UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLETE GENOMICS, INC.
Petitioner

v.

ILLUMINA CAMBRIDGE LTD.
Patent Owner

Case IPR2017-02174
Patent 7,566,537 B2

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,566,537 B2

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1503	Roger Y. Tsien et al., WO 91/06678 A1 (published May 16, 1991) ("Tsien")
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1506	Bernard Loubinoux et al., *Protection of Phenols by the Azidomethylene Group Application to the Synthesis of Unstable Phenols*, TETRAHEDRON 44:6055-64 (1988), including translation, supporting affidavit and original publication ("Loubinoux")
1507	James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, SCIENCE 238:336-41 (1987) ("Prober")
1508	Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications*, TETRAHEDRON LETTERS 32:7593-96 (1991) ("Zavgorodny")
1509	S.G. Zavgorodny et al., *S,X-Acetals in Nucleoside Chemistry, III, Synthesis of 2′- and 3′-O-Azidomethyl Derivatives of Ribonucleosides*, NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS 19:1977-91 (2000) ("Zavgorodny 2000")
1510	J.D. Watson & F.H.C. Crick, *Molecular Structure of Nucleic Acids*, NATURE 171:737-38 (1953)
1511	Steven M. Carr, *Deoxyribose versus Ribose Sugars* (2014), *at* https://www.mun.ca/biology/scarr/Ribose_sugar.html (downloaded Sept. 25, 2017)
1512	Michael L. Metzker, *Emerging Technologies in DNA Sequencing*, GENOME RES. 15:1767-76 (2005) ("Metzker 2005")
1513	A. Kornberg et al., *Enzymatic Synthesis of deoxyribonucleic acid*, BIOCHIM. BIOPHYS. ACTA 21:197-198 (1956) ("Kornberg")
1514	Bruce Merrifield, *Solid Phase Synthesis*, SCIENCE 232:341-47 (1986) ("Merrifield")

1515	William C. Copeland et al., *Human DNA Polymerases α and β Are Able to Incorporate Anti-HIV Deoxynucleotides Into DNA*, J. BIOL. CHEM. 267:21459-64 (1992) ("Copeland")
1516	Hamilton O. Smith & K.W. Wilcox, *A Restriction Enzyme from Hemophilus influenzae. I. Purification and General Properties*, J. MOL. BIOL. 51:379-91 (1970)
1517	Thomas J. Kelly, Jr. & Hamilton O. Smith, *A restriction enzyme from Hemophilus influenzae. II. Base sequence of the recognition site*, J. MOL. BIOL. 51:393-409 (1970)
1518	F. Sanger & A.R. Coulson, *A Rapid Method for Determining Sequences in DNA by Primed Synthesis with DNA Polymerase*, J. MOL. BIOL. 94:441-48 (1975) ("Sanger & Coulson")
1519	Allan M. Maxam & Walter Gilbert, *A New Method for Sequencing DNA*, PROC. NATL. ACAD. SCI. USA 74:560-64 (1977) ("Maxam & Gilbert")
1520	F. Sanger et al., *DNA Sequencing with Chain-Termination Inhibitors*, PROC. NATL. ACAD. SCI. USA 74:5463-67 (1977) ("Sanger")
1521	Radoje Drmanac et al., *Sequencing of Megabase Plus DNA by Hybridization*, GENOMICS 4:114-28 (1989) ("Drmanac")
1522	Edwin Southern & William Cummings, U.S. Patent 5,770,367 (June 23, 1998)
1523	ALDRICH HANDBOOK OF FINE CHEMICALS AND LABORATORY EQUIPMENT 2000-2001 (Sigma Aldrich Co. 2000)
1524	Bruno Canard & Robert S. Sarfati, *DNA Polymerase Fluorescent Substrates with Reversible 3'-tags*, GENE 148:1-6 (1994) ("Canard 1994")
1525	Robert A. Stockman, Book Review, J. AM. CHEM. SOC. 122:426-26 (*reviewing* Greene & Wuts) (2000)
1526	Joyce, C.M. *Choosing the right sugar: How polymerases select a nucleotide substrate*, PROC. NATL. ACAD. SCI. USA 94:1619-1622 (March 1997)
1527	Jari Hovinen et al., *Synthesis of 3'-O-(ω-Aminoalkoxymethyl)thymidine 5'-Triphosphates, Terminators of DNA Synthesis that Enable 3'-Labelling*, J. CHEM. SOC. PERKIN TRANS. 1:211-17 (1994)
1528	Yuri G. Gololobov & Leonid F. Kasukhin, *Recent Advances in the Staudinger Reaction*, TETRAHEDRON 48:1353-406 (1992) ("Gololobov 1992")

1529	Eliana Saxon & Carolyn R. Bertozzi, *Cell Surface Engineering by a Modified Staudinger Reaction*, SCIENCE 287:2007-10 (2000) ("Saxon & Bertozzi")
1530	D.H. Dube and C.R. Bertozzi, *Metabolic oligosaccharide engineering as a tool for glycobiology*, CURR. OPIN. CHEM. BIOL. 7:616-625 (2003)
1531	Eliana Saxon & Carolyn R. Bertozzi, U.S. Pub. 2002/0016003 A1, Chemoselective Ligation (published Feb. 7, 2002)
1532	Eliana Saxon et al., *Investigating Cellular Metabolism of Synthetic Azidosugars with the Staudinger Ligation*, J. AM. CHEM. SOC. 124:14893-902 (2002)
1533	Saul Kit, *Deoxyribonucleic Acids*, ANNU. REV. BIOCHEM. 32:43–82 (1963) ("Kit")
1534	Che-Hung Lee et al., *Unwinding of Double-stranded DNA Helix by Dehydration*, PROC. NATL. ACAD. SCI. USA 78:2838-42 (1981) ("Lee")
1535	Gordon et al., Abstract, Biophysical Society 6th Annual Meeting (Washington, 1962)
1536	Lawrence Levine et al., *The Relationship of Structure to the Effectiveness of Denaturing Agents for Deoxyribonucleic Acid*, BIOCHEM. 2:168-75 (1963)
1537	Derek L. Stemple et al., U.S. Patent No. 7,270,951 B1 (Sept. 18, 2007) ("Stemple III")
1538	Jingyue Ju et al., U.S. Patent 6,664,079 B2 (Dec. 16, 2003) ("Ju")
1539	David Bentley et al., *Accurate Whole Human Genome Sequencing Using Reversible Terminator Chemistry*, NATURE 456:53-59 (2008) ("Bentley")
1540	Elaine R. Mardis, *A Decade's Perspective on DNA Sequencing Technology*, NATURE 470:198-203 (2011) ("Mardis")
1541	Michael L., Metzker, et al., *Termination of DNA synthesis by novel 3′-modified deoxyribonucleoside 5′-triphosphates*, NUC. ACIDS RES. 22:4259-67 (1994) ("Metzker 1994")
1542	Bruno Canard et al., *Catalytic Editing Properties of DNA Polymerases*, PROC. NATL. ACAD. SCI. USA 92:10859-63 (1995) ("Canard 1995")
1543	Fabrice Guillier et al., *Linkers and Cleavage Strategies in Solid-Phase Organic Synthesis and Combinatorial Chemistry*, CHEM. REV. 100, 100:2091-157 (2000) ("Guillier")
1544	Y.G. Gololobov et al., *Sixty years of Staudinger reaction*, TETRAHEDRON 37:437-72 (1981) ("Gololobov 1981")

1545	Kevin Davies, *The British Invasion*, in THE $1,000 GENOME: THE REVOLUTION IN DNA SEQUENCING AND THE NEW ERA OF PERSONALIZED MEDICINE 102-15 (Ch. 5), 298-99 (Ch. 5 Notes) (2010) ("Davies")
1546	Vincent P. Stanton et al., WO 02/21098 A2 (published Sept. 5, 2000) ("Stanton")
1547	Seela, U.S. Patent No. 4,804,748 (Feb. 14, 1989)
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1550	Declaration of Thomas Hyatt (Sept. 28, 2017) (Attachment filed as Ex. 1051)
1551	Attachment to Declaration of Thomas Hyatt: Travis Young, *A Strategy for the Synthesis of Sulfated Peptides*, A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry) at the University of Wisconsin-Madison (2001) ("Young")
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1553	Pentti Oksman et al., *Solution Conformations and Hydrolytic Stability of 2'- and 3'-Substituted 2',3'-Dideoxyribonucleosides, Including some Potential Inhibitors of Human Immunodeficiency Virus*, J. OF PHYSICAL ORGANIC CHEM. 5:741-47 (1992) ("Oksman")
1554	Eric F.V. Scriven et al., *Azides: Their Preparation and Synthetic Uses*, CHEMICAL REVIEWS 88:297-368 (1988)

1555	Peter C. Cheeseman, U.S. Patent No. 5,302,509 (Apr. 12, 1994) ("Cheeseman")
1556	M. Vaultier et al., *General Method to Reduce Azides to Primary Amines by Using the Staudinger Reaction*, TETRAHEDRON LETTERS 24:763-64 (1983). including translation, supporting affidavit and original publication ("Vaultier")
1557	John A. Burns et al., *Selective Reduction of Disulfides by Tris(2-carboxyethyl)phosphine*, J. OF ORGANIC CHEM. 56:2648-2650 (1991) ("Burns")
1558	Anthony L. Handlon & Norman J. Oppenheimer, *Thiol Reduction of 3′-Azidothymidine to 3′-Aminothymidine: Kinetics and Biomedical Implications*, PHARM. RES. 5:297-99 (1988) ("Handlon")
1559	Mark D. Uehling, *Wanted: The $1000 Genome*, Bio-IT World (Nov. 15, 2002), http://www.bio-itworld.com/archive/111202/genome (printed Oct. 2, 2017)
1560	Kevin Davies, *13 years ago, a beer summit in an English pub led to the birth of Solexa and—for now at least —the world's most popular second-generation sequencing technology*, Bio-IT World (Sept. 28, 2010), http://www.bio-itworld.com/2010/issues/sept-oct/solexa.html (printed Aug. 2, 2017)
1561	Wikipedia, Shankar Balasubramanian, https://en.wikipedia.org/wiki/Shankar_Balasubramanian (last visited Aug. 2, 2017)
1562	Past Group Members - Balasubramanian Group, http://www.balasubramanian.co.uk/past-group-members (printed Aug. 2, 2017)
1563	Sarah Houlton, Profile: Flexibility on the move, Chemistry World (Nov. 29, 2010) https://www.chemistryworld.com/news/profile-flexibility-on-the-move/3003307.article (printed Aug. 2, 2017)
1564	LinkedIn, Harold Swerdlow, https://www.linkedin.com/in/harold-swerdlow-9aa6981/ (printed Aug. 2, 2017)
1565	LinkedIn, Xiaolin Wu, https://www.linkedin.com/in/xiaolin-wu-68821313/?ppe=1 (printed Aug. 2, 2017)
1566	Xiaolin Wu, *Synthesis of 5′-C- and 2′-O-Substituted Oligoribonucleotide Analogues and Evaluation of their Pairing Properties*, A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Nature Science at the Swiss Federal Institute of Technology (ETH) Zurich (2000)

1567	LinkedIn, Colin Barnes, https://www.linkedin.com/in/colin-barnes-73678145/?ppe=1 (printed Aug. 2, 2017)
1568	The Chinese Society of Chemical Science and Technology in the UK, Members of the Fourth Executive Committee, https://www.jiscmail.ac.uk/cgi-bin/filearea.cgi?LMGT1=CHEM-CSCST-UK&a=get&f=/4cmmtt.htm (printed Aug. 2, 2017)
1569	Jonathan A. Eisen, *Sequencing: The Now Generation*, presentation at the Bodega Bay Applied Phylogenetics, slide 39 (Mar. 4, 2013), downloaded from http://treethinkers.org/wp-content/uploads/2013/01/EisenBodega2013.pdf
1570	Number Not Used
1571	Illumina, *Genome Analyzer System Specification Sheet* (2007), http://www.geneworks.com.au/library/GenomeAnalyzer_SpecSheet.pdf (downloaded Oct. 2, 2017)
1572	A. Masoudi-Nejad et al., *Emergence of Next-Generation Sequencing*, Ch. 2 in NEXT GENERATION SEQUENCING AND SEQUENCE ASSEMBLY, 11-39, 15 (2013)
1573	J. Bidwell et al., *Cytokine gene polymorphism in human disease: on-line databases*, GENES & IMMUNITY 1:3-19 (1999) ("Bidwell")
1574	Pui-Yan Kwok, *Methods for Genotyping Single Nucleotide Polymorphisms*, ANN. REV. GENOMICS HUMAN GENETICS 2:235-58 (2001) ("Kwok")
1575	Ann-Christine Syvanen, *Accessing genetic variation: genotyping single nucleotide polymorphisms*, NATURE REVIEWS GENETICS 2:920-942 (2001) ("Syvanen")
1576	A. A. Kraeveskii et al., *Substrate inhibitors of DNA biosynthesis*, MOLECULAR BIOLOGY 21:25-29 (1987) ("Kraeveskii")
1577	William B. Parker et al., *Mechanism of Inhibition of Human Immunodeficiency Virus Type 1 Reverse Transcriptase and Human DNA Polymerases α, β, and γ by the 5′-Triphosphates of Carbovir, 3′-Azido-3′-deoxythymidine, 2′,3′-Dideoxyguanosine, and 3′-Deoxythymidine*, J. BIOL. CHEM. 266:1754-1762 (1991) ("Parker")
1578	Elise Burmeister Getz et al., *A comparison between the Sulfhydryl reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry*, ANALYTICAL BIOCHEM. 273:73-80 (1999) ("Getz")
1579	William S. Mungall et al., *Use of the Azido Group in the Synthesis of 5′-Terminal Aminodeoxythymidine Oligonucleotides*, J. ORG. CHEM. 40:1659-1662 (1975) ("Mungall")

1580	Serge Pilard et al., *A stereospecific synthesis of (+) α-conhydrine and (+) β-conhydrine*, TETRAHEDRON LETTERS 25:1555-56 (1984)
1581	R. Ranganathan et al., *Facile conversion of adenosine into new 2'-substituted-2'-deoxy-arabinofuranosyladenine derivatives: stereospecific syntheses of 2'-azido-2'-deoxy-,2'-amino-2'deoxy-, and 2'-mercapto-2'deoxy-β-D-arabinofuranosyladenines*, TETRAHEDRON LETTERS 45:4341-4344 (1978).
1582	K.S. Kirby, *A New Method for the Isolation of Deoxyribonucleic Acids: Evidence on the Nature of Bonds between Deoxyribonucleic Acid and Protein*, BIOCHEM. J. 66:495-504 (1957) ("Kirby")
1583	David Moore & Dennis Dowhan, *2.1.1 - Manipulation of DNA* in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Wiley, 2002) ("Moore")
1584	G.E. Tiller et al., *Dinucleotide insertion/deletion polymorphism in intron 50 of the COL2A1 gene*, NUCLEIC ACIDS RESEARCH 19, 4305 (1991) ("Tiller")
1585	*Kamada, Ltd. v. Grifols Therapeutics Inc.*, IPR2014-00899, Paper 22 (Mar. 4, 2015)
1586	Summary Table of Prior IPR Proceedings
1587	2014-1547, Appellee's Brief (Dec. 29, 2014) (appeal of IPR2012-00006)
1588	IPR2013-00518, Paper 28, Illumina Request for Adverse Judgment (May 5, 2014)
1589	IPR2013-00518, Paper 29, Judgment Request for Adverse Judgment (May 6, 2014)
1590	IPR2013-00517, Paper 7, Revised Petition for Inter Partes Review of U.S. Pat. No. 7,566,537 (Aug. 13, 2013)
1591	IPR2013-00517, Paper 16, Decision - Institution of *Inter Partes* Review (Feb. 13, 2014)
1592	IPR2013-00517, Paper 32, Illumina's Patent Owner Response (May 5, 2014) (Redacted)
1593	IPR2013-00517, Paper 54, Petitioner IBS's Reply (July 28, 2014) (Redacted)
1594	IPR2013-00517, Paper 87, Final Written Decision (Feb. 11, 2015)
1595	2015-1693, Brief of Patent Owner-Appellee Illumina Cambridge Ltd. (Oct. 28, 2015)
1596	Number Not Used
1597	Illumina, Inc. v. Qiagen, N.V (N.D. Cal, Aug. 25, 2016) Plaintiff's Reply in Support of Motion for Preliminary Injunction

1598	IPR2013-00517, Ex. 2011, Declaration of Floyd Romesberg, Ph.D. (May 5, 2014) (Redacted) ("Romesberg Decl.")
1599	IPR2013-00517, Ex. 2089, Declaration of Dr. Kevin Burgess (May 5, 2014) (Redacted) ("Burgess Decl.")
1600	IPR2013-00517, Ex. 1026, Transcript, July 15, 2014 Deposition of Kevin Burgess, Ph.D. (Redacted)
1601	Declaration of John D. Sutherland (IPR2017-02174) ("Sutherland Decl.")
1602	Curriculum Vitae of Dr. John D. Sutherland
1603	Number Not Used
1604	Number Not Used
1605	IPR2013-00266, Paper 73, Final Written Decision (Oct. 28, 2014)
1606	G.M. Church, WO 00/53812 A2 (Sept. 14, 2000) ("Church")
1607	Timothy M. Herman, U.S. Patent No. 3,772,692 (Sep. 20, 1988) ("Herman")
1608	Ely Michael Rabani, WO 96/27025 A1 (published Sep. 6, 1996) ("Rabani")
1609	Barbara A. Dawson et al., *Affinity Isolation of Transcriptionally Active Murine Erythroleukemia Cell DNA using a Cleavable Biotinylated Nucleotide Analog*, J. BIOL. CHEM. 264:12830-12837 (1989).
1610	S. W. Ruby et al., *Affinity Chromatography with Biotinylated RNAs*, METHODS IN ENZYMOL. 191:97-121 (1990)
1611	Jeffrey Van Ness et al., U.S. Patent No. 6,312,893 (Nov. 6, 2001) ("Van Ness")
1612	Mary Shimkus et al., *A chemically cleavable biotinylated nucleotide: Usefulness in the recovery of protein-DNA complexes from avidin affinity columns*, PROC. NATL. ACAD. SCI. USA 82:2593-97 (1985) ("Shimkus")

I. INTRODUCTION

Petitioner requests *inter partes* review of claims 1-6, and 8 of U.S. Patent No. 7,566,537 B2 ("'537," Ex. 1501) as obvious under 35 U.S.C. § 103. The '537 patent claims a method for labeling nucleic acid molecules where the label is attached to the base via a cleavable linker, and the 3'-OH of the sugar moiety is reversibly blocked with a protecting group comprising an azido group, such as azidomethyl. Each of these features was known in the prior art, and as detailed herein, their combination would have been obvious to a person of ordinary skill in the art ("POSITA").

The '537 patent was previously challenged by another party in two IPRs. One resulted in cancellation of claims 7 and 11-14 in response to Illumina's request for adverse judgment. Exs. 1588 & 1589 (IPR2013-00518). The only elements of the claims challenged herein that were not recited in the cancelled claims are the azido and azidomethyl ("CH_2N_3") protecting groups recited claims 1 and 5. Thus, the obviousness of the azido and azidomethyl protecting groups is the crux of this proceeding.

The other prior petition was instituted on the basis of Tsien (Ex. 1503) or Ju (Ex. 1538) in combination with Zavgorodny (Ex. 1508). Ex. 1591, 5, 15 (IPR2013-00517). The Board found that Tsien in combination with Zavgorodny disclosed each element of the claims, but that the petitioner nevertheless failed to meet its burden to establish obviousness. Ex. 1594, 7, 18, 21-22. On review, the Federal Circuit noted that the "Board's precise legal underpinnings are difficult to discern,"

and that the Board's decision was improper to the extent it was based on an absence of a reasonable expectation of success. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1365-67 (Fed. Cir. 2016). The Federal Circuit affirmed the Board's judgment on the basis that "the petitioner's ***sole*** argument for why one of skill in the art would be motivated to combine Zavgorodny's azidomethyl group with Tsien's [sequencing-by-synthesis ("SBS")] method was because it would meet Tsien's quantitative deblocking method" and that the Board had not abused its discretion in refusing to consider new arguments raised in IBS's Reply brief and evidence filed therewith. *Id.* at 1368-70. Because many critical "motivation to combine"-related issues were not adequately addressed in the Petition, and were then belatedly — and still inadequately — addressed in the Reply and supporting declarations, the Board's decision and the Federal Circuit's affirmance were based on an incomplete and factually flawed record presented by the prior petitioner. *See id.*; Ex. 1594, 14-19. These issues are addressed in detail in CGI's Petition for *Inter Partes* Review in IPR2017-02172, which relies on some of the same prior art as the prior IPR.

Nevertheless, the prior IPRs and Federal Circuit decisions demonstrate several key facts and legal conclusions. First, Zavgorodny (Ex. 1508) discloses an azidomethyl (CH_2N_3) protecting group for the 3′-OH of a nucleoside. 821 F.3d at 1367. Second, Prober discloses a deazapurine base for use with SBS, as recited in dependent claim 3. 821 F.3d at 1363-64; Ex. 1594, 22; Ex. 1591, 12. Third, none of the challenged claims require removal of the protecting group (*i.e.*, deblocking),

much less quantitative or high efficiency deblocking. 821 F.3d at 1367.

Compared to the prior IPR by IBS and CGI's Petition in IPR2017-02172, this Petition provides new prior art, arguments, and testimony demonstrating why the challenged claims would have been obvious over Dower (Ex. 1504) in combination with Church (Ex. 1606) and Zavgorodny (Ex. 1508). Dower describes a sequencing by synthesis ("SBS") method with a reversible protecting group on the 3′-OH of the ribose moiety and the attachment of the label to the nucleobase. *See* Part IX.A, *infra*; Ex. 1601, ¶¶25-28. This method is useful for a variety of applications, including detection of single nucleotide polymorphisms. Church describes the use of a cleavable disulfide linker between the nucleobase and the label, which was previously found by the Board and affirmed by the Federal Circuit to have been obvious to combine with an SBS method as of the priority date of the '537 patent. 638 Fed. Appx. at 1004; Ex. 1605, 11-25. Zavgorodny indisputably discloses an azidomethyl protecting group for the 3'-OH, and several references demonstrate that a POSITA would have appreciated that azidomethyl was appropriate for use with Dower, had advantageous properties for use in SBS methods, and would have been particularly well-suited for use in combination with Church's disulfide linker. *See* Ex. 1551; Ex 1506; Ex. 1505; Ex. 1558; Ex. 1601, ¶¶138-147, 149-150, 172. Moreover, whereas the Board apparently credited Illumina's reading of the prior art (Loubinoux, Ex. 1506) as suggesting that azidomethyl could not be deblocked with sufficiently high efficiency for Tsien's SBS, Dower has no such efficiency criteria and, in any event, this Petition illustrates the errors in that analysis and provides new

evidence (*e.g.*, Young, Ex. 1551), demonstrating that a POSITA would have considered Loubinoux to be encouraging for the use of the azidomethyl protecting group and that, in fact, it could be removed quantitatively. Thus, as detailed herein, Dower's method and nucleotides in combination with Church's disulfide linker and Zavgorodny's azidomethyl protecting group would have been obvious to a POSITA. Petitioner therefore submits that this Petition does not present redundant grounds with the Petition in IPR2017-02172 and respectfully requests institution of *inter partes* review and cancellation of the challenged claims.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

In accordance with 37 C.F.R. §42.8(b)(1), Petitioner Complete Genomics, Inc. ("CGI") identifies itself and the following entities as real parties-in-interest: BGI Shenzhen Co., Ltd.; BGI Groups USA Inc.; BGI Genomics Co., Ltd.; and BGI Americas Corporation.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner is concurrently filing IPR2017-02172, which challenges the '537 patent on different grounds than asserted herein.

Prior proceedings between Illumina and other parties may also affect this proceeding because they involved the challenged patent or patents with similar disclosures and/or claims. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) (appeal from IPR2013-00517); *Ilumina Cambridge Ltd. v. Intelligent Bio-Systems, Inc.*, 638 Fed. Appx. 999 (Fed. Cir.

2016) (unpublished) (appeals from IPR2013-00128 and IPR2013-00266); *Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 620 Fed. Appx. 916 (Fed. Cir. 2015) (unpublished) (appeals from IPR2012-00006, IPR2012-00007, and IPR2013-00011); *The Trustees of Columbia University in the City of New York v. Illumina, Inc.*, 1:12-cv-00376-GMS (D. Del.) ("Delaware Litigation"); *Illumina, Inc. et al. v. Qiagen, NV et al.*, 3-16-cv-02788 (N.D. Cal.); IPR2013-00128; IPR2013-00324; IPR2013-00266; IPR2013-00517; IPR2013-00518; IPR2012-00006; IPR2012-00007; IPR2013-00011. *See also* Ex. 1586 (summary chart).

In the Delaware Litigation, in 2012, Illumina and Intelligent Bio-Systems, Inc. ("IBS") each asserted that the other was infringing their respective SBS-related patents. Illumina asserted the '537 patent and two other related patents against IBS. In addition, The Trustees of Columbia University in the City of New York ("Columbia"), from whom IBS had licensed its SBS patents, asserted that Illumina was infringing five patents owned by Columbia and licensed to IBS (the "Ju patents"). The Ju patents have an earlier priority date than Illumina's and address the same subject matter — the use of reversibly terminated and labeled nucleotides in DNA sequencing reactions such as SBS. The Delaware Litigation was stayed while the parties filed IPRs against each other, challenging 60 claims of 6 patents in 8 IPRs (listed above). As of the date of the filing of this petition, all of those IPRs and appeals thereof are concluded. All challenged claims in 7 of the 8 IPRs were either cancelled by Illumina or by the PTAB, but as described below, certain claims

of the ’537 patent survived.

IBS challenged the ’537 patent in two IPRs (IPR2013-00517 and -00518). In IPR2013-00518, claims 7 and 11-14 were cancelled in response to Illumina’s request for adverse judgment. Exs. 1088 & 1089.

In IPR2013-00517, the Board found that all elements of claims 1-6 and 8 were disclosed by both Tsien and Ju, each in combination with the azidomethyl protecting group of Zavgorodny (Ex. 1508), and for claim 3, the claimed deazapurine base was further disclosed in Prober. Ex. 1594, 10-11, 18. However, because Petitioner’s sole asserted motivation to combine was “to improve the efficiency, reliability, and robustness” of Tsien or Ju’s SBS methods, the Board was persuaded by Illumina’s counterarguments that, due to the reaction conditions and yields disclosed in Zavgorodny and Loubinoux, a POSITA would be deterred from combining Tsien or Ju’s SBS method with Zavgorodny’s azidomethyl protecting group due to purported concerns that Tsien’s “quantitative deblocking” requirement would not be met and that the reaction conditions could denature DNA. Ex. 1594, 12-14. While IBS attempted to address Illumina’s arguments in its Reply, the Board found that IBS’s arguments were improper because they were not presented in the Petition and that the Reply improperly incorporated by reference arguments from a supplemental expert declaration and evidence cited therein.

On appeal, the Federal Circuit implicitly agreed that the prior art taught all of the claim elements, finding that, to the extent the Board based its decision on a lack of reasonable expectation of success, the decision was erroneous. 821 F.3d at 1367.

However, the Federal Circuit also found that the Board did not abuse its discretion in refusing to consider IBS's arguments and evidence made in its Reply. Without considering the Reply's argument or evidence, the Federal Circuit affirmed the Board's decision that IBS had failed to establish that a POSITA would have been motivated to combine Zavgorodny's azidomethyl protecting group with Tsien or Ju's SBS methods "in order to improve the efficiency, reliability, and robustness" of those methods, and that was the only motivation that IBS had provided in the Petition. 821 F.3d at 1367-70 (citing Petition, Ex. 1590, 24, 42).

C. Lead and Back-up Counsel (37 C.F.R. §42.8(b)(3)-(4))

Petitioner designates the following Lead and Back-up Counsel:

Lead Counsel	Backup Counsel
Jennifer A. Sklenar (Reg. No. 40,205) ARNOLD & PORTER KAYE SCHOLER LLP 777 South Figueroa Street, 44th Floor Los Angeles, CA 90017-5844 Tel: (213) 243-4027 Fax: (213) 243-4199 Jennifer.Sklenar@apks.com	Michael J. Malececk (*pro hac vice to be filed*) Katie J.L. Scott (*pro hac vice to be filed*) ARNOLD & PORTER KAYE SCHOLER LLP Five Palo Alto Square, Suite 500 3000 El Camino Real Palo Alto, California 94306 Tel: (650) 319-4700 Fax: (650) 319-4900 Michael.Malecek@apks.com Katie.Scott@apks.com

A concurrently filed power of attorney identifies the practitioners of Arnold & Porter Kaye Scholer LLP, including Jennifer A. Sklenar, Michael J. Malecek, and Katie J.L. Scott as attorneys of record.

D. Service Information (37 C.F.R. §42.8(b)(4))

Petitioner may be served by mail or hand-delivery at the service addresses

found in Part C, *supra*, with courtesy copies sent to the following email addresses: Jennifer.Sklenar@apks.com, Michael.Malecek@apks.com, Katie.Scott@apks.com. Petitioner hereby consents to electronic service at these email addresses.

III. REQUIREMENTS FOR INTER PARTES REVIEW

A. Payment of Fees (37 C.F.R. §42.103)

The required fees are submitted herewith. If any additional fees are due at any time, the Office is authorized to charge such fees to Deposit Account No. 502387.

B. Grounds for Standing (37 C.F.R. §42.104(a))

Petitioner certifies pursuant to 37 C.F.R. §42.104(a) that the patent for which review is sought is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review.

C. Identification of Challenge and Precise Relief Requested (37 C.F.R. §42.104(b)(1)-(2))

Petitioner requests *inter partes* review and cancellation of Claims 1-6 and 8 as obvious under 35 U.S.C. §103(a), on the following grounds:

Ground 1: Claims 1-2, 4-6, and 8 are obvious over William J. Dower et al., U.S. Patent No. 5,547,839 (Aug. 20, 1996) ("Dower"), Ex. 1504, in combination with G.M. Church, WO 00/53812 A2 (Sept. 14, 2000) ("Church"), Ex. 1606, and Sergey Zavgorodny et al., *1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications*, TETRAHEDRON LETTERS 32:7593-96 (1991) ("Zavgorodny"), Ex. 1508.

Ground 2: Claim 3 is obvious over Dower, Church, and Zavgorodny, in

further combination with James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, SCIENCE 238:336-41 (1987) ("Prober"), Ex. 1507.

IV. THE '537 PATENT

A. The '537 Patent

The '537 patent, titled "Labelled Nucleotides," was filed as a divisional of application No. 10/227,131, which was filed on August 23, 2002. Ex. 1501. The '537 patent claims priority to an earlier foreign application (GB0129012.1), but the challenged claims are not entitled to an earlier priority date because the recited azido or azidomethyl protecting groups were not disclosed. Ex. 1502, 5 (GB0129012.1); *see also* Ex. 1592, 4 (conceding August 2002 priority date).

Claims 1 and 6 are of primary significance to this petition. Claim 1 recites:

> A method of labeling a nucleic acid molecule, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule,
> wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker and the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2′ or 3′ oxygen atom,
> and said protecting group can be modified or removed to expose a 3′ OH group
> ***and the protecting group comprises an azido group***.

Ex. 1501, 19:49-59 (emphasis added). Dependent claim 6 recites "[t]he method according to claim 1, wherein the protecting group is CH_2N_3," *i.e.*, an "azidomethyl" group. *Id.*, 20:3-4.

The words "azido" and "azidomethyl" do not appear in the '537 specification. Such protecting groups are only disclosed in Figure 3 as one of 20 different substituted protecting groups (annotated version below), where R_1 and R_2, are "each selected from H, OH, or any group than can be transformed into an OH, including a carbonyl." Ex.1501, Fig.3.

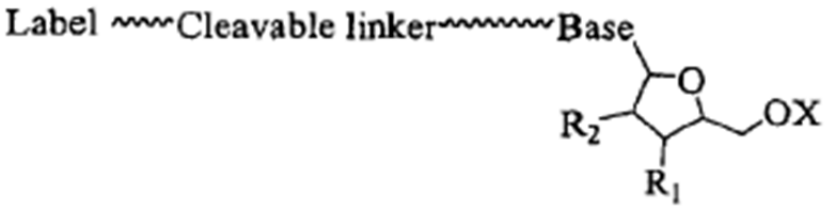
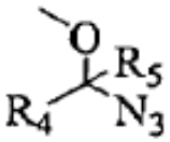


Figure 3 further states that R_1 and R_2 groups may include the following group,



which is azidomethyl when R_4 and R_5 are both hydrogen. *Id.*

The '537 patent does not identify any benefit of using an azido protecting group; does not mention any difficulty selecting conditions for incorporating an azido group with a polymerase or removing it to reveal a 3′-OH; and does not describe any unexpected results from arising from the use of an azido-containing protecting group. In fact, the only place where "azido" or "CH_2N_3" (azidomethyl) appears in the '537 patent is in the limitations of the claims, which were added in

amendments submitted August 16, 2007— nearly 5 years after the patent's earliest claimed priority date. Ex. 1502, 103.

The lack of detail regarding the azido protecting group is not surprising given that the alleged point of novelty described in the specification was that "[i]n the present invention, a nucleoside or nucleotide molecule is linked to a detectable label *via a cleavable linker group attached to the base*[.]" Ex. 1501, 2:3-5 (emphasis added). The specification emphasized that "[t]he molecules of the present invention are in contrast to the prior art, where the label is attached to the ribose or deoxyribose sugar, or where the label is attached via a non-cleavable linker." *Id.*, 2:15-18, 7:54-57.

In contrast to this detailed discussion of the linkage for the label, the '537 specification describes the selection of a protecting group and the conditions for deblocking as known within the art. *See id*., 7:57-67 ("Suitable protecting groups will be apparent to the skilled person, and can be formed from ***any suitable protecting group disclosed in Greene and Wuts***, supra." (emphasis added)), 9:49-10:3, 8:59-9:10; *see also* Part VI.B.4, *infra*.

Finally, the claimed method recited in claim 1 only requires a single step of "incorporating" the reversibly blocked, labelled nucleotide or nucleoside "into the nucleic acid molecule." Ex. 1501, 19:49-50. Claim 1 does not require removal of the protecting group; it only requires that "said protecting group *can be* modified or removed to expose a 3' OH group." *Id.*, 19:57-58 (emphasis added). Thus, while the claimed labeling method could certainly be used for SBS, claim 1 requires no

more than a single incorporation step. Ex. 1594, 7; 821 F.3d at 1367. With only one or a few incorporated labeled nucleotides, the method of claims 1-6 and 8 could also be used to detect polymorphisms, such as Single Nucleotide Polymorphisms (SNPs), small-scale insertions/deletions (INDELs), and multi-nucleotide mutations. Ex. 1601, ¶¶116-117. Indeed, the '537 patent itself teaches that the disclosed method is useful where only a single incorporation event occurs, and only a single round of incorporation is required by the challenged claims. *See* Ex. 1501, 2:7-9.

B. Impact of Prior Proceedings Regarding the '537 Patent

The '537 patent was previously challenged by IBS in two petitions. IPR2013-00517 and -00518. In IPR2013-00518, claims 7 and 11-14 were cancelled in response to Illumina's request for adverse judgment. Exs. 1588 & 1589. Therefore, Illumina is "precluded from taking any action inconsistent with the adverse judgment…." 37 C.F.R. §42.73(d)(3). Cancelled claim 7 has the same limitations of claim 1, except that where claim 1 recites that "the protecting group comprises an azido group," claim 7 recites "the protecting group and cleavable linker are removable under identical conditions." Additionally, the limitations of cancelled dependent claims 11-14 (which depend from claim 7) are identical to challenged dependent claims 2-5 (which depend from claim 1). Thus, Illumina's concession that claims 7 and 11-14 are not patentable should preclude Illumina from advancing any patentability argument that is not related to the azido or azidomethyl limitations of claims 1 or 6. *See id*.

Due to the findings in IPR2013-00517 and in the Federal Circuit decision

thereon, Illumina cannot reasonably contest the following facts:

(1) Zavgorodny (Ex. 1508) discloses an azidomethyl (CH_2N_3) protecting group for the 3′-OH of a nucleoside;

(2) Prober (Ex. 1507) discloses a deazapurine base for use with SBS, as recited in dependent claim 3 (821 F.3d at 1363-64; Ex. 1594, 22; Ex. 1591, 12); and

(3) none of the challenged claims require removal of the protecting group (*i.e.*, deblocking), much less quantitative or high efficiency deblocking. 821 F.3d at 1367.

V. DEFINITION OF A PERSON OF ORDINARY SKILL IN THE ART

Factors that may be considered in determining the level of ordinary skill in the art include: (1) the "type of problems encountered in the art;" (2) "prior art solutions to those problems;" (3) "rapidity with which innovations are made;" (4) "sophistication of the technology; and" (5) "educational level of active workers in the field." *In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Based on these factors, Petitioner proposes the following definition of a POSITA:

> A POSITA at the time of the invention would have been a member of a team of scientists working on the research and development of DNA analysis and sequencing techniques. Such a person would have held a doctoral degree related to bioorganic chemistry, biological chemistry or a closely related discipline, and had at least five years of practical academic or industrial laboratory experience directed toward the research and development of DNA analysis and sequencing technologies.

See Ex. 1601, ¶74.[1]

The "Summary of the Invention" of the '537 patent describes that the claimed invention would be useful for a wide variety of techniques for the analysis of DNA (or RNA), including "sequencing reactions, … nucleic acid hybridization assays, [SNP] studies, and other techniques using enzymes ….". Ex. 1501, 2:7-14. In 2002, DNA sequencing-related art was rapidly evolving and combined a variety of disciplines, including chemistry, engineering, biology, and computer science. Ex. 1538, 1:22-26; Ex. 1601, ¶81; Part VI, *infra*. A POSITA would have necessarily had a high level of education and experience to understand and utilize the full scope of the claimed inventions for these applications. Ex. 1601, ¶81. "Active workers" in the field usually had doctoral degrees and substantial laboratory experience, as evidenced by the backgrounds of the inventors and the authors of prior art in the field. Ex. 1601, ¶¶77-78; *see also* Exs. 1160-1168.

This high level of skill in the art is further demonstrated by the numerous highly technical choices that the '537 patent (and the prior art) describe as being within the ordinary skill of a POSITA at the time. For example, a POSITA would have known how to select a suitable reversible blocking group, select an enzyme for incorporating the modified nucleotide, utilize methods to label and detect the

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[1] This definition is substantially similar to the definition proposed by Illumina in the prior IPR of the '537 Patent. Ex. 1592, 9-10. The Board did not address the level of ordinary skill in the art in the prior proceeding. Exs. 1591 & 1594.

modified nucleotide, select deblocking conditions, and optimize reaction conditions such as temperature, pH, and time for each step. Ex. 1601, ¶81; *see also* Part VI.B, *infra*.

VI. THE STATE OF THE ART

A. Advances in DNA Science

Natural DNA is composed of two strands, arranged in a double helical structure.[2] Each strand is made up of a series of nucleotides, which are made up of three distinct chemical components: a nucleobase (or "base"), sugar, and a phosphate group. DNA polymerase catalyzes strand extension by formation of a new phosphodiester bond between the 5′ carbon of each additional nucleotide and the 3'-OH group of the last nucleotide in the strand. *See* Ex. 1601, ¶¶8-12.

One major use for DNA technology is sequencing, which typically requires labeled nucleotides to detect and identify the bases in the sequence. Early methods used radioactive labeling and gel electrophoresis to separate fragments by size. *See, e.g.*, Exs. 1518 & 1519. One such method was Sanger's dideoxy chain termination method, published in 1977, in which nucleotide analogues without hydroxyl groups on the 2' and 3' positions of the sugar ("dideoxynucleotides") terminated the

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[2] Petitioner assumes that the Board is familiar with many of the basic scientific principles underlying the structure and function of DNA. However, out of an abundance of caution, the declaration of Dr. Sutherland reviews the principles that are necessary background for this Petition. *See* Ex. 1615, ¶¶8-12.

extension activity of DNA polymerase after their incorporation. Ex. 1520; *see also* Ex. 1601, ¶14. However, Sanger's use of radioisotopes and electrophoresis were substantial drawbacks to the method. Ex. 1503, 3:1-8; Ex. 1504, 2:19-39; Ex. 1601, ¶¶14-15. These problems led the industry to look for "next-generation" sequencing methods to reduce the cost of whole-genome sequencing.

By 1990, at least two independent groups filed patents that taught the use of reversibly blocked and labeled nucleotides to achieve SBS. Tsien, Ex. 1503; Dower, Ex. 1504. These references disclose the use of terminators with reversible blocking groups to protect the 3′-OH, a label attached to the base via a cleavable linker, and cycles of incorporation and deprotection to add and detect a single labeled nucleotide, one at a time, to a growing strand of DNA that is complementary to a template strand of an unknown sequence. Ex. 1503, 10-14; Ex. 1504, 4:44-5:6. Tsien and Dower both demonstrate that a POSITA would have known how to select a 3′-OH blocking group, label, linker, incorporation and deblocking conditions, and would have been optimistic that a 3′-OH blocked, labeled nucleotide would be incorporated by DNA polymerase into DNA. Ex. 1503, 22-25; Ex. 1504, 18:1-20; Ex. 1601, ¶¶17-28.

Before August 2002, nucleotide analog chemistry was a focus of significant scientific and commercial resources. Rapid development was driven by immense market pressure to acquire genetic information and translate it into novel, effective therapies, including technologies such as next-generation sequencing, gene therapy, and small-interfering RNA. Ex. 1601, ¶118. The use of organic chemistry that was

compatible with biological systems was also expanding and was of enormous interest to scientists in these rapidly developing fields. Ex. 1529; Ex. 1551; Ex. 1601, ¶¶40-41, 118.

B. Knowledge of a POSITA Relating to Sequencing by Synthesis

The prior art references and admissions in the '537 patent demonstrate that well before the priority date of the '537 patent, a POSITA would have been familiar with techniques for SBS, as well as the use of labelled nucleotides in methods such as the detection of polymorphisms, which do not require more than a few cycles of nucleotide addition, detection and deblocking. Moreover, these sources establish that a POSITA would have known how to select a reversible 3′-OH protecting group and a label with a cleavable linker for use with nucleotides, and further would have known how to select appropriate incorporation and cleavage conditions. A POSITA also would have known of techniques for optimizing SBS processes independent of the chosen protecting group. Ex. 1601, ¶¶110-112.

1. Use of the solid phase was well known in the art.

As a starting point, a POSITA would have known that SBS would take place in the solid phase, typically with the template and growing DNA strands attached to a solid support. Ex. 1601, ¶¶25, 60, 101; Ex. 1504, Figs.8A-B, 1:21-25; Ex. 1503, 10:16-18:34, 32:9-34:34; Ex. 1538, 4:4-10, 4:21-65. The '537 patent admits that the incorporation is "preferably carried out with the target polynucleotide arrayed on a solid support" and that methods for doing so were "well known in the art." Ex. 1501, 9:1-2, 9:9-17.

Use of the solid phase typically results in significantly higher yield and lower reaction time compared to the same reaction performed with all reactants in the liquid phase. Ex. 1601, ¶¶25, 60, 101. This is because solid phase permits use of excess reactants to drive a reaction to completion, while avoiding the reduction in yield that would be caused by the purification of liquid products from the excess of reactants in a liquid phase reaction. *Id.*; *see also* Ex. 1504, 23:34-37; Ex. 1503, 20:18-20. There would be no loss of material during the purification process because any impurities, cleavage products, or excess reagents are simply washed away from the immobilized product. Ex. 1601, ¶¶101, 173. For reversible cleavage reactions, the removal of cleavage products also prevents the reverse reaction from occurring. *Id.*, ¶101. A POSITA would therefore have appreciated that the anticipated yield at each step in the solid phase with a substantial excess of reactants would be substantially higher than if the same reaction were performed in the liquid phase. *Id.*, ¶¶101, 173; Ex. 1504, 8:19-21; Ex. 1503, 20:18-22; Ex. 1514, 341.

A POSITA would also have known that the solid phase permits the use of a multitude of identical copies of the subject DNA so that numerous copies of the complementary molecule can be synthesized simultaneously. Ex. 1504, 7:51-63 (describing the use of "clusters" which are "localized group[s] of substantially homogeneous polymers which are positionally defined as corresponding to a single sequence"); *see also* Ex. 1503, 6:34-7:9; Ex. 1555, 3:14-47, 5:44-47. A POSITA would have understood that an advantage of solid phase methods using multiple DNA copies was that the sequence can continue to be determined even if the yield

from the incorporation or deprotection steps is not 100% because nucleotide identity is determined by the signal from the entire cluster, not just one strand of DNA. Ex. 1601, ¶101, 108; Ex. 1504, 7:58-6-66, 14:32-37; Ex. 1555, 7:29-47.

2. Labels and cleavable linkers were well known in the art.

The prior art demonstrates that a variety of labels and cleavable linkers were well-known by the priority date of the '537 patent. *See* Ex. 1504, 15:52-59; Ex. 1606, 68:2-11; Ex. 1402, 32:29-33; Ex. 1503, 26:28-30, 28:19-29:2; Ex. 1538, 2:50-64. The '537 patent admits that "[t]he present invention can make use of conventional detectable labels. Detection can be carried out by any suitable method …. Although fluorescent labels are preferred, other forms of detectable labels will be apparent as useful to those of ordinary skill." Ex. 1501, 5:19-44. The '537 patent also admits that "[c]leavable linkers are known in the art" and "can be adapted from standard chemical protecting groups, as disclosed in Greene & Wuts …." Ex. 1501, 6:9-19.

3. Enzymes capable of incorporation and conditions for their use were well known in the art.

Prior art to the '537 patent demonstrates that enzymes suitable for incorporation of nucleotide analogs were known and readily available. *See* Ex. 1004, 18:21-32; Ex. 1503, 19:3-18. Illumina admitted this fact in the '537 patent: "Many different polymerase enzymes exist, and it will be evident to the person of ordinary skill which is most appropriate to use." Ex. 1501, 8:62-64.

The prior art further acknowledges that "appropriate reaction conditions" for

the incorporation reaction were "those used for conventional sequencing reactions with the respective polymerases. The conditions are then modified in the usual ways to obtain the optimal conditions for the particular terminator compound[.]" Ex. 1504, 17:25-27, 25:4-14; *see also* Ex. 1503, 19:19-23. The '537 patent admits the same: "Other conditions necessary for carrying out the polymerase reaction, including temperature, pH, buffer compositions etc., will be apparent to those skilled in the art." Ex. 1501, 9:49-10:12.

4. A POSITA would have known how to select a suitable protecting group and deblocking conditions.

A POSITA would have focused on three primary issues when selecting a reversible 3′-OH protecting group to use with his SBS methods: (1) the ability of a polymerase to incorporate the modified nucleotide with the protecting group, (2) the selection of deblocking conditions that do not harm the DNA, and (3) the incorporation and deblocking steps that result in a yield that is reasonable for the desired application. Ex. 1601, ¶127.

As described in the prior art, the ability of a polymerase to incorporate protected nucleotides is dependent on the size of the protecting group. Ex. 1538, 2:50-57, 3:1-3:5; Ex. 1601, ¶104 (citing Ex. 1526). With respect to the deblocking conditions, the prior art taught that "[o]ptimally, the blocking agent should be removable under mild conditions … thereby allowing for further elongation of the primer strand with next synthetic cycle." Ex. 1504, 18:3-8; Ex. 1503, 20:33-34. In this context, a POSITA would have appreciated that "mild conditions" are those that

would not "degrade the DNA template moiety." Ex. 1538, 26:25-27. Ex. 1601, ¶113. Notably, a POSITA would have expected the substantial excess of deblocking reagents, which may be used in solid phase methods, to achieve nearly quantitative deblocking in reduced time. Ex. 1601, ¶101; *see also* Ex. 1538, 26:27-30.

The '537 patent also admits that "[s]uitable protecting groups ***will be apparent to the skilled person,*** and can be formed from ***any suitable protecting group disclosed in Greene & Wuts***, supra." Ex. 1501, 7:65-8:1 (emphasis added). "The protecting group should be removable (or modifiable) to produce a 3' OH group. The process used to obtain the 3' OH group can be any suitable chemical or enzymic reaction." *Id.*, 8:1-4. Thus, the selection of a protecting group and deblocking conditions from the literature was within the skill of a POSITA.

5. A POSITA would have known other methods to optimize the SBS process.

A POSITA would also have appreciated that reaction conditions are easily modified and additional steps could be employed to optimize the sequencing process. For example, Dower describes the use of a capping step, which irreversibly blocks any remaining unblocked 3′-OH groups after the incorporation step, thereby improving the signal-to-noise ratio. Ex. 1504, 26:13-18. Additional optimization steps were known in the art, including the use non-chemical assistance to improve deblocking (Ex. 1503, 25:26-30), as well as performing detection cycles both before and after the deblocking step, and only considering sequence data when

both steps were successful. Ex. 1538, 21:42-53; Ex. 1537, 15:17-40; Ex. 1601, ¶111.

In sum, the optimization of all of these variables—(1) the use of solid phase DNA synthesis; (2) the selection of appropriate labels and cleavable linkers; (3) the selection or engineering of a polymerase for the incorporation of nucleotides and the optimization of incorporation conditions; (4) the selection of a suitable protecting group and optimization of deblocking conditions; and (5) the manipulation of additional variables to further optimize the SBS process— are described in the prior art and admitted in the '537 as being within the knowledge and skill of a POSITA.

C. A POSITA Would Have Appreciated Multiple Uses for Modified Nucleotides

While many SBS-practitioners seek to optimize the length of the available "read" (i.e., the number of sequential bases read), modified nucleotides were also useful for methods that did not require many cycles of incorporation, detection, and deblocking, such as the detection of SNPs, INDELs, and multi-nucleotide mutations. *See* Ex. 1601, ¶¶116-117 (citing Ex. 1573; Ex. 1574, 235; Ex. 1575). As the '537 patent admits, the modified nucleotides may also be useful in "sequencing reactions, polynucleotide synthesis, nucleic acid amplification, nucleic acid hybridization studies, and other techniques using enzymes…." Ex. 1501, 2:7-14. As one example, Dower's method could be combined with a disulfide linker and the azidomethyl group to modify the Arrayed Primer Extension (APEX)

technique, allowing it to be used for the characterization of multi-nucleotide polymorphisms, many of which were known to correlate to disease. Ex. 1601, ¶117; Ex. 1574, 250. Several potential applications would require identification of only 1 or a few bases and would not require many (or any) steps of repetition. Ex. 1601, ¶¶116-117.

VII. CLAIM CONSTRUCTION

Claim 1 should be construed according to the Board's prior Final Written Decision, i.e., "as encompassing the use of any protecting group attached via the 2' or 3' oxygen atom of a [sugar] moiety, in which the protecting group can be modified or removed to expose a 3′OH group." Ex. 1594, 6. In addition, the claims require that "the protecting group comprises an azido group." Ex. 1501, 19:58-9; 821 F.3d at 1363. This construction was not contested by Illumina and was accordingly relied on by the Federal Circuit. 821 F.3d at 1364.

Additionally, consistent with the Federal Circuit's decision, Claim 1 must be construed such that it "'does not require removal of the protecting group to allow subsequent nucleotide incorporation,' let alone quantitative removal." *Id*. at 1364, 1367 ("removal is simply not required") ; Ex. 1001, Claims 1-6, 8.

VIII. LEGAL STANDARDS OF OBVIOUSNESS

KSR identifies numerous rationales that support an obviousness conclusion, including:

> (B) Simple substitution of one known element for another to obtain predictable results; …

> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

MPEP §2143; s*ee also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). A finding of obviousness requires "a motivation to combine the prior art to achieve the claimed invention and … a reasonable expectation of success in doing so." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). With regard to the "reasonable expectation of success," the POSITA need only have a reasonable expectation of success of developing the claimed invention, as opposed to an expectation of success of developing commercial products or methods containing elements in addition to those embodied in the claims. 821 F.3d at 1367.

The person of ordinary skill in the art is "presumed to be aware of all the pertinent prior art," including secondary references and background knowledge. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). The person of ordinary skill in the art is also expected to utilize common sense and ordinary creativity, and is not merely an automaton. *KSR*, 550 U.S. at 414, 420-21. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.*, 420. Optimization is considered routine. *See Pfizer Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007).

For the purposes of an invalidity analysis, lack of disclosure within a patent

specification may be evidence of that a person of skill in the art would have been expected to know the necessary details or processes required to implement the claimed invention. *See In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (noting that when a patent's specification does not provide the detail Patent Owner contends must be present in the prior art, this absence supports a finding that a POSITA would have known how to implement the features at issue).

IX. GROUND 1: CLAIMS 1-2, 4-6 & 8 ARE OBVIOUS OVER THE COMBINATION OF DOWER, CHURCH AND ZAVGORODNY

Dower, which was filed in 1990 and issued in 1996, describes SBS in much the same way as the '537 patent. For instance, Dower discloses nucleotides that "have a removable blocking moiety to prevent further elongation" and that "both a blocking moiety and labeling moiety will be often used." Ex. 1504, 4:65-5:2. Dower also describes attaching a fluorophore via a "linkage that is easily and efficiently cleaved" and that the "fluorophore and 3' blocking group are removed by the same treatment in a single step (preferably) …." *Id.*, 25:23-40. Figure 8(b) depicts the overall SBS process:

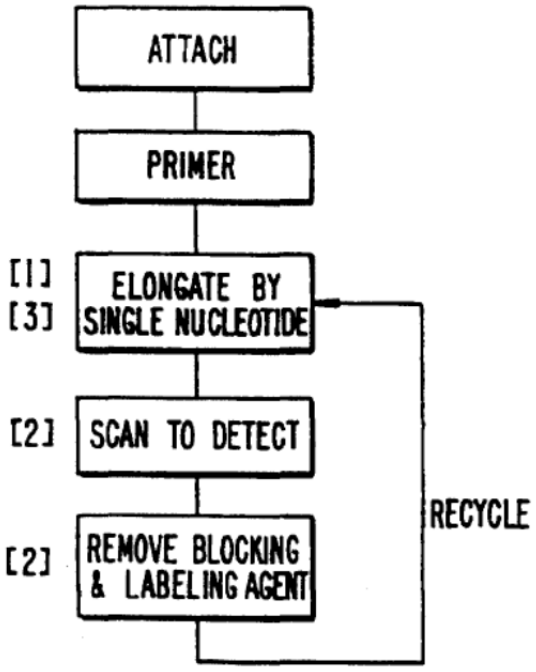


FIG. 8.

Ex. 1504, Fig.8(b); *see also* Fig.8(a); 5:28-33, 14:44-59; 24:48-26:27. As detailed in Part A below, the only elements of claims 1–2, 4–6 & 8 that are not described in Dower are the use of an azido or azidomethyl protecting group, which are disclosed in Zavgorodny, and the use of a linker when the label is attached to the base. While Dower discloses attaching the label to the 3'-O via a linker and attaching a label to the nucleobase, a working example of using a cleavable linker to attach the label to the nucleobase is disclosed in Church. As described in Parts IX-X below, a POSITA would have found the combination of Dower with Church and Zavgorodny to be obvious.

A. All of the Limitations of Claims 1-2, 4-6 & 8 Were Present In the Prior Art

As described below, and detailed in Dr. Sutherland's Declaration, each

limitation of claims 1-2, 4-6, and 8 are disclosed in Dower (Ex. 1504) in combination with Church (Ex. 1606) and Zavgorodny (Ex. 1508). Ex. 1601, ¶93.

1. Claim 1

a. "A method of labeling a nucleic acid molecule, the method comprising incorporating into the nucleic acid molecule a nucleotide or nucleoside molecule."

Dower discloses a method of labeling comprising incorporating into a nucleic acid molecule a nucleotide or nucleoside molecule. Ex. 1504, 15:62-16:1, 18:1-7, 19:11-18, Fig.8; *see also* Ex. 1601, ¶93.

b. "wherein the nucleotide or nucleoside molecule has a base that is linked to a detectable label via a cleavable linker."

Dower discloses the attachment of fluorescent probes to a nucleobase and the use of cleavable linkers. Dower explicitly discloses the use of a cleavable linker to attach the label when the label is attached at the 3'-O position, and further states that the label may be attached elsewhere on the nucleotide. Ex. 1504, 14:56-59 ("This analog is also labeled with a removable moiety, e.g. a fluorescent label…."), 15:56-58 ("The label position may be anywhere in the molecule compatible with appropriate polymerization...."), 15:62-16:6, 25:25-28, 25:35-40; Ex. 1601, ¶93. For example, Figure 9 shows the "FMOC" label as attached to the base "(B)." Ex. 1504, Fig.9, 18:64-19:2; Ex. 1601, ¶95.

As acknowledged by Illumina in the '537 patent, "[c]leavable linkers [were] known in the art, and conventional chemistry can be applied to attach a linker to a nucleotide base and label." Ex. 1501, 6:9-11. Church's disulfide linker was one

such known linker for attaching a fluorophore to a nucleobase. Ex. 1606, 68:12-21, Fig.5, 17:10-11, 85:13-87:2.; *see also* Herman, Ex. 1607, 4:33-60; Rabani, Ex. 1608, 32:29-35; Ex. 1605, 24 ("[t]he record contains numerous publications that utilize a disulfide bond linker to join a label to a nucleotide base"); Ex. 1601, ¶30.

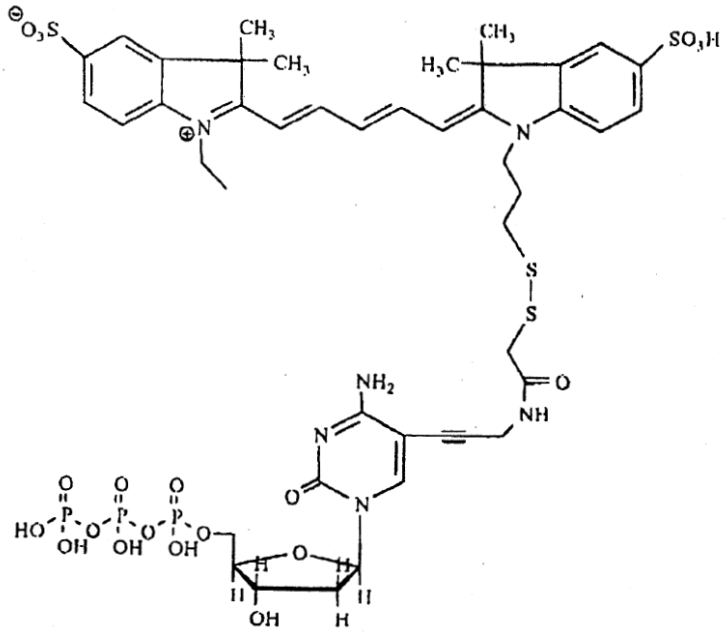


Figure 5

Ex.1606, Fig.5. Figure 5 shows Church's linker, attaching a fluorophore to the base with a linker that is cleavable at the disulfide (S–S) bond. *Id.*; Ex. 1601, ¶98.Church also demonstrates incorporation of the nucleotide, detection of the label, and subsequent cleavage of the linker. *Id*., Ex. 1606, 85:13-87:2.

c. "the nucleotide or nucleoside molecule has a ribose or deoxyribose sugar moiety, wherein the ribose or deoxyribose sugar moiety comprises a protecting group attached via the 2′ or 3′ oxygen atom."

Dower discloses this limitation. Ex. 1504, 10:50-52, 14:50-56 ("The primer is elongated one nucleotide at a time by use of a particular modified nucleotide

analog to which a blocking agent is added and which prevents further elongation…. [I]n certain embodiments here, the blockage is reversible."), 15:33-37, 15:65-66 ("As the blocking agent will usually be on the 3′ hydroxyl position of the sugar on the nucleotide...."), 18:1-7; *see also* Ex. 1501, 9:32-10:1, 12:27-29, 20:25-27; Ex. 1601, ¶93.

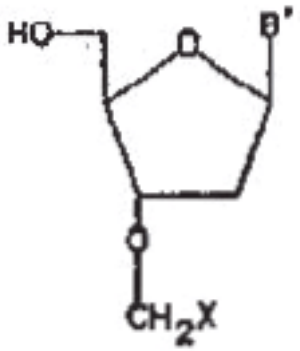
d. "said protecting group can be modified or removed to expose a 3′ OH group"

Dower discloses this limitation. Ex. 1504, 15:35-40 ("Usually, the nucleotide will be blocked at the 3′ hydroxyl group where successive nucleotides would be attached. In contrast to a dideoxy nucleotide, typically the blocking agent will be a reversible blocking agent thereby allowing for deblocking and subsequent elongation."), 23:15-22, 25:26-28 ("placement on the 3' hydroxyl through a linkage that is easily and efficiently cleaved (removing the label and leaving the free 3'OH) by light, heat, pH shift, etc."); *see also* Ex. 1503, 23:28-31, Fig.3; Ex. 1601, ¶93.

e. "the protecting group comprises an azido group"

Zavgorodny discloses an azidomethyl protecting group for the 3'-OH of a nucleoside, and therefore discloses a protecting group that comprises "an azido group," as well as dependent claim 6's limitation that "the protecting group is CH_2N_3," which is azidomethyl. *See* Ex. 1601, ¶93.

Zavgorodny discloses a 3′-O substituted nucleoside (formula 5, excerpted below), where X can be N_3. Ex. 1508, 7594-95.



5 B' = Thy, Cyt, Ade, Guo

When X is N_3, the 3′-OH of the sugar moiety is protected by azidomethyl, $–CH_2N_3$, as recited in claim 6. Ex. 1601, ¶93. Zavgorodny further teaches that "[a]zidomethyl group is of special interest, since it can be removed under very specific and mild conditions, *viz.* with triphenylphosphine in aqueous pyridine at 20°C[.]" Ex. 1508, 7595. This protecting group was also disclosed in other prior art, including Young, Loubinoux, Greene & Wuts, and Zavgorodny 2000. *See* Ex. 1551, 52-68; Ex. 1506, 6055; Ex. 1505, 260; Ex. 1509, 180; *see also* Ex. 1601, ¶¶93, 129-131.

2. Dependent Claims 2, 4-6, 8

a. Claim 2: "wherein said incorporating is accomplished via a terminal transferase, a polymerase or a reverse transcriptase"

Dower discloses that "[a] polymerase is used to extend a primer complementary to a target template." Ex. 1504, 14:48-50, 15:3-5, 17:46-67, 23:18-22; *see also* Ex. 1601, ¶93.

b. Claim 4: "the nucleotide is a deoxyribonucleotide triphosphate"

Dower discloses the use of a nucleotide that is a deoxyribonucleotide triphosphate. Ex. 1504, 23:18-22 ("DNA polymerase, or similar polymerase, is used to extend the chains by one base by incubation in the presence of dNTP[3] analogs which function as both chain terminators and fluorescent labels."); *see also* Ex. 1601, ¶93.

c. Claim 5: "the label is a fluorophore"

Dower discloses the use of a fluorophore label: "This analog is also labeled with a removable moiety, e.g. a fluorescent label, so that the scanning system can detect the particular nucleotide incorporated after its addition to the polymerization primer." Ex. 1504, 14:56-59; *see also* Ex. 1601, ¶93.

d. Claim 6: "wherein the protecting group is CH_2N_3"

As described above with respect to the "azido" protecting group recited in claim 1, Zavgorodny discloses the CH_2N_3 (azidomethyl) protecting group recited in claim 6. *See* Part IX.A.1.e, *supra*; *see also* Ex. 1551, 52-68; Ex. 1506, 6055; Ex. 1505, 260; Ex. 1509, 180.

e. Claim 8: "detecting the detectable label and cleaving the cleavable linker"

Dower discloses detecting the label and cleaving the linker. *See* Ex. 1504, 15:11-14 ("Step 2 is a scan, where the signal at the position corresponding to

[3] "dNTP" stands for deoxyribonucleoside triphosphate.

template 82 indicates that the guanosine analog was incorporated. Reaction 2 is performed, which removes both the label and the blocking group."), 14:56-59; *see also* Ex. 1601, ¶93.

Moreover, when Church's disulfide linker is used with Dower's method, it can be cleaved using DTT, as disclosed in Church, or with other reducing agents known in the art. Ex. 1606, 86:20-21; Ex. 1557, 2648; Ex. 1578, 74; Ex. 1529, 2009; Ex. 1601, ¶¶32, 99.

Thus, Dower in combination with Church and Zavgorodny disclose all the elements of claims 1-2, 4-6, and 8.

B. It Would Have Been Obvious To Combine Dower's SBS Method With Church's Disulfide Linker

Disulfide linkers, as disclosed in Church, were well-known in the art and had been disclosed by many others. *See, e.g.*, Ex. 1607, 4:36-60; Ex. 1608, 32:29-35; Ex. 1605, 24. Indeed, in response to Illumina's previous attempts to amend similar claims to include a disulfide linker limitation, the Board rejected such claims as obvious and the Federal Circuit affirmed. *See*, Ex.1605, *aff'd*, 638 Fed.Appx. 999, 1004 (2016) ("The prior art taught the use of linkers containing disulfide linkages for attaching a label to a nucleotide …."). The Board concluded that it would have been obvious to modify SBS methods similar to those in Dower with Church's cleavable disulfide linker on the nucleobase, stating that the "improvement claimed is no more than 'the predictable use of prior art elements according to their established functions.'" Ex. 1605, 24 (quoting *KSR*). The Federal Circuit agreed,

finding that "[t]he prior art taught the use of linkers containing disulfide linkages for attaching a label to a nucleotide" and a POSITA "would have been motivated to modify SBS prior art with a disulfide linkage as claimed." 638 Fed.Appx. at 1004. Similarly, it would have been obvious to combine Dower's SBS method with Church's disulfide linker.

Moreover, teachings in Dower would have motivated a POSITA to utilize Church's disulfide linker. Dower instructs a POSITA to find a linker and fluorophore system whose compatibility with polymerases had already been demonstrated. *See* Ex. 1504, 18:28-30 ("[T]here is a functional constraint that the polymerase be compatible with the monomer analogues selected."). Church had already demonstrated that nucleotide analogs bearing a fluorophore linked to the nucleobase via a disulfide linker were compatible with and incorporated by polymerases. Ex. 1606, 17:10-14, 85:13-87:2, Example 17. Therefore, a POSITA would have been motivated to combine Church with Dower's SBS method. Ex. 1601, ¶¶97-98.

A POSITA would also have been motivated to use Church's disulfide linker because they would have expected to achieve efficient cleavage using mild conditions. Ex. 1606, 86:20-21 (demonstrating linker cleavage with dithiothreitol ("DTT") following incorporation); *see also* Ex. 1601, ¶99 (citing Ex. 1608, 32:31-33). A POSITA also would have known that disulfides could be reduced with phosphine reducing agents, such as water-soluble trialkylphosphines, which were known to cleave disulfides quantitatively. Ex. 1557, 2648; Ex. 1578, 74; Ex. 1529,

2009; Ex. 1601, ¶¶99, 123-124.

C. It Would Have Been Obvious to Further Combine Dower's SBS Method and Church's Disulfide Linker with Zavgorodny's Azidomethyl Protecting Group

A POSITA would have found it obvious to further combine Dower's reversibly blocked labeled nucleotides and Church's disulfide linker with Zavgorodny's azidomethyl protecting group because (1) it would have been "a simple substitution of one known element for another to obtain predictable results" and (2) a POSITA would have been motivated to use azidomethyl because of its advantageous properties and its ability to be simultaneously cleaved with Church's disulfide linker. *See* Ex. 1601, ¶¶128, 180-183.

1. The azidomethyl group would have been obvious as a simple substitution of one element for another and the results of the substitution would have been predictable.

Obviousness based on a "simple substitution of one known element for another" requires (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components; (2) a finding that the substituted components and their functions were known in the art; (3) a finding that one of ordinary skill in the art could have substituted one known element for another, and [(4)] the results of the substitution would have been predictable …." MPEP §2143(B). The substitution of Zavgorodny's azidomethyl protecting group for the removable protecting groups in Dower meets each of these requirements. Ex. 1601, ¶¶128-148.

a. The only difference between the combination of Dower and Church and the claimed invention is the substitution of an azidomethyl protecting group

As discussed in Part IX.A, Dower and Church disclose each of the elements of claims 1-2, 4-6, and 8 except for the azido and azidomethyl protecting groups. Moreover, as previously acknowledged by the Board, Church demonstrates that nucleotides bearing disulfide linkers on the nucleobase are compatible with SBS methods, such a Dower's method. *See* Ex. 1605, 15; Ex. 1606, 85:12-87:2. Thus, Dower and Church disclose a prior art method and nucleotides used therein that differ from the '537's claimed method only by the substitution of Dower's removable 3′-OH protecting group with an azidomethyl protecting group. Ex, 1601, ¶119.

b. Azidomethyl and its function as a protecting group were known

The 3′-OH azidomethyl protecting group was known in the art. Ex. 1508, 7594; Ex. 1506, 6057; Ex. 1551, 52-72; Ex. 1601, ¶¶129-132. It was known to serve the function of protecting a hydroxyl moiety[4] from reaction until specifically de-blocked, as well as being capable of being deblocked under mild conditions. Ex. 1508, 7595; Ex. 1506, 6056-57; Ex. 1551, 67-68; *see also* Ex. 1601, ¶¶129-132,

[4] Azidomethyl was known to protect both aliphatic hydroxyl moieties and phenolic hydroxyl moieties. Ex. 1508,7594 (aliphatic); Ex. 1506, 6058 (phenolic); Ex. 1551, 55, 74 (phenolic on tyrosine and aliphatic on serine and threonine); Ex. 1005, 260 (reporting on Loubinoux).

158-159. Indeed, Zavgorodny even disclosed azidomethyl as a protecting group for the 3′-hydroxyl moiety of a nucleoside — precisely the same chemical group and location as it is claimed to protect in the ’537. Ex. 1508, 7594-95. In other words, azidomethyl was not only known to serve the same function as a protecting group for a hydroxyl functionality, it had served that function in precisely the same chemical context (i.e., the 3′-OH of a nucleoside). Ex. 1601, ¶131.

c. A POSITA would have known that the protecting groups disclosed in Dower could be substituted with the azidomethyl protecting group.

As discussed above in Part VI.B.4, *supra*, POSITA could have physically substituted the azidomethyl protecting group for the protecting groups disclosed in Dower. Ex. 1601, ¶¶126-128. A POSITA would have needed only to substitute the azidomethyl-blocked labeled nucleotides for the blocked labeled nucleotides of Dower, and then use ordinary skill to select appropriate incorporation and deblocking conditions. *Id*., Ex. 1504, 18:61-63.

The ability of a POSITA to substitute an azidomethyl group is further demonstrated by the ’537’s statement that “[s]uitable protecting groups ***will be apparent to the skilled person,*** and can be formed from ***any suitable protecting group disclosed in Greene & Wuts***, supra.” Ex. 1501, 7:65-8:1 (emphasis added). Thus, given that Greene & Wuts discloses using azidomethyl to protect a hydroxyl functionality (as described in Loubinoux), the ’537 rightly acknowledges that a POSITA would have known that another protecting group, such as azidomethyl, could be substituted for the removable 3′-OH protecting group of Dower.

The ’537 patent also presumes that a POSITA is sufficiently skilled to select appropriate deblocking conditions for a given protecting group: “The protecting group should be removable (or modifiable) to produce a 3′ OH group. The process used to obtain the 3′ OH group can be any suitable chemical or enzymic reaction.” Ex. 1501, 8:1-4. Had the selection of deblocking conditions for azidomethyl been outside the ordinary skill of a POSITA, it would have been incumbent upon the inventors of the ’537 to provide more guidance so as meet their burden of describing and enabling the invention.

Similarly, Dower teaches that the invention may be used with a wide variety of protecting groups, deblocking conditions appropriate for those groups, and enzymes for incorporation. Ex. 1504, 18:1-32, 18:52-63, 15:52-61, 25:15-22, 19:11-20, 24:61-25:3. Dower further states that “[t]he structures of the fluorescently labeled and reversible terminator base analogs are selected to be compatible with efficient incorporation into the growing chains by the particular DNA polymerase(s) chosen to catalyze extension,” suggesting that such selection is within the skill of a POSITA. *Id*., 26:6-9. In addition, Dower states that “[t]he chain elongation block is reversed . . . by suitable methods that depend on the particular base analogues chosen[,]” demonstrating that a POSITA would have known how to select appropriate deprotection conditions, once they have selected a protecting group. *Id*., 26:22-24.

The fact that neither Dower nor the inventors of the ’537 patent thought it was necessary to provide detailed instructions for selecting a protecting group,

deblocking conditions, or incorporation conditions demonstrates that by August 2002, a POSITA was sufficiently skilled to have substituted one protecting group for another and determined appropriate incorporation and deblocking conditions for the substituted blocking group. Similarly, these disclosures (or lack thereof) demonstrate that a POSITA would have considered the substitution to be reasonably predictable, which is further bolstered by the lack of any discussion of unexpected results with the azidomethyl group in the '537 patent.

Likewise, the Federal Circuit has found that the "Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references and would have concluded that the reference disclosures would have been enabling." *In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994); *see also I/P Engine, Inc. v. AOL Inc.*, 576 Fed. Appx. 982, 987 (Fed. Cir. 2014).

d. A POSITA would have considered the result of substituting azidomethyl for the protecting group in Dower to be predictable.

A POSITA would have considered the substitution of azidomethyl for the protecting group in Dower to predictably serve the function of a protecting group, as described by Dower: (1) "have functional properties of blocking further elongation of the polymer[,]" (2) allow for "reversib[le]" blocking of the 3'-OH, (3) be "inert[] to the sequencing reactions[,]" and (4) "be compatible with the selected polymerase." Ex. 1504, 18:11-16. Based on this disclosure, a POSITA would have

sought a protecting group that satisfied these conditions. Ex. 1601, ¶133. Because Church had already demonstrated a working example of nucleotide incorporation, label detection and linker cleavage, a POSITA would only have been concerned with whether specific use of the azidomethyl group would be predictable with respect to Dower's conditions. Ex. 1601, ¶¶126-128.

First, a POSITA would have expected that the azidomethyl-blocked nucleotide would have been incorporated into the growing nucleic acid chain and would have prevented of subsequent nucleotide additions. Ex. 1601, ¶¶134, 142-147. As described in Part IX.C.2.c, *infra*, a POSITA would have expected the azidomethyl-protected nucleotide to be incorporated by the enzyme because it is a small group and the incorporation of nucleotides bearing azido groups had previously been demonstrated. Ex. 1601, ¶¶144-145; .Ex. 1503, 21:17-19 (citing Ex. 1576, 28).

A POSITA would also have considered it predictable that, after incorporation, the azidomethyl group would terminate further chain elongation. Ex. 1601, ¶134. It was widely acknowledged that a free 3′-OH was necessary for chain elongation. *Id*. (citing Ex. 1504, 15:33-37; Ex. 1503, 12:27-29). Protection with an azidomethyl group converts the free 3′-OH into an azidomethyl ether, which would terminate chain elongation. *Id*.; Ex. 1503, 21:9-13. Neither the polymerase nor other reagents used during incorporation would cause removal of the azidomethyl ether to permit chain elongation. Ex. 1601, ¶¶138-142; *see also* Ex. 1503, 38:5-27; Ex. 1507, 339. Zavgorodny's statement that azidomethyl is of "special interest" because "it can be removed under *very specific* and mild conditions." would have informed a POSITA

that the azidomethyl group would be able to block the 3′-OH until and unless the specific deblocking reagents were added to the reaction chamber. *See* Ex. 1508, 7595 (emphasis added). Thus, a POSITA would have expected azidomethyl to predictably and successfully prevent chain elongation.

Second, a POSITA would have expected the azidomethyl group to allow for reversible blocking of the 3′-OH. Zavgorodny emphasized that the azidomethyl on the 3′-OH of the nucleoside could be *removed* under specific conditions, implying reformation of a free 3′-OH group. *See* Ex. 1508, 7595; Ex. 1601,¶¶135-137. A POSITA would have readily appreciated that Zavgorodny utilizes the well-known Staudinger reaction to remove the azidomethyl group, conditions which were known to be highly specific and irreversible. Ex. 1601, ¶101, 135-136. Moreover, cleavage of the azidomethyl group was known to occur through a two-step mechanism that resulted in a free hydroxyl group.[5] *See* Ex. 1506, 6056-57; Ex. 1551, 53; Ex. 1601, ¶¶135-136.

Furthermore, a POSITA would have been capable of substituting Dower's removal conditions with appropriate deblocking reagents for an azidomethyl protecting group. *See, e.g.*, Ex. 1504,15:51-16:2; Ex. 1555, 6:2-5; Ex. 1601, ¶¶105-

[5] The first step entails azide reduction to form a hemiaminal via the Staudinger reaction, while the second step entails a spontaneous collapse of the hemiaminal, resulting in a free hydroxyl group. Ex. 1506, 6055-56; Ex. 1551, 53.; Ex. 1615, ¶136.

107. While Zavgorodny identifies triphenylphosphine in aqueous pyridine for deblocking (Ex. 1508, 7595), a POSITA would have readily appreciated that other deblocking reagents could be used. S*ee, e.g.*, Ex. 1506, 6057; Ex. 1529, 2008; Ex. 1601, ¶¶158-160. In particular, a POSITA would have known that the Staudinger reaction could utilize other phosphine reagents and water. Ex.1554, 350; Ex. 1529, 2008; Ex. 1601, ¶¶158-160. Because DNA is water-soluble, a POSITA would have appreciated that a water-soluble phosphine, such as the strongly-reducing TCEP, would be preferable, as it would not require an organic co-solvent. Ex. 1601, ¶160; Ex. 1529, 2008-09. With these options for deprotection available, a POSITA would have considered removal of the azidomethyl group to yield a 3′-OH to be predictable, and would have reasonably expected success. Ex. 1601,¶137.

Third, the azidomethyl protecting group would have been inert to the sequencing conditions. Deprotection of the azidomethyl group typically entails reduction of the using highly specific reducing agents, such as the phosphines used in the Staudinger reaction. Ex. 1508, 7595; Ex. 1529, 2008; Ex. 1551, 52; *see also* Part IX.C.2.a, *infra*. These reducing agents are not present during the incorporation reactions, which are typically performed in buffer at near neutral pH. *See, e.g.*, Ex. 1504, 27:39-67 (describing conditions for testing the compatibility of a blocked nucleotide and a polymerase); *see also* Ex. 1507, 339; Ex. 1601, ¶138. As discussed above, a POSITA would have also expected the azidomethyl to be unreactive towards the polymerase. Ex. 1601, ¶142.

Lastly, a POSITA would have expected the azidomethyl group to be

compatible with most selected polymerases because it is a small and bioorthogonal group. Ex. 1601, ¶¶138-147. As described above, the azidomethyl group is small and the azide is linear, and as a result, a POSITA would have expected it to be compatible with many polymerases. Ex. 1601, ¶¶143-147. In addition, azides were known to be bio-orthogonal and therefore unreactive towards biological systems, such as polymerases. *See* Ex. 1529, 2007 (describing azides as "abiotic and chemically orthogonal to native cellular components."); Ex. 1601, ¶¶138-141.

In sum, because an azidomethyl group would have served those functions of the protecting group that were described by Dower, a POSITA would have found its substitution for the protecting groups of Dower to be obvious and predictable. Moreover, the substitutability and predictability of azidomethyl group would have motivated a POSITA to make such substitution, and they would have had a reasonable expectation of success in doing so, as detailed in Part IX.D, *infra*.

2. A POSITA would have been further motivated to combine the azidomethyl group because of its extremely favorable properties for use as a protecting group

In addition to being a simple substitution with a predictable result (*see* Part IX.C.1, *supra*), a POSITA would also have been highly motivated to combine an azidomethyl protecting group with the reversibly blocked labeled nucleotides of Dower and Church's disulfide linker due to the advantageous properties of azidomethyl as a protecting group, as described below. Moreover, because these properties were predictable, a POSITA would have also had a reasonable expectation of success in arriving at the claimed invention, as described in Part

IX.D, *infra*. Ex. 1601, ¶149.

a. Mild and specific removal conditions

First and foremost, a POSITA would have been motivated to combine an azidomethyl protecting group with Dower due to statements in Zavgorodny, Loubinoux and Young that tout the mild and specific removal conditions of the azidomethyl protecting group. *See, e.g.*, Ex. 1508, 7595("[a]zidomethyl group is of special interest, since it can be removed under very specific and mild conditions …."); Ex. 1506, 6055 (Abstract) ("its utility lies in the ease with which it can be removed under very mild conditions."). Loubinoux describes azidomethyl's removal mechanism as an "advantage," including "the very mild conditions of reductions of organic azides to primary amines" and "the instability of the aryloxymethylamines [] which evolve very rapidly" to the deprotected phenolic hydroxyl. Ex. 1506, 6055; Ex. 1601, ¶¶150-156. Young echoes Loubinoux and Zavgorodny in noting that the azidomethyl group is "removed under mild conditions." Ex. 1551, iii &42.[6]

A POSITA would have understood from Loubinoux's description of the two step cleavage mechanism that the first step of the deprotection could be achieved

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[6] *See also* Exs. 1548-1552 (demonstrating public availability of Young thesis prior to August 2002 via University of Wisconsin-Madison Library catalog (Exs. 1548-49), inclusion in WorldCat catalog (*id.*), availability for sale from ProQuest/UMI (Ex. 1550-52), and publication and circulation of the abstract in DAI (Exs. 1550-52).

using known conditions for azide reduction, including the well-known Staudinger reaction that was first taught in 1919. Ex. 1506, 6056; Ex. 1544, 438; Ex, 1528, 1354; Ex. 1529, 2007; Ex. 1601, ¶¶135-136. Loubinoux and Zavgorodny both use triphenylphosphine as the reducing agent; however, a POSITA would have known that the Staudinger reaction would work with other phosphines. Furthermore, a co-solvent was only required to ensure solubility of the phosphine and the azide. *See* Ex. 1529, 2008 (Fig.1.A only showing water and phosphine); Ex. 1601, ¶¶157-158. For example, Zavgorodny and Loubinoux, who both emphasize the mildness and specificity of removal, use different co-solvents with different substrates.[7] Ex. 1551, 67-68. Thus, a POSITA would have appreciated that azidomethyl could be removed with different phosphines and that a co-solvent was not necessarily required. Ex. 1601, ¶¶157-158.

In addition, DNA is water-soluble and as a result, a POSITA would have been highly motivated to use azidomethyl, because it could be deprotected using a water-soluble phosphine, such as TCEP. *Id*.; Ex. 1529, 2007. Such an approach

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[7] Zavgorodny suggests "triphenylphosphine in aqueous pyridine." Ex. 1508, 7595. Loubinoux suggests "triphenylphosphine followed by water, in tetrahydrofuran" and also cites to Vaultier, which discloses using triphenylphosphine in water and THF in a single step. Ex. 1506, 6057; Vaultier, Ex. 1556, 764. Moreover, Young states that azide reduction generally "can be accomplished through the action of numerous mild reducing agents."

would have the advantage of avoiding the avoid the use of a co-solvent entirely, removing potential complications. Ex. 1601, ¶¶157-158. As of 2002, a POSITA would have been familiar with TCEP (a water-soluble trialkylphosphine), as it had been commercially available for roughly a decade. *See* Ex. 1578, 74; *see also* Ex. 1557, 2648; Ex. 1523, 1337.

Furthermore, in 2000, Saxon & Bertozzi published an article in *Science* that highlighted the Staudinger reaction as the foundation for a new ligation mechanism, and in so doing, brought the Staudinger reaction to the forefront of bioorganic chemistry. Ex. 1529, 2007. Saxon & Bertozzi described several advantages of azide reduction using the Staudinger reaction that would make it particularly appealing in the context of Dower's sequencing method: "The Staudinger reaction occurs between a phosphine and an azide to produce an aza-ylide (Fig.2A) (7, 8). In the presence of water, this intermediate hydrolyzes spontaneously to yield a primary amine and the corresponding phosphine oxide. The phospine [*sic*] and the azide react with each other rapidly in water at room temperature in high yield. Both are abiotic and essentially unreactive toward biomolecules …." *Id.*, 2007.

Thus, by August 2002, a POSITA would have been well aware of these advantages of the Staudinger reaction, particularly when used with a water-soluble phosphine, and these advantages would have motivated a POSITA to use azidomethyl as a protecting group for Dower's sequencing method. *See* Ex. 1601, ¶¶158-159.

b. Simultaneous cleavage with Church's disulfide

A POSITA would have been motivated to utilize the azidomethyl group of Zavgorodny because it could be removed using conditions that would simultaneously cleave the disulfide linker of Church. Ex. 1601, ¶¶159-161. Dower teaches that when the fluorophore and protecting group are placed in separate parts of the nucleotide, it is preferable that "[t]he fluorophore and the 3' blocking group are removed by the same treatment in a single step[.]" Ex. 1504, 25:37-39.

Church teaches that the disulfide linker can be cleaved using commonly used reducing agents, including DTT. Ex. 1606, 68:12-13 ("As one example of a cleavable linkage, a disulfide linkage may be reduced using thiol compound reducing agents such as dithiothreitol."), 86:20-21.

Similarly, a POSITA would have known that phosphines, like those used to deprotect the azidomethyl group, would also cleave Church's disulfide linker. *See* Ex. 1508, 7595; Ex. 1506, 6057; Ex. 1601, ¶¶159-161. For example, Saxon & Bertozzi reported using phosphines for the reduction of both azides and disulfides. Ex. 1529, 2008, Figure 1.A (depicting azide reduction using a generic phosphine (R_3P:), 2009, Fig 5.B (demonstrating the ability of TCEP to reduce disulfide bonds on the cell surface). In addition, Getz had demonstrated that TCEP and DTT were essentially interchangeable for the reduction of disulfides and that "TCEP has a number of advantages over DTT." Ex. 1578, 74. Burns even emphasizes that TCEP, a trialkylphosphine, "reduce[s] organic disulfides to thiols smoothly and quantitatively in water," suggesting that TCEP would achieve both quantitative

linker cleavage and azidomethyl deprotection in a single step. *See* Ex. 1557, 2648. Thus, a POSITA would have known that the use of could the azidomethyl group could allow for the simultaneous deprotection and linker cleavage that Dower taught as "preferable." Ex. 1504, 25:37-39; Ex. 1601, ¶¶159-161, 180-181. Finally, a POSITA would have been motivated to use the 3′-azidomethyl with Church's disulfide linker because they would have expected both to be compatible with the polymerase used in Dower's method. *See* Parts IX.B & IX.C.1.d, *supra*; Ex. 1601, ¶183.

c. Incorporation of blocked nucleotides by polymerase

A POSITA would also have been motivated to use an azidomethyl group with Dower's SBS method and nucleotides due to the high likelihood that they would be incorporated by a DNA polymerase into the growing nucleic acid. *Id*.

It was widely reported that the structure of DNA polymerase leads it to discriminate against the incorporation of nucleotide analogues bearing a large 3'-OH protecting group. Ex. 1601, ¶¶103-104; *see also* Ex. 1526, 1621; Ex. 1538, 2:46-59; Ex. 1527. Although some polymerases had been shown to incorporate nucleotides with rather bulky groups at the 3'-position (*see, e.g.*, Ex. 1524), a POSITA nonetheless would have been motivated to use smaller groups in expectation that they would allow incorporation by a greater selection of polymerases. Ex. 1601, ¶¶104, 143-144. Because azidomethyl is relatively small and can adopt "rotameric states" that can reduce its steric profile, a POSITA would have expected it to exhibit minimal steric interference during incorporation. *Id*.; *see*

also Part IX.C.1.d, *supra*.

In addition, a POSITA would have expected azidomethyl to be inert to the polymerase. Ex. 1601, ¶¶138; 162-167. As described above in Part IX.C.2.a, *supra*, by 2002, azides were well-known to be bio-orthogonal and generally inert to natural biological molecules, such as polymerases. *See* Ex. 1601, ¶¶33-34, 164; Ex. 1529, 2007. This expectation of compatibility with the polymerase would have been further bolstered by prior art demonstrating that azides were unreactive towards polymerases. *See* Ex. 1601, ¶¶144-145; Ex. 1515, 21459; Ex. 1503, 21:13-15. Kraevskii and Copeland demonstrate incorporation of nucleotides bearing azido groups at the 3′ position by several polymerases. Ex. 1576, 28; Ex. 1515, 21462; Ex. 1601, ¶¶144-145. In addition, a 3'-azide was used as a terminator in the well-known, heavily-studied, antiviral drug AZT. *See* Ex. 1601, ¶¶118, 144. Accordingly, a POSITA would have been further motivated to use an azidomethyl protecting group because they would have expected an azido protecting group (such as azidomethyl) to be incorporated by polymerases. Ex., 1601, ¶144.

d. Deblocking efficiency

As recognized by Dower, the SBS method and nucleotides used therein would have useful for a variety applications, including those that do not require long "read" lengths. *See* Ex. 1601, ¶¶116-117 (citing Ex. 1573, 930; Ex. 1574, 235; Ex. 1575, 938). Applications of SBS that utilized only one or few rounds of nucleotide incorporation were widely described in the art and would have been well-known to a POSITA. *Id.*. Thus, a POSITA considering using Dower's

disclosed SBS method would not necessarily need to use a protecting group with a very high deblocking efficiency. *Id*. The '537 patent similarly states that its labelled nucleotides are "useful in techniques" such as "single nucleotide polymorphism studies[.]" Ex. 1501, 2:3-11. Tellingly, none of the claims of the '537 patent require any more than one round of incorporation and deblocking.

However, for applications where maximizing read length is particularly useful, a POSITA would have found it advantageous to use a protecting group with a high deblocking efficiency. Ex. 1601, ¶172. In that context, the desire for high deblocking efficiency would have been yet another motivating factor for a POSITA considering the use of an azidomethyl protecting group, particularly in light of the teachings of Young and Loubinoux.

(i) Young

In 2001, Young reported a quantitative deblocking efficiency for azidomethyl-protected hydroxyl groups during the solid-phase synthesis of sulfated peptides. *See* Ex. 1551, 68 ("Cleavage of the dipeptide 2.73 from the resin followed by proton NMR spectroscopy confirmed the expected structure and the quantitative cleavage of the Azm [(azidomethyl)] group"). Young also reported that the azidomethyl "could be used to protect the hydroxyl functions of serine and threonine for the selective unmasking of these residues on solid support," both of which are alkyl hydroxyl groups, like the 3′-OH. *See id.*, 74. Thus, Young's disclosure of quantitative cleavage during solid phase synthesis would have been highly motivating to a POSITA seeking to utilize azidomethyl in the context of

SBS, which is also performed on the solid phase. *See* Ex. 1601, ¶176.

Young selected the azidomethyl protection strategy based on his knowledge that "[a]zide reduction can be accomplished through the action of numerous mild reducing agents," and choose azidomethyl as a "minimalist design approach," likely based on the group's small size. *See* Ex. 1551, 52-55. Young also reported that a search of the literature, specifically including Loubinoux (described below), provided "encouragement" to use the azidomethyl protecting group. *Id.*, 52-53. Thus, in addition to motivating a POSITA to use azidomethyl, Young also provides evidence that a POSITA (or even a Ph.D. candidate with less than "ordinary" skill) would have viewed Loubinoux as encouraging the application of the azidomethyl group in the context of a solid phase synthesis where high efficiency deblocking is advantageous. Ex. 1601, ¶176.

(ii) Loubinoux

Loubinoux reported "pure product yields" of 60-80% for the synthesis of highly-unstable phenols in the solution phase, a disclosure that would have suggested to a POSITA that the azidomethyl group could be deblocked in extremely high efficiency when used with Dower's nucleotides and SBS method. Ex. 1601, ¶¶171-174. "Pure product yields," as used in Loubinoux, refers to the percentage recovery of the isolated unstable phenol products after purification of the products using liquid chromatography on a silica column. *Id.*; Ex. 1506, 6057. A POSITA in August 2002 would have known that Loubinoux's reported results were impacted by two factors that would not be present in the context of SBS: purification by

liquid chromatography over silica and inherently unstable deprotection products. *Id.*, 6055-56; Ex. 1601, ¶¶171-174. A POSITA would have expected significant loss of product during Loubinoux's purification step, which would not be an issue in Dower's solid phase SBS method. *See* Ex. 1504, 23:34-37.

Moreover, a POSITA would have expected the purification step in Loubinoux to cause an inordinately large loss of product given the admittedly unstable nature of those products. Ex. 1506, 6055; Ex. 1601, ¶¶171-173. Thus, a POSITA would have understood that Loubinoux's reported "pure product yields" of 60-80% suggest that the reaction efficiency must actually have been very high, not excluding over 99%. Ex. 1601, ¶174. Otherwise, the pure isolated product yields would have been far lower. *Id*. Loubinoux's reported "pure product yields" would have led a POSITA to expect that azidomethyl could be removed with a very high yield in the solid phase. *Id.*, ¶¶171-174. This is precisely the understanding demonstrated by Young, a graduate student, who was able to easily apply Loubinoux's azidomethyl protecting group in a solid phase synthesis to achieve quantitative deblocking of the azidomethyl group. Ex. 1551, 52-55; Ex. 1601, ¶176.

However, in IPR2013-00517, Illumina misrepresented the overall yields described in Loubinoux as corresponding to the "removal *efficiency* for phenolic azidomethyl groups." *Id*., 24 (emphasis added); Ex. 1601, ¶¶173-175. As described above, Loubinoux actually reports pure product ***yields*** of an unstable phenol product as between 60 and 80% after purification, ***not*** only the "efficiency" of the removal. Ex. 1601, ¶¶171-174. As evidenced by Young, a POSITA would have readily

understood this distinction — and given the expectation that much of the lost yield would be due to purification of the unstable products — would have known that the reported yields in Loubinoux should be considered as encouraging that azidomethyl could be deblocked in high yield on the solid phase. *Id.*, ¶176. Moreover, Illumina's argument is inconsistent with Young having found Loubinoux to be encouraging, and with Young's reported quantitative cleavage of the azidomethyl group. Ex. 1551, 51-52, 55.

Thus, for each of the reasons above, a POSITA would have been motivated to combine an azidomethyl group with the SBS method and nucleotides disclosed in Dower.

D. A POSITA Would Have Had A Reasonable Expectation of Success in Arriving at Claims 1-2, 4-6, and 8

A POSITA would have had a reasonable expectation of success in the use of a cleavable disulfide linker disclosed in Church for the attachment of the label to the nucleobase and to cleave the linker (as required by claims 1 and 8). Church had already established that nucleotides bearing the disulfide linker were incorporated by a polymerase, that the fluorescent probe could be detected, and that the linker could be subsequently cleaved, releasing the fluorophore. Ex. 1606, 85:13-87:2 (Example 17); Ex. 1601, ¶¶29-32, 97. Moreover, a POSITA would have appreciated that the addition of Church's disulfide linker between Dower's nucleobase and label would, if anything, make incorporation of the labeled nucleotide by the polymerase more likely to be successful than without the linker

because the linker further extends the distance between the label and the active site of the polymerase, thereby reducing potential steric interference. Ex. 1601, ¶104. Accordingly, a POSITA would have had a reasonable expectation of success in utilizing Church's disulfide linker with Dower's nucleotides and SBS method to achieve the method claimed by the '537 patent.

A POSITA also would have had a reasonable expectation of success in the use of Zavgorodny's azidomethyl protecting group with Dower's SBS method and nucleotides and Church's disulfide linker, as recited in the challenged claims. A POSITA would have expected to be able to (1) incorporate a deoxyribonucleotide triphosphate molecule with a fluorescent label attached to that base via Church's cleavable linker and Zavgorodny's azidomethyl protecting group on the 3′ position (claims 1, 4, 5, and 6); (2) where such incorporation occurs via a polymerase or reverse transcriptase (claim 2); (3) detect the label and cleave the cleavable linker (claim 8); and (4) remove the azidomethyl protecting group to expose a 3′ OH group (claim 1). *See* Ex. 1601, ¶93. By expecting to be able to perform these four functions, a POSITA would have had a reasonable expectation of success of meeting all the limitations of claims 1-2, 4-6, and 8.

First, a POSITA would have expected to be able to produce the required modified nucleotide by attaching the azidomethyl group to the 3′-position of the nucleotides disclosed in Dower. Zavgorodny specifically teaches attachment of the azidomethyl group at the 3'-OH position. Ex. 1508, 7594. A POSITA would have combined an azidomethyl-protected nucleotide with Church's disulfide cleavable

linker, connecting the fluorescent label to the base. Ex. 1601, ¶¶119-125. Indeed, Dower acknowledges that the synthesis of labeled nucleotides would be straightforward for a POSITA. Ex. 1504, 19:3-4 ("Various nucleotides possessing features useful in the described method can be readily synthesized."). Such nucleotide would have been expected to be readily incorporated into the growing DNA strand, in a similar manner to that demonstrated by Church. Ex. 1606, 85:12-87:2.

Second, Dower teaches that various enzymes "are useful in connection with the invention," and lists several polymerases. *Id*., 17:46-63. Dower also teaches that once an enzyme is selected, the conventional incorporation conditions can be optimized in a routine manner. Ex. 1504, 17:25-29; Ex. 1601, ¶105. Moreover, a POSITA would have known that the azidomethyl group would be compatible with incorporation because it is small and biorthogonal. *See supra*, Part C.2; Ex. 1529, 2007. Thus, a POSITA would have been extremely confident that the azidomethyl modified nucleotide analogue would be incorporated by at least one of the many known polymerases.

Third, detection in the context of sequencing was well known in the art. *See, e.g.*, Ex. 1504, 18:43-49. Dower teaches that several fluorescent moieties are available, including those "for which detection is quite sensitive." *Id*., 18:41-42. Moreover, the prior art teaches conditions for cleavage of the disulfide linker following detection, and these conditions are advantageously compatible with simultaneous removal of the azidomethyl protecting group. *See* Ex. 1601, ¶¶98-99

(citing Ex. 1606, 86:26-27; Ex. 1557, 2648; Exs. 1529, 2008-09).

Finally, a POSITA would have known that the 3'-*O*-azidomethyl group could be removed, exposing the 3′-OH. Zavgorodny teaches removal of the azidomethyl group on the 3′-OH of a nucleoside. Ex. 1508, 7595. Young and Loubinoux also supply conditions for the deprotection of the azidomethyl group and a POSITA would have known of other reducing agents capable of effecting deprotection. Ex. 1601, ¶¶172-179. Indeed, though not required by the challenged claims, a POSITA would have had a reasonable expectation of success at simultaneously cleaving Church's disulfide linker and Zavgorodny's azidomethyl protecting group because both could be removed with phosphine reducing agents. *See* Part IX.B, C.2, *supra*.

Thus, in light of the foregoing, a POSITA would have had a reasonable expectation of success in achieving the claimed invention by combining the teachings of Dower and Church with the azidomethyl group of Zavgorodny.

X. GROUND 2: CLAIM 3 WOULD HAVE BEEN OBVIOUS OVER DOWER, CHURCH, AND ZAVGORODNY, IN FURTHER COMBINATION WITH PROBER.

Claim 3, which depends from claim 1, recites the additional limitation "wherein the base is a deazapurine." Claim 3 is obvious over Dower, Church, and Zavgorodny (*see* Part IX, *supra*), in further combination with Prober (Ground 2).

A. The "Deazapurine" Limitation of Claim 3 Was Disclosed in Prober and Was Well-Known In the Art.

The "deazapurine" base limitation of claim 3 is disclosed in Prober, which was published in 1987. Ex. 1507, 337. Prober discloses the use of a fluorescent

dye attached "to the 7 position in the 7-deazapurines." *Id.*; *see also* Ex. 1601, ¶¶16, 93, 189. Other prior art references suggest the use of deazapurine bases and/or refer to Prober for teaching useful nucleotide analogs for SBS. *See* Ex. 1538, 7:53-8:9, 10:53-55, 24:42-44, 35:33-36; Ex. 1503, 29:10-14; Ex. 1601, ¶¶185-187.

B. A POSITA Would Have Been Motivated to Combine Prober's Deazapurine Base with Dower's SBS Method.

Prober's teaching that the use of 7-deazapurines "facilitate stable linker arm attachment at that site," would have motivated a POSITA to substitute the adenine and guanine bases in Dower's SBS method with deaza-adenine or deaza-guanine (i.e., a "deazapurine base") to facilitate attachment of the linker between the base and the label. Ex. 1507, 337; Ex. 1606, 86:30-87:2; Ex. 1601, ¶¶188-189. A POSITA also would have been motivated to use Prober's deazapurine bases due to Dower's repeated citation to Prober for sequencing-related principles, thereby demonstrating Prober's relevance to SBS. *See* Ex. 1504, 17:33-36, 20:41, 23:18-24, 25:4-12, 25:44-46, 28:7-12; Ex. 1503, 29:10-14; Ex. 1601, ¶187.

Providing further motivation to combine, Prober is cited by other prior art for its disclosure of the use of nucleotide analogs, such as a deazapurine base, with SBS. For example, Ju describes that the "label is attached through a cleavable linker to the 5-position of cytosine or thymine or to the 7-position of deaza-adenine or deaza-guanine." Ex. 1538, 8:6-9,10:53-55; *see also id.*, 7:53-8:6, 24:42-44 (citing Prober for "well-established procedures" for synthesis of 7-deaza-alkynylamino-dGTP), 35:33-36. This teaching would have motivated a POSITA to

combine Prober's deazapurine bases (deaza-adenine and deaza-guanine) with Dower's SBS method for use with Church and Zavgorodny. Ex. 1601, ¶¶186-189.

As Illumina previously argued to the Board, a POSITA would also have been motivated to utilize deazapurines because "[d]eazapurines were part of the DNA sequencing art since the late 1980s and had become ubiquitous in the 1990s due to numerous well-known benefits of deazapurines for sequencing …." Ex. 1587, 3; *see also* 620 Fed.Appx. 916, 925 (2015). The Federal Circuit agreed with Illumina's arguments: "deazapurine nucleotides can advantageously be used . . . in polymerase-based sequencing methods, such as SBS." *Id.*, 928 (discussing Seela, *see* Ex. 1547, 2:65-66 (analogues "do not form aggregates"), 4:24-28). Thus, a POSITA also would have been motivated to use 7-deazapurines.

C. A POSITA Would Have Had a Reasonable Expectation of Success in Combining Prober's Deazapurine Base with Dower's SBS Method, Church's Linker, and Zavgorodny's Protecting Group to Arrive at the Claimed Combination.

A POSITA would also have had a reasonable expectation of success in achieving the claimed method with Dower, Young, Zavgorodny and Prober. As described in Part IX.D, *supra*, a POSITA would have had a reasonable expectation of success in combining Dower's method with the disulfide linker of Church and the 3′-azidomethyl protecting group of Zavgorodny. The further combination of Prober's deazapurines would have been no more than a simple substitution for a POSITA. Ex. 1601, ¶190. Synthesis of deazapurines bearing linkers and detectable labels had already been disclosed in the art. Ex. 1507, 337; Ex. 1538, 8:1-9;

Herman, Ex. 1607, 2:33-35; Ex. 1601, ¶186. Such nucleotides were already known to be incorporated by polymerases. Ex. 1507, 337. Moreover, the use of a deazapurine would not have been expected to hinder the detection and cleavage steps, both of which were well known and do not directly involve the nucleobase. *Id.*, 338-40, Ex. 1538, 6:12-17; Ex. 1601, ¶190. Indeed, use of deazapurines in combination with reversible terminators and labels attached via a cleavable linker had already been suggested for use in SBS by Ju. Ex. 1538, 10:53-55. Thus, a POSITA would have reasonably expected success in combining Prober with Dower, Church, and Zavgorodny to arrive at the alleged invention of claim 3. Ex. 1601, ¶190.

XI. OBJECTIVE INDICIA OF NONOBVIOUSNESS DO NOT SUPPORT THE PATENTABILITY OF THE CHALLENGED CLAIMS

Illumina will not be able to rebut the prima facie case of obviousness with evidence of secondary considerations. As detailed below, each of the arguments previously raised by Illumina is without merit because the requisite "nexus" between the challenged claims and the alleged secondary considerations cannot be met.[8] *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013).

[8] Illumina previously made confidential arguments and cited confidential exhibits in support of secondary considerations (Ex. 1592, 47-49), and the prior Petitioner also referenced confidential information in its Reply (Ex. 1593, 11), such that Petitioner herein cannot address these issues at this time.

A. No Nexus between the Satisfaction of a Long-Felt, Unmet Need and the Claimed Azidomethyl Group

Illumina previously asserted that its invention satisfied a long-felt, unmet need for "protecting groups that could be efficiently and rapidly cleaved under conditions compatible with DNA sequencing," a "fast and efficient SBS method," and "for SBS nucleotides and methods capable of very high efficiency (quantitative or nearly quantitative) cleavage under DNA-friendly mild reaction conditions." Ex. 1592, 44-49; Ex. 1593, 10-11. However, none of these purported long-felt, unmet needs are commensurate in scope or have nexus with the claims, which do not require removal of the protecting group, much less removal with a high degree of efficiency or rapidity, and have no requirements regarding reaction conditions.

Moreover, Illumina did not provide any evidence that its purported satisfaction of a long felt need for "fast and efficient SBS methods" was due to the claimed azidomethyl protecting group, as opposed to other factors, and thus did not establish the necessary nexus. Illumina's argument relied on two publications, but neither article supports the proposition that the alleged success was causally linked to the azidomethyl protecting group. *See* Ex. 1592, 45-46 (discussing Bentley, Ex. 1539 and Mardis, Ex. 1540, and Dr. Romesberg's discussion thereof, Ex.1598, ¶¶61-65).

Bentley — which identifies all six of the '537's named inventors as coauthors — describes ***numerous*** factors that contributed to the alleged success described therein, including the use of an engineered polymerase to improve the efficiency of incorporation of the nucleotides, the use of a particular cleaving agent to remove the

protecting group, and hardware and software improvements. Ex. 1539, 53, 58 & Supp. Info. 16, Fig.S2b; Ex. 1601, ¶¶196-200.

Similarly, Mardis does not even mention, much less credit, Illumina's claimed azidomethyl group as causing an increase in data output. Yet, Illumina relies on Mardis for the proposition that Illumina's "protected nucleotides demonstrate long read lengths in SBS and can generate superior amounts of sequence information" and "were recognized for increasing data output by eight orders of magnitude." Ex. 1592, 46 (citing Mardis, Ex. 1540, 1999). Rather, Mardis provides an overview comparing the development of sequencing platforms between 2001 and 2011, and does not discuss any details regarding Illumina's products. Thus, Mardis simply provides no basis for concluding that the particular claimed protecting group is responsible for any alleged increase in data output. Ex. 1601, ¶¶201-202 (discussing Ex. 1540, Fig.1 & Table 1).

Moreover, during the deposition of Illumina's expert in the prior IPR, Dr. Burgess admitted that numerous factors would impact the read length in a SBS process, including selection of cleaving agent, concentration of cleaving agent, the pH of the cleaving conditions, temperature, and selection of the polymerase. Ex. 1600, 49:1-24, 50:1-3, 52:14-17. Thus, any alleged success of Illumina's commercial SBS product is inseparable from these other, unclaimed, features of the product.

B. Illumina's Arguments for New and Unexpected Results Do Not Have a Sufficient Nexus to the Claims and Are Based on Hindsight Bias

Illumina's assertion that the 3′-O-azidomethyl group performs unexpectedly better than other protecting groups fails to account for other, unclaimed factors, such as choice of polymerase and removal conditions, and is therefore is insufficient to support nonobviousness. *See* Part X.A (discussing Bentley).

Notably, Illumina alleged that Ju, Tsien, and other prior art did not suggest that 3'-*O*-azidomethyl groups "are cleaved with surprisingly greater speed" (Ex. 1592, 51), but removal of the protecting group, much less removal at high speed, is not claimed. Moreover, the '537 specification says nothing about the alleged superiority of azido-containing protecting groups or the alleged "dramatically improved results relative to SBS methods in the prior art." *Id*., 51. Rather, the '537 includes azido groups as one of a multitude of possible protecting groups that a POSITA could select, and states that such a person would be sufficiently skilled to identify suitable conditions for their use. Thus, Illumina's arguments reflect a hindsight bias because what was explicitly described in the patent as being within the knowledge and skill of a POSITA is now alleged to be both nonobvious and the basis of new and unexpected results.

Illumina also further relied on experimental comparisons between 3′-*O* allyl groups and 3′-*O*-azidomethyl groups, but the details of those comparisons were filed under seal such that Petitioner cannot address them at this time. *See* Ex. 1592, 51-55 (redacted); Ex. 1598, ¶¶79-81; Ex. 1601, ¶¶203-205.

C. Evidence of Copying is Completely Absent

Illumina previously asserted that evidence of copying by the prior Petitioner "confirms the superiority of [Illumina's] 3′-*O*-azidomethyl group over other protecting groups for SBS." Ex. 1592, 55-59. This argument was partially redacted in the public filing (*id.*, 58-59), such that Petitioner can only partially address this argument at this time. However, this argument appears to have been erroneous, as there was apparently no evidence that Dr. Ju's group attempted to replicate any specific product of Illumina (*id.*, 56-58), as required for it to constitute objective evidence of nonobviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *see also Kamada, Ltd. v. Grifols Therapeutics Inc.*, IPR2014-00899, Paper 22, 4 (Mar. 4, 2015) (Ex. 1585).

D. Praise by Others Was Likely Unrelated to the Claim Limitations

Illumina previously asserted that praise by others was a relevant secondary consideration (Ex. 1592, 59-60), but that argument was completely redacted in public filings such that Petitioner cannot address it at this time. However, based on the prior petitioner's argument in reply, it appears that Illumina failed to establish the requisite "nexus" because the praise was not specifically directed to the alleged novel feature of the invention. *See* Ex. 1593, 15.

XII. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests inter partes review and cancellation of claims 1-6, and 8 of the '537 patent.

Dated: October 5, 2017

Respectfully Submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 CFR §42.24(a), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this Petition for *Inter Partes* Review, that the number of words in this Petition is 13,983. Pursuant to 37 C.F.R. § 42.24(a)(1), this word count does not include the table of contents, table of authorities, table of exhibits, mandatory notices, certificate of word count, or the certificate of service.

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§42.6(e)(4)(i) *et seq*. and 42.105(b), the undersigned Certifies that on October 4, 2017, a true and entire copy of this **PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 7,566,537 B2**, and all supporting exhibits , were served by EXPRESS MAIL to the Patent Owner by serving the correspondence address of record, indicated below.

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