNA polymerase, T7 DNA polymerase or Vent DNA polymerase.

Claim 22. The method of claim [[1]] 18, wherein in step a) a plurality of different nucleic acid templates are attached to the solid surface.

Claim 23. The method of claim [[1]] 18, wherein said nucleic acid template comprises an RNA template.

Claim 24. The method of claim [[6]] 23, wherein the polymerase is reverse transcriptase.

Claim 25. A plurality of different nucleic acid templates immobilized on a solid surface, wherein a nucleic acid primer is hybridized to such nucleic acid templates each such nucleic acid primer comprising a labeled incorporated nucleotide analogue, at least one of which is deaza-substituted, wherein each labeled nucleotide analogue comprises a base labeled with a unique label and contains a removable chemical moiety capping the 3'-OH group of the sugar of the nucleotide analogue.

Claim 26. The plurality of nucleic acids of claim [[11]] 25, wherein said plurality are present in a microarray.

Claim 27. The method of claim [[2]] 19, 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.

Claim 28. The method of claim [[1]] 18, wherein said template is attached to said solid surface via a chemical group introduced into said template by a polymerase chain reaction.

Claim 29. The method of claim [[1]] 18, wherein the chemical moiety capping the 3'-OH group is not a fluorescent dye.