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

(71) Applicant: **The Trustees of Columbia University in the City of New York**, New York, NY (US)

(72) Inventors: **Jingyue Ju**, Englewood Cliffs, NJ (US); **Zengmin Li**, Flushing, NY (US); **John Robert Edwards**, St. Louis, MO (US); **Yasuhiro Itagaki**, New York, NY (US)

(73) Assignee: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK**, New York, NY (US)

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(56) **References Cited**
U.S. PATENT DOCUMENTS

4,711,955	A	12/1987	Ward et al.
4,772,691	A	9/1988	Herman
4,804,748	A	2/1989	Seela
4,824,775	A	4/1989	Dattagupta et al.
4,863,849	A	9/1989	Melamede
4,888,274	A	12/1989	Radding et al.
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

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2425112	4/2002
CA	2408143	11/2002

(Continued)

OTHER PUBLICATIONS

Aug. 19, 2013 Petition 2 of 2 for Inter Partes Review of U.S. Pat. No. 7,566,537, issued Aug. 19, 2013.

(Continued)

Primary Examiner — Jezia Riley
(74) *Attorney, Agent, or Firm* — John P. White; Cooper & Dunham LLP

(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.

2 Claims, 28 Drawing Sheets



(56)

References Cited

U.S. PATENT DOCUMENTS

5,242,796	A	9/1993	Prober et al.	6,274,320	B1	8/2001	Rothberg et al.
5,302,509	A	4/1994	Cheeseman	6,277,607	B1	8/2001	Tyagi et al.
5,308,990	A	5/1994	Takahashi et al.	6,287,821	B1	9/2001	Shi et al.
5,328,824	A	7/1994	Ward et al.	6,294,324	B1	9/2001	Bensimon et al.
5,332,666	A	7/1994	Prober et al.	6,309,829	B1	10/2001	Livak et al.
5,383,858	A	1/1995	Reilly et al.	6,309,836	B1	10/2001	Kwiatkowski
5,424,186	A	6/1995	Fodor et al.	6,312,893	B1	11/2001	Van Ness et al.
5,436,143	A	7/1995	Hyman	6,316,230	B1	11/2001	Egholm et al.
5,437,975	A	8/1995	McClelland et al.	6,335,155	B1	1/2002	Wells et al.
5,449,767	A	9/1995	Ward et al.	6,361,940	B1	3/2002	Van Ness et al.
5,476,928	A	12/1995	Ward et al.	6,380,378	B1	4/2002	Kitamura et al.
5,516,664	A	5/1996	Hyman	6,432,360	B1	8/2002	Church
5,534,424	A	7/1996	Uhlen et al.	6,495,680	B1	12/2002	Gong
5,547,839	A	8/1996	Dower et al.	6,524,829	B1	2/2003	Seeger
5,547,859	A	8/1996	Goodman et al.	6,555,349	B1	4/2003	O'Donnell
5,556,748	A	9/1996	Douglas	6,613,508	B1	9/2003	Ness et al.
5,599,675	A	2/1997	Brenner	6,613,513	B1	9/2003	Parce et al.
5,602,000	A	2/1997	Hyman	6,627,436	B2	9/2003	Sorge et al.
5,614,365	A	3/1997	Tabor et al.	6,627,748	B1	9/2003	Ju et al.
5,637,469	A	6/1997	Wilding et al.	6,632,655	B1	10/2003	Mehta et al.
5,654,419	A	8/1997	Mathies et al.	6,639,088	B2	10/2003	Kwiatkowski
5,658,736	A	8/1997	Wong	6,664,079	B2	12/2003	Ju et al.
5,709,999	A	1/1998	Shattuck-Eidens et al.	6,664,399	B1	12/2003	Sabesan
5,714,330	A	2/1998	Brenner et al.	6,713,255	B1	3/2004	Makino et al.
5,728,528	A	3/1998	Mathies et al.	6,780,591	B2	8/2004	Williams et al.
5,763,594	A	6/1998	Hiatt et al.	6,787,308	B2	9/2004	Balasubramanian et al.
5,770,365	A	6/1998	Lane et al.	6,818,395	B1	11/2004	Quake et al.
5,770,367	A	6/1998	Southern et al.	6,833,246	B2	12/2004	Balasubramanian
