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**Ju et al.**

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(54) **MASSIVE PARALLEL METHOD FOR DECODING DNA AND RNA**

(58) **Field of Classification Search**  
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(Continued)

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(56) **References Cited**

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U.S. PATENT DOCUMENTS

4,711,955 A 12/1987 Ward et al.  
4,772,691 A 9/1988 Herman  
(Continued)

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FOREIGN PATENT DOCUMENTS

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CA 2425112 4/2002  
CA 2408143 11/2002  
(Continued)

This patent is subject to a terminal disclaimer.

OTHER PUBLICATIONS

U.S. Application for a Method for Direct Nucleic Acid Sequencing; U.S. Appl. No. 09/266,187, filed Mar. 10, 1999.  
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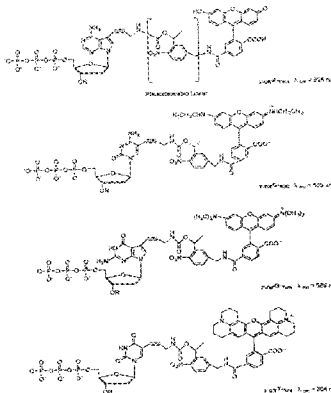
(57) **ABSTRACT**

This invention provides methods for attaching a nucleic acid to a solid surface and for sequencing nucleic acid by detecting the identity of each nucleotide analog after the nucleotide analog is incorporated into a growing strand of DNA in a polymerase reaction. The invention also provides nucleotide analogs which comprise unique labels attached to the nucleotide analog through a cleavable linker, and a cleavable chemical group to cap the —OH group at the 3'-position of the deoxyribose.

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**1 Claim, 28 Drawing Sheets**



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(58) **Field of Classification Search**  
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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,804,748 A 2/1989 Seela  
 4,824,775 A 4/1989 Dattagupta et al.  
 4,863,849 A 9/1989 Melamede  
 5,043,272 A 8/1991 Hartley  
 5,047,519 A 9/1991 Hobbs, Jr. et al.  
 5,118,605 A 6/1992 Urdea  
 5,151,507 A 9/1992 Hobbs, Jr. et al.  
 5,174,962 A 12/1992 Brennan  
 5,175,269 A 12/1992 Stavrianopoulos  
 5,242,796 A 9/1993 Prober et al.  
 5,302,509 A 4/1994 Cheeseman  
 5,308,990 A 5/1994 Takahashi et al.  
 5,328,824 A 7/1994 Ward et al.  
 5,332,666 A 7/1994 Prober et al.  
 5,383,858 A 1/1995 Reilly et al.  
 5,436,143 A 7/1995 Hyman  
 5,437,975 A 8/1995 McClelland et al.  
 5,449,767 A 9/1995 Ward et al.  
 5,476,928 A 12/1995 Ward et al.  
 5,516,664 A 5/1996 Hyman  
 5,534,424 A 7/1996 Uhlen et al.  
 5,547,839 A 8/1996 Dower et al.  
 5,547,859 A 8/1996 Goodman et al.  
 5,556,748 A 9/1996 Douglas  
 5,599,675 A 2/1997 Brenner  
 5,602,000 A 2/1997 Hyman  
 5,637,469 A 6/1997 Wilding et al.  
 5,654,419 A 8/1997 Mathies et al.  
 5,658,736 A 8/1997 Wong  
 5,709,999 A 1/1998 Shattuck-Eidens et al.  
 5,714,330 A 2/1998 Brenner et al.  
 5,728,528 A 3/1998 Mathies et al.  
 5,763,594 A 6/1998 Hiatt et al.

5,789,167 A 8/1998 Konrad  
 5,798,210 A 8/1998 Canard et al.  
 5,804,386 A 9/1998 Ju  
 5,808,045 A 9/1998 Hiatt et al.  
 5,814,454 A 9/1998 Ju  
 5,821,356 A 10/1998 Khan et al.  
 5,834,203 A 11/1998 Katzir et al.  
 5,844,106 A 12/1998 Seela et al.  
 5,849,542 A 12/1998 Reeve et al.  
 5,853,992 A 12/1998 Glazer et al.  
 5,856,104 A 1/1999 Chee et al.  
 5,869,255 A 2/1999 Mathies et al.  
 5,872,244 A 2/1999 Hiatt et al.  
 5,876,936 A 3/1999 Ju  
 5,885,775 A 3/1999 Hoff et al.  
 5,908,755 A 6/1999 Kumar et al.  
 5,945,283 A 8/1999 Kwok et al.  
 5,948,648 A 9/1999 Khan et al.  
 5,952,180 A 9/1999 Ju  
 5,959,089 A 9/1999 Hannessian  
 5,962,228 A 10/1999 Brenner  
 6,001,566 A 12/1999 Canard et al.  
 6,001,611 A 12/1999 Will  
 6,008,379 A 12/1999 Benson et al.  
 6,013,445 A 1/2000 Albrecht et al.  
 6,028,190 A 2/2000 Mathies et al.  
 6,046,005 A 4/2000 Ju et al.  
 6,074,823 A 6/2000 Koster  
 6,087,095 A 7/2000 Rosenthal et al.  
 6,136,543 A 10/2000 Anazawa et al.  
 6,175,107 B1 1/2001 Juvinal  
 6,197,557 B1 3/2001 Makarov et al.  
 6,207,831 B1 3/2001 Auer et al.  
 6,210,891 B1 4/2001 Nyren et al.  
 6,214,987 B1 4/2001 Hiatt et al.  
 6,218,118 B1 4/2001 Sampson et al.  
 6,218,530 B1 4/2001 Rothschild et al.  
 6,221,592 B1 4/2001 Schwartz et al.  
 6,232,465 B1 5/2001 Hiatt et al.  
 6,242,193 B1 6/2001 Anazawa et al.  
 6,245,507 B1 6/2001 Bogdanov  
 6,255,083 B1 7/2001 Williams  
 6,255,475 B1 7/2001 Kwiatkowski  
 6,274,320 B1 8/2001 Rothberg et al.  
 6,277,607 B1 8/2001 Tyagi et al.  
 6,287,821 B1 9/2001 Shi et al.  
 6,294,324 B1 9/2001 Bensimon et al.  
 6,309,829 B1 10/2001 Livak et al.  
 6,309,836 B1 10/2001 Kwiatkowski  
 6,312,893 B1 11/2001 Van Ness et al.  
 6,316,230 B1 11/2001 Egholm et al.  
 6,335,155 B1 1/2002 Wells et al.  
 6,361,940 B1 3/2002 Van Ness et al.  
 6,380,378 B1 4/2002 Kitamura et al.  
 6,495,680 B1 12/2002 Gong  
 6,524,829 B1 2/2003 Seeger  
 6,555,349 B1 4/2003 O'Donnell  
 6,613,508 B1 9/2003 Ness et al.  
 6,613,513 B1 9/2003 Parce et al.  
 6,627,748 B1 9/2003 Ju et al.  
 6,632,655 B1 10/2003 Mehta et al.  
 6,639,088 B2 10/2003 Kwiatkowski  
 6,664,079 B2 12/2003 Ju et al.  
 6,664,399 B1 12/2003 Sabesan  
 6,713,255 B1 3/2004 Makino et al.  
 6,780,591 B2 8/2004 Williams et al.  
 6,787,308 B2 9/2004 Balasubramanian et al.  
 6,818,395 B1 11/2004 Quake et al.  
 6,833,246 B2 12/2004 Balasubramanian  
 6,858,393 B1 2/2005 Anderson et al.  
 6,864,052 B1 3/2005 Drmanac et al.  
 6,911,345 B2 6/2005 Quake et al.  
 6,934,636 B1 8/2005 Skierczynski et al.  
 6,982,146 B1 1/2006 Schneider et al.  
 7,037,687 B2 5/2006 Williams et al.  
 7,056,661 B2 6/2006 Korch et al.  
 7,056,666 B2 6/2006 Dower et al.

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

U.S. PATENT DOCUMENTS			DE		
			DE	4141178	6/1993
			DE	20122767	8/2007
			DE	112007002932.3	8/2015
7,074,597	B2	7/2006	EP	0251786	B1 11/1994
7,078,499	B2	7/2006	EP	0995804	4/2000
7,105,300	B2	9/2006	EP	1182267	2/2002
7,270,951	B1	9/2007	EP	1291354	3/2003
7,279,563	B2	10/2007	EP	0808320	4/2003
7,329,496	B2	2/2008	EP	1337541	B1 3/2007
7,345,159	B2	3/2008	EP	1218391	4/2007
7,414,116	B2	8/2008	EP	1790736	A2 5/2007
7,427,673	B2	9/2008	EP	0992511	3/2009
7,459,275	B2	12/2008	EP	2209911	B1 10/2013
7,566,537	B2	7/2009	EP	2000 0013276	6/2000
7,622,279	B2	11/2009	GB	2001 0029012	12/2001
7,635,578	B2	12/2009	GB	2446083	3/2011
7,713,698	B2	5/2010	GB	2446084	3/2011
7,790,869	B2	9/2010	GB	2457402	9/2011
7,883,869	B2	2/2011	GB	WO 89/09282	10/1989
7,982,029	B2	7/2011	WO	WO 89/11548	11/1989
8,088,575	B2	1/2012	WO	WO 90/13666	11/1990
8,158,346	B2	4/2012	WO	WO 91/06678	5/1991
8,298,792	B2	10/2012	WO	WO 92/10587	6/1992
8,399,188	B2	3/2013	WO	WO 93/05183	3/1993
8,796,432	B2	8/2014	WO	WO 93/12340	10/1993
8,889,348	B2	11/2014	WO	WO 93/21340	10/1993
9,115,163	B2	8/2015	WO	WO 94/14972	7/1994
9,133,511	B2	9/2015	WO	WO 96/07669	3/1996
9,159,610	B2	10/2015	WO	WO 96/23807	8/1996
9,175,342	B2	11/2015	WO	WO 96/27025	9/1996
9,255,292	B2	2/2016	WO	WO 97/08183	3/1997
9,297,042	B2	3/2016	WO	WO 97/27317	7/1997
2002/0012966	A1	1/2002	WO	WO 97/35033	9/1997
2002/0168642	A1	11/2002	WO	WO 98/30720	7/1998
2003/0008285	A1	1/2003	WO	WO 98/33939	8/1998
2003/0022225	A1	1/2003	WO	WO 98/44151	10/1998
2003/0027140	A1	2/2003	WO	WO 99/05315	2/1999
2003/0044871	A1	3/2003	WO	WO 99/49082	9/1999
2003/0054360	A1	3/2003	WO	WO 99/57321	11/1999
2003/0099972	A1	5/2003	WO	WO 00/02895	1/2000
2003/0166282	A1	9/2003	WO	WO 00/06770	2/2000
2003/0180769	A1	9/2003	WO	WO 00/09753	2/2000
2003/0186256	A1	10/2003	WO	WO 00/15844	3/2000
2003/0190680	A1	10/2003	WO	WO 00/18956	4/2000
2003/0198982	A1	10/2003	WO	WO 00/21974	4/2000
2004/0014096	A1	1/2004	WO	WO 00/50172	8/2000
2004/0096825	A1	5/2004	WO	WO 00/50642	8/2000
2005/0032081	A1	2/2005	WO	WO 00/53805	9/2000
2005/0170367	A1	8/2005	WO	WO 00/53812	9/2000
2005/0239134	A1	10/2005	WO	WO 00/70073	11/2000
2006/0003352	A1	1/2006	WO	WO 01/16375	3/2001
2006/0057565	A1	3/2006	WO	WO 01/23610	4/2001
2006/0105461	A1	5/2006	WO	WO 01/25247	4/2001
2006/0160081	A1	7/2006	WO	WO 01/27625	4/2001
2006/0160113	A1	7/2006	WO	WO 01/32930	5/2001
2006/0240439	A1	10/2006	WO	WO 01/57248	8/2001
2006/0252038	A1	11/2006	WO	WO 01/57249	8/2001
2007/0166705	A1	7/2007	WO	WO 01/92284	12/2001
2009/0088332	A1	4/2009	WO	WO 02/02813	1/2002
2009/0240030	A1	9/2009	WO	WO 02/21098	3/2002
2010/0159531	A1	6/2010	WO	WO 02/22883	3/2002
2011/0014611	A1	1/2011	WO	WO 02/29003	4/2002
2011/0124054	A1	5/2011	WO	WO 02/072892	9/2002
2012/0052489	A1	3/2012	WO	WO 02/079519	10/2002
2012/0142006	A1	6/2012	WO	WO 02/088381	11/2002
2013/0264207	A1	10/2013	WO	WO 02/088382	11/2002
2014/0315191	A1	10/2014	WO	WO 03/002767	1/2003
2015/0037788	A1	2/2015	WO	WO 03/020968	3/2003
2015/0080232	A1	3/2015	WO	WO 03/048178	6/2003
2015/0111759	A1	4/2015	WO	WO 03/048387	6/2003
2015/0119259	A1	4/2015	WO	WO 03/085135	10/2003
2015/0197800	A1	7/2015	WO	WO 2004/018493	3/2004
2015/0368710	A1	12/2015	WO	WO 2004/018497	3/2004
2016/0024570	A1	1/2016	WO	WO 2004/055160	7/2004
2016/0024574	A1	1/2016	WO	WO 2005/084367	9/2005

(56)

**References Cited**

## FOREIGN PATENT DOCUMENTS

WO	WO 2007/062105	5/2007
WO	WO 2008/069973	6/2008
WO	WO 2012/083249	6/2012
WO	WO 2012/162429	11/2012
WO	WO 2013/154999	10/2013
WO	WO 2013/191793	12/2013
WO	WO 2014/144883	9/2014
WO	WO 2014/144898	9/2014
WO	WO 2015/123430	8/2015
WO	WO 2015/148402	10/2015
WO	WO 2015/179284	11/2015

## OTHER PUBLICATIONS

U.S. Appl. No. 90/008,149, filed Aug. 4, 2006, Gitten.  
 U.S. Appl. No. 90/008,152, filed Aug. 3, 2006, Gitten.  
 International Search Report dated Sep. 26, 2003 in connection with PCT/US03/21818.  
 International Preliminary Examination Report dated Mar. 18, 2005 in connection with PCT/US03/21818.  
 Notification of Transmittal of International Search Report and Written Opinion, dated May 22, 2008 in connection with International Application No. PCT/US06/45180.  
 International Preliminary Report on Patentability dated on Sep. 5, 2006 in connection with PCT/US05/06960.  
 International Search Report dated Oct. 29, 2007 in connection with PCT International Application No. PCT/US07/13559.  
 Supplementary European Search Report dated Feb. 9, 2007 in connection with European Patent Application No. 03764568.6.  
 Supplementary European Search Report dated Sep. 9, 2008 in connection with PCT International Application No. PCT/US05/06960.  
 International Search Report dated Jan. 23, 2002 in connection with PCT/US01/28967.  
 International Search Report dated Sep. 18, 2002 in connection with PCT/US02/09752.  
 International Preliminary Examination Report dated on Mar. 17, 2003 in connection with PCT/US02/09752.  
 Supplementary European Search Report dated May 25, 2005 in connection with European Patent Application No. 02728606.1.  
 Written Opinion of the International Searching Authority dated Oct. 27, 2005 in connection with PCT/US05/06960.  
 Written Opinion of the International Searching Authority dated Dec. 15, 2006 in connection with PCT/US05/13883.  
 International Search Report dated Jun. 8, 2004 in connection with PCT/US03/39354.  
 International Search Report dated Nov. 4, 2005 in connection with PCT/US05/06960.  
 International Search Report dated Dec. 15, 2006 in connection with PCT/US05/13883.  
 Aug. 19, 2013 Petition 2 of 2 for Inter Partes Review of U.S. Pat. No. 7,566,537, issued Aug. 19, 2013.  
 Exhibit 1015, filed Aug. 19, 2013 in connection with IPR2013-00518: Aug. 16, 2013 Declaration of Dr. Bruce Branchaud.  
 Exhibit 1016, filed Aug. 19, 2013 in connection with IPR2013-00518: Excerpts from the '537 Patent File History.  
 Exhibit 1017, filed Aug. 19, 2013 in connection with IPR2013-00518: Excerpts from the file history of European Patent Application No. 02781434.2.  
 Feb. 13, 2014 Decision of Institution of Inter Partes Review IPR2013-00518.  
 May 5, 2014 Patentee Request for Adverse Judgment in IPR2013-00518.  
 May 6, 2014 Decision of Adverse Judgment in IPR2013-00518.  
 Exhibit 2025, filed Jun. 24, 2013 in connection with IPR2012-

Exhibit 2026, filed Jun. 24, 2013 in connection with IPR2012-00006: Pennisi (2000) DOE Team Sequences Three Chromosomes, *Science*. 288:417-419.  
 Exhibit 2027, filed Jun. 24, 2013 in connection with IPR2012-00006: Welch and Burgess (1999) Synthesis of Fluorescent, Photolabile 3'-O-Protected nucleoside Triphosphates for the Base Addition Sequencing Scheme, *nucleosides & Nucleotides*. 18:197-201.  
 Exhibit 2028, filed Jun. 24, 2013 in connection with IPR2012-00006: Hyman (1998) A New Method of Sequencing DNA, *Analytical Biochemistry* 174:423-436.  
 Exhibit 2030, filed Jun. 24, 2013 in connection with IPR2012-00006: Canard and Sarfati (1994) DNA polymerase fluorescent substrates with reversible 3'-tags, *Gene*. 1481-6.  
 Exhibit 2032, filed Jun. 24, 2013 in connection with IPR2012-00006: Sarfati et al. (1987) Synthesis of Fluorescent or Biotinylated Nucleoside Compounds, *Tetrahedron Letters*. 43:3491-3497.  
 Exhibit 2033, filed Aug. 30, 2013 in connection with IPR2012-00006: Jun. 25, 2013 Substitute Declaration of Dr. George L. Trainor [redacted].  
 Exhibit 2034, filed Jun. 25, 2013 in connection with IPR2012-00006: Jingyue Ju et. al. (2006) Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators, *Proceedings of the National Academy of Sciences*. 103:19635-19640.  
 Exhibit 2035, filed Jun. 25, 2013 in connection with IPR2012-00006: Batista et al. (2008) PRG-1 and 21U-RNAs Interact to Form the piRNA Complex Required for Fertility in *C. elegans*. *Molecular Cell* 31:1-12.  
 Exhibit 2036, filed Jun. 25, 2013 in connection with IPR2012-00006: Form 7 Review Context and Analysis, Biomedical Engineering and Research to Aid Persons with Disabilities Programs Dec. 19-20, 2000 Panel Review, Fluorescence Imaging Chip System for Massive Parallel DNA Sequencing. Proposal No. BES-0097793.  
 Exhibit 2037, filed Jun. 25, 2013 in connection with IPR2012-00006: Oct. 1, 2006 Request for opinion on manuscript by J. Ju et. al., *Proceedings of National Academy of Sciences, U.S.A.*  
 Exhibit 2038, filed Jun. 25, 2013 in connection with IPR2012-00006: Correspondence between George Rupp, Chancellor, Columbia University and Richard T. Schlossberg, President, The David and Lucile Packard Foundation (2001).  
 Exhibit 2039, filed Jun. 25, 2013 in connection with IPR2012-00006: The David and Lucile Packard Foundation, Packard Fellowships for Science and Engineering, <http://www.packard.org/what-wefund/conservation-and-science/packard-fellowships-for-science-and-engineering/> (last visited Jun. 25, 2013).  
 Exhibit 2040, filed Jun. 25, 2013 in connection with IPR2012-00006: "Chemistry for Next-Generation Sequencing." [http://www.illumina.com/technology/sequencing\\_technology.ilmn](http://www.illumina.com/technology/sequencing_technology.ilmn).  
 Exhibit 2041, filed Jun. 25, 2013 in connection with IPR2012-00006: Chiang et al. (2010) Mammalian microRNAs: experimental evaluation of novel and previously annotated genes, *Genes & Dev*. 24:992, 993.  
 Exhibit 2042, filed Jun. 25, 2013 in connection with IPR2012-00006: Seo et al. (2004) Photocleavable fluorescent nucleotides for DNA sequencing on a chip constructed by site-specific coupling chemistry, *Proc. Natl Acad. Sci.* 101(15):5488-5493.  
 Exhibit 2043, filed Jun. 25, 2013 in connection with IPR2012-00006: Curriculum vitae of Mr. Raymond S. Sims.  
 Exhibit 2044, filed Jun. 25, 2013 in connection with IPR2012-00006: Prior Testimony of Mr. Raymond S. Sims.  
 Exhibit 2045, filed Jun. 25, 2013 in connection with IPR2012-00006: Documents reviewed by Mr. Raymond S. Sims in this Proceeding.  
 Exhibit 2052, filed Jun. 25, 2013 in connection with IPR2012-00006: Gary Schroth Proof of Chiang Paper.  
 Exhibit 2074, filed Jun. 25, 2013 in connection with IPR2012-00006: Information about Dr. Ju's intellectual property sent to Illumina.  
 Exhibit 2090, filed Jun. 26, 2013 in connection with IPR2012-00006: IPR Default Protective Order.

(56)

## References Cited

## OTHER PUBLICATIONS

Exhibit 2092, filed Oct. 10, 2013 in connection with IPR2012-00006: Rough Transcript of the Sep. 4, 2013 deposition of Dr. George L. Trainor.

Exhibit 2093, filed Oct. 1, 2013 in connection with IPR2012-00006: Excerpt from Protective Groups in Organic Synthesis, 3rd Ed. (Theodora W. Greene and Peter G.M. Wuts ed., John Wiley & Sons, Inc. 1999).

Exhibit 2094, filed Oct. 1, 2013 in connection with IPR2012-00006: Final transcript of the Sep. 4-6, 2013 deposition of Dr. George L. Trainor.

Exhibit 2095, filed Oct. 1, 2013 in connection with IPR2012-00006: Final transcript of the Sep. 3, 2013 deposition of Raymond S. Sims. Nov. 12, 2013 Petitioner Motion to Exclude Evidence in connection with IPR2012-00006.

Exhibit 1056, filed Nov. 19, 2013 in connection with IPR2012-00006: Videotaped Deposition Transcript of Kevin Burgess, Ph.D., Oct. 28, 2013, signed with errata.

Nov. 12, 2013 Patent Owner Motion for Observations on the Cross-Examination Testimony of Kevin Burgess, Ph.D. in connection with IPR2012-00006.

Nov. 12, 2013 Patent Owner Motion to Exclude Evidence in connection with IPR2012-00006.

Exhibit 2099, filed Nov. 12, 2013 in connection with IPR2012-00006: Welch, M., et al (2005) Corrigenda to Syntheses of Nucleosides Designed for Combinatorial DNA Sequencing Chem. Eur.J., 1999, 951-960. Published in Chem. Eur. J, 2005, 11, 7136-7145.

Exhibit 2100, filed Nov. 12, 2013 in connection with IPR2012-00006: Welch, M (1999) "Base Additions Sequencing Scheme (BASS) and Studies Toward New Sequencing Methodologies." PhD. Dissertation, Texas A&M University.

Exhibit 2101, filed Nov. 12, 2013 in connection with IPR2012-00006: Lu and Burgess (2006) "A Diversity Oriented Synthesis of 3'-O-modified nucleoside triphosphates for DNA 'Sequencing by Synthesis'." Bioorganic & Medicinal Chemistry Letters, 16, 3902-3905.

Exhibit 2102, filed Nov. 12, 2013 in connection with IPR2012-00006: Advanced Sequencing Technology Awards 2004. <http://www.genome.gov/12513162> (accessed Oct. 14, 2013).

Exhibit 2103, filed Nov. 12, 2013 in connection with IPR2012-00006: Welch and Burgess (2006) Erratum to Synthesis of Fluorescent, Photolabile 3'-O-Protected Nucleoside Triphosphates for the Base Addition Sequencing Scheme, Nucleosides & Nucleotides, 18: 197-201. Published in Nucleosides, Nucleotides and Nucleic Acids, 25:1, 119.

Nov. 26, 2013 Petitioner Response to Motion for Observations in connection with IPR2012-00006.

Nov. 26, 2013 Patent Owner Opposition to Petitioner's Motion to Exclude in connection with IPR2012-00006.

Nov. 26, 2013 Petitioner Opposition to Motion to Exclude in connection with IPR2012-00006.

Dec. 3, 2013 Petitioner Reply to Patent Owner's Opposition to Motion to Exclude in connection with IPR2012-00006.

Dec. 3, 2013 Patent Owner Reply on Motion to Exclude in connection with IPR2012-00006.

Exhibit 2105, filed Dec. 15, 2013 in connection with IPR2012-00006: Columbia's Demonstratives Under 42.70(b) for Dec. 17, 2013 Oral Hearing in connection with IPR2012-00006, IPR2012-00007, and IPR2013-00011.

Exhibit 1057, filed Dec. 16, 2013 in connection with IPR2012-00006: Illumina's Invalidation Demonstratives for Final Hearing Dec. 17, 2013 in connection with IPR2012-00006, IPR2012-00007, and IPR2013-00011.

Feb. 10, 2014 Record of Dec. 17, 2013 Oral Hearing in connection with IPR2012-00006, IPR2012-00007, and IPR2013-00011.

Arbo et al. (1993) "Solid Phase Synthesis of Protected Peptides Using New Cobalt (III) Amine Linkers," Int. J. Peptide Protein Res. 42:138-154.

Axelrod, V.D. et al. (1978) "Specific termination of RNA polymerase synthesis as a method of RNA and DNA sequencing," Nucleic Acids Res. 5(10):3549-3563.

Badman, E. R. et al. (2000) "A Parallel Miniature Cylindrical Ion Trap Array," Anal. Chem. (2000) 72:3291-3297.

Badman, E. R. et al. (2000) "Cylindrical Ion Trap Array with Mass Selection by Variation in Trap Dimensions," Anal. Chem. 72:5079-5086.

Bai et al. (2003) "Photocleavage of a 2-nitrobenzyl Linker Bridging a Fluorophore to the 5' end of DNA," PNAS, vol. 100, No. 2, pp. 409-413.

Bai, X., Kim, S., Li, Z., Turro, N.J. and Ju, J. (2004) "Design and Synthesis of a Photocleavable Biotinylated Nucleotide for DNA Analysis by Mass Spectrometry," Nucleic Acids Research, 32(2):534-541.

Benson, S.C., Mathies, R.A., and Glazer, A.N. (1993) "Heterodimeric DNA-binding dyes designed for energy transfer: stability and applications of the DNA complexes," Nucleic Acids Res. 21:5720-5726.

Benson, S.C., Singh, P., and Glazer, A.N. (1993) "Heterodimeric DNA-binding dyes designed for energy transfer: synthesis and spectroscopic properties," Nucleic Acids Res. 21:5727-5735.

Bergmann et al. (1995) "Allyl As Internucleotide Protecting Group in DNA Synthesis to be Cleaved Off by Ammonia," Tetrahedron, 51:6971-6976.

Bergseid M., Baytan A.R., Wiley J.P., Ankener W.M., Stolowitz, Hughs K.A., and Chestnut J.D. (2000) "Small-molecule base chemical affinity system for the purification of proteins," BioTechniques 29:1126-1133.

Bi, L., Kim D.H., and Ju, J. (2006) "Design and Synthesis of a Chemically Cleavable Fluorescent Nucleotide, 3'-O-Allyl-dGTP-allyl-Bodipy-FL-510, as a Reversible Terminator for DNA Sequencing by Synthesis" J. Am. Chem. Soc., 128:2542-2543.

Braslavsky I.; Hebert, B.; Kartalov, E.; et al. (2003) "Sequence information can be obtained from single DNA molecules." Proc. Natl. Acad. Sci. 100(7):3960-3964.

Brunckova, J. et al. (1994) "Intramolecular Hydrogen Atom Abstraction in Carbohydrates and Nucleosides: Inversion of an  $\alpha$ -to  $\beta$ -Manopyranoside and Generation of Thymidine C-4' Radicals." Tetrahedron Letters, vol. 35, pp. 6619-6622.

Buck, G.A. et al. (1999) "Design Strategies and Performance of Custom DNA Sequencing Primers," BioTechniques 27(3):528-536.

Burgess, K. et al. (1997) "Photolytic Mass Laddering for Fast Characterization of Oligomers on Single Resin Beads," J. Org. Chem. 62:5662-5663.

Buschmann et al. (1999) "The Complex Formation of  $\alpha,\omega$ -Dicarboxylic Acids and  $\alpha,\omega$ -Diols with Cucurbituril and  $\alpha$ -Cyclodextrin," Acta Chim. Slov. 46(3):405-411.

Buschmann et al. (2003) "Spectroscopic Study and Evaluation of Red-Absorbing Fluorescent Dyes," Bioconjugate Chem., 14:195-204.

Canard B. et al. (1994) "DNA polymerase fluorescent substrates with reversible 3'-tags," Gene, 148:1-6.

Canard, B. et al. (1995) "Catalytic editing properties of DNA polymerases," Proc. Natl. Acad. Sci. USA 92:10859-10863.

Caetano-Anolies (1994) "DNA Amplification Fingerprinting Using Arbitrary Mini-hairpin Oligonucleotide Primers." Nature Biotechnology, 12:619-623.

Caruthers, M.H. (1985) "Gene synthesis machines: DNA chemistry and its uses," Science 230:281-285.

Chee, M. et al. (1996) "Accessing genetic information with high density DNA arrays," Science 274:610-614.

Chen X. and Kwok, P.-Y. (1997) "Template-directed dye-terminator incorporation (TDI) assay: a homogeneous DNA diagnostic method

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