5,789,167	A	8/1998	Konrad	6,858,393	B1	2/2005	Anderson et al.
5,798,210	A	8/1998	Canard et al.	6,864,052	B1	3/2005	Drmanac et al.
5,804,386	A	9/1998	Ju	6,911,345	B2	6/2005	Quake et al.
5,808,045	A	9/1998	Hiatt et al.	6,934,636	B1	8/2005	Skierczynski et al.
5,814,454	A	9/1998	Ju	6,982,146	B1	1/2006	Schneider et al.
5,821,356	A	10/1998	Khan et al.	7,037,687	B2	5/2006	Williams et al.
5,834,203	A	11/1998	Katzir et al.	7,056,661	B2	6/2006	Korlach et al.
5,844,106	A	12/1998	Seela et al.	7,056,666	B2	6/2006	Dower et al.
5,849,542	A	12/1998	Reeve et al.	7,057,026	B2	6/2006	Barnes et al.
5,853,992	A	12/1998	Glazer et al.	7,057,031	B2	6/2006	Olejniak et al.
5,856,104	A	1/1999	Chee et al.	7,074,597	B2	7/2006	Ju
5,858,671	A	1/1999	Jones	7,078,499	B2	7/2006	Odedra et al.
5,869,255	A	2/1999	Mathies et al.	7,105,300	B2	9/2006	Parce et al.
5,872,244	A	2/1999	Hiatt et al.	7,270,951	B1	9/2007	Stemple et al.
5,876,936	A	3/1999	Ju	7,279,563	B2	10/2007	Kwiatkowski
5,885,775	A	3/1999	Haff et al.	7,329,496	B2	2/2008	Dower et al.
5,885,813	A	3/1999	Davis et al.	7,345,159	B2	3/2008	Ju et al.
5,908,755	A	6/1999	Kumar et al.	7,393,533	B1	7/2008	Crotty et al.
5,945,283	A	8/1999	Kwok et al.	7,414,116	B2	8/2008	Milton et al.
5,948,648	A	9/1999	Khan et al.	7,427,673	B2	9/2008	Balasubramanian et al.
5,952,180	A	9/1999	Ju	7,459,275	B2	12/2008	Dower et al.
5,959,089	A	9/1999	Hannessian	7,541,444	B2	6/2009	Milton et al.
5,962,228	A	10/1999	Brenner	7,566,537	B2	7/2009	Balasubramanian et al.
6,001,566	A	12/1999	Canard	7,622,279	B2	11/2009	Ju
6,001,611	A	12/1999	Will	7,635,578	B2	12/2009	Ju et al.
6,008,379	A	12/1999	Benson et al.	7,713,698	B2	5/2010	Ju et al.
6,013,445	A	1/2000	Albrecht et al.	7,771,973	B2	8/2010	Milton et al.
6,028,190	A	2/2000	Mathies et al.	7,785,790	B1	8/2010	Church et al.
6,046,005	A	4/2000	Ju et al.	7,790,869	B2	9/2010	Ju et al.
6,074,823	A	6/2000	Koster	7,883,869	B2	2/2011	Ju et al.
6,087,095	A	7/2000	Rosenthal et al.	7,982,029	B2	7/2011	Ju et al.
6,111,116	A	8/2000	Benson et al.	8,088,575	B2	1/2012	Ju et al.
6,136,543	A	10/2000	Anazawa et al.	8,158,346	B2	4/2012	Balasubramanian et al.
6,175,107	B1	1/2001	Juvinall	8,298,792	B2	10/2012	Ju et al.
6,197,557	B1	3/2001	Makarov et al.	8,399,188	B2	3/2013	Zhao et al.
6,207,831	B1	3/2001	Auer et al.	8,796,432	B2	8/2014	Ju et al.
6,210,891	B1	4/2001	Nyren et al.	8,889,348	B2	11/2014	Ju
6,214,987	B1	4/2001	Hiatt et al.	9,115,163	B2	8/2015	Ju et al.
6,218,118	B1	4/2001	Sampson et al.	9,133,511	B2	9/2015	Ju et al.
6,218,530	B1	4/2001	Rothschild et al.	9,159,610	B2	10/2015	Zhang et al.
6,221,592	B1	4/2001	Schwartz et al.	9,175,342	B2	11/2015	Ju et al.
6,232,465	B1	5/2001	Hiatt et al.	9,255,292	B2	2/2016	Ju et al.
6,242,193	B1	6/2001	Anazawa et al.	9,297,042	B2	3/2016	Ju et al.
6,245,507	B1	6/2001	Bogdanov	9,708,358	B2	7/2017	Ju et al.
6,248,884	B1	6/2001	Lam et al.	9,718,852	B2	8/2017	Ju et al.
				9,719,139	B2	8/2017	Ju et al.
				9,725,480	B2	8/2017	Ju et al.
				9,868,985	B2	1/2018	Ju et al.
				2002/0012966	A1	1/2002	Shi et al.

(56)

References Cited

U.S. PATENT DOCUMENTS

2003/0022225	A1	1/2003	Monforte et al.	WO	WO1992/10587	6/1992
2003/0027140	A1	2/2003	Ju et al.	WO	WO 1993/05183	3/1993
2003/0044871	A1	3/2003	Cutsforth et al.	WO	WO 93/12340	10/1993
2003/0054360	A1	3/2003	Gold et al.	WO	WO 1993/21340	10/1993
2003/0099972	A1	5/2003	Olejnik et al.	WO	WO 1994/14972	7/1994
2003/0166282	A1	9/2003	Brown et al.	WO	WO 1996/07669	3/1996
2003/0180769	A1	9/2003	Metzker	WO	WO 96/23807	8/1996
2003/0186256	A1	10/2003	Fischer	WO	WO 1996/23807	8/1996
2003/0190680	A1	10/2003	Rothschild et al.	WO	WO 96/27025	9/1996
2003/0198982	A1	10/2003	Seela et al.	WO	WO 1996/27025	9/1996
2004/0014096	A1	1/2004	Anderson et al.	WO	WO 1997/08183	3/1997
2004/0096825	A1	5/2004	Chenna et al.	WO	WO 1997/27317	7/1997
2005/0032081	A1	2/2005	Ju et al.	WO	WO 1997/35033	9/1997
2005/0170367	A1	8/2005	Quake et al.	WO	WO 1998/30720	7/1998
2005/0239134	A1	10/2005	Gorenstein et al.	WO	WO 1998/30720	7/1998
2006/0003352	A1	1/2006	Lipkin et al.	WO	WO 98/33939	8/1998
2006/0057565	A1	3/2006	Ju et al.	WO	WO 1998/33939	8/1998
2006/0105461	A1	5/2006	Tom-Moy et al.	WO	WO 1998/44151	10/1998
2006/0160081	A1	7/2006	Milton et al.	WO	WO 1998/44151	10/1998
2006/0160113	A1	7/2006	Korlach et al.	WO	WO 98/53300	11/1998
2006/0240439	A1	10/2006	Smith et al.	WO	WO 1999/05315	2/1999
2006/0252038	A1	11/2006	Ju	WO	WO 1999/49082	9/1999
2007/0166705	A1	7/2007	Milton et al.	WO	WO 1999/57321	11/1999
2009/0088332	A1	4/2009	Ju et al.	WO	WO 2000/02895	1/2000
2009/0240030	A1	9/2009	Ju et al.	WO	WO 2000/06770	2/2000
2010/0159531	A1	6/2010	Gordon et al.	WO	WO 2000/09753	2/2000
2010/0323350	A1	12/2010	Gordon et al.	WO	WO 2000/15844	3/2000
2011/0014611	A1	1/2011	Ju et al.	WO	WO 2000/18956	4/2000
2011/0124054	A1	5/2011	Olejnik et al.	WO	WO 2000/21974	4/2000
2012/0052489	A1	3/2012	Gordon et al.	WO	WO 2000/50172	8/2000
2012/0142006	A1	6/2012	Ju et al.	WO	WO 2000/50642	8/2000
2013/0264207	A1	10/2013	Ju et al.	WO	WO 00/53812	9/2000
2014/0315191	A1	10/2014	Ju et al.	WO	WO 2000/53805	9/2000
2015/0037788	A1	2/2015	Ju	WO	WO 2000/53812	9/2000
2015/0080232	A1	3/2015	Ju et al.	WO	WO 2000/70073	11/2000
2015/0111759	A1	4/2015	Ju et al.	WO	WO 2001/16375	3/2001
2015/0119259	A1	4/2015	Ju et al.	WO	WO 2001/23610	4/2001
2015/0197800	A1	7/2015	Ju et al.	WO	WO 2001/25247	4/2001
2015/0368710	A1	12/2015	Fuller et al.	WO	WO 2001/27625	4/2001
2016/0024570	A1	1/2016	Ju et al.	WO	WO 2001/32930	5/2001
2016/0024574	A1	1/2016	Ju et al.	WO	WO 2001/57248	8/2001
2016/0041179	A1	2/2016	Ju et al.	WO	WO 2001/57249	8/2001
2016/0090621	A1	3/2016	Ju et al.	WO	WO 01/92284	12/2001
2016/0264612	A1	9/2016	Ju et al.	WO	WO 2001/92284	12/2001
2017/0088574	A1	3/2017	Ju et al.	WO	WO 2002/02813	1/2002
2017/0088575	A1	3/2017	Ju et al.	WO	WO 02/21098	3/2002
2017/0088891	A1	3/2017	Ju et al.	WO	WO 2002/22883	3/2002
2017/0313737	A1	11/2017	Ju et al.	WO	WO 02/29003	4/2002
2018/0201642	A1	7/2018	Ju et al.	WO	WO 2002/29003	4/2002
				WO	WO 2002/72892	9/2002
				WO	WO 2002/079519	10/2002
				WO	WO 2002/88381	11/2002
				WO	WO 2002/88382	11/2002
				WO	WO 2003/02767	1/2003
				WO	WO 2003/20968	3/2003
				WO	WO 2003/48178	6/2003
				WO	WO 2003/48387	6/2003
				WO	WO 2003/85135	10/2003
				WO	WO 04/18493	3/2004
				WO	WO 04/18497	3/2004
				WO	WO 2004/18493	3/2004
				WO	WO 2004/018493	3/2004
				WO	WO 2004/018497	3/2004
				WO	WO 2004/18497	3/2004
				WO	WO 2004/055160	7/2004
				WO	WO 2005/084367	9/2005
				WO	WO 2006/73436	7/2006
				WO	WO 2007/002204	1/2007
				WO	WO 2007/62105	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 1989/09282	10/1989
				WO	WO 89/10977	11/1989
				WO	WO 1989/11548	11/1989
				WO	WO 1990/13666	11/1990

FOREIGN PATENT DOCUMENTS

DE	4141178	6/1993				
DE	20122767	8/2007				
DE	112007002932.3	8/2015				
EP	0251786	B1 11/1994				
EP	0995804	4/2000				
EP	1182267	2/2002				
EP	1291354	3/2003				
EP	0808320	4/2003				
EP	1337541	B1 3/2007				
EP	1218391	4/2007				
EP	0992511	3/2009				
EP	2209911	B1 10/2013				
GB	2000 0013276	6/2000				
GB	2001 0029012	12/2001				
GB	2446083	3/2011				
GB	2446084	3/2011				
GB	2457402	9/2011				
WO	WO 1989/09282	10/1989				
WO	WO 89/10977	11/1989				
WO	WO 1989/11548	11/1989				
WO	WO 1990/13666	11/1990				

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO WO 2015/148402 10/2015
 WO WO 2015/179284 11/2015

OTHER PUBLICATIONS

- Aug. 16, 2013 Declaration of Dr. Bruce Branchaud (Exhibit 1015, filed Aug. 19, 2013 in connection with IPR2013-00518).
 Excerpts from the '537 Patent file History (Exhibit 1016, filed Aug. 19, 2013 in connection with IPR2013-00518).
 Excerpts from the file history of European Patent Application No. 02781434.2 (Exhibit 1017, filed Aug. 19, 2013 in connection with IPR2013-00518).
- 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.
- Krečmerová (1990) "Synthesis of 5'-O-Phosphonomethyl Derivatives of Pyrimidine 2'-Deoxynucleosides." *Coll. Czech. Chem. Commun.*, 55:2521-2536.
 Kurata et al. (2001) "Fluorescent quenching-based quantitative detection of specific DNA/RNA using BODIPY® FL-labeled probe of primer," *Nucleic Acids Research*, vol. 29, No. 6, p. e34.
 Kvam et al., (1994) "Characterization of singlet oxygen-induced guanine residue damage after photochemical treatment of free nucleosides and DNA," *Biochemica et Biophysica Acta.*, 1217:9-15.
 Lee, L.G., et al. (1992) "DNA sequencing with dye labeled terminators and T7 DNA polymerase effect of dyes and dNTPs on incorporation of dye terminators and probability analysis of termination fragments," *Nucleic Acids Res.* 20:2471-2483.
 Lee L.G. et al. (1997) "New energy transfer dyes for DNA sequencing," *Nucleic Acids Res.* 25:2816-2822.
 Leroy, E.M. et al. (2000) "Diagnosis of Ebola Haemorrhagic Fever by RT-PCR in an Epidemic Setting," *Journal of Medical Virology* 60:463-467.
 Lewis et al. (2002) "Click Chemistry in Situ: Acetylcholinesterase as a Reaction Vessel for the Selective Assembly of a Femtomolar Inhibitor from an Array of Building Blocks," *Angew. Chem. Int. Ed.* 41(6):1053-1057.
 Li, J. (1999) "Single Oligonucleotide Polymorphism Determination Using Primer Extension and Time-of-Flight Mass Spectrometry," *Electrophoresis* 20:1258-1265.
 Li et al. (2003) "A photocleavable Fluorescent Nucleotide for DNA Sequencing and Analysis," *PNAS* 100(2):414-419.
 Liu, H. et al. (2000) "Development of Multichannel Devices with an Array of Electrospray Tips for High-Throughput Mass Spectrometry," *Anal. Chem.* 72:3303-3310.
 Loubinoux, B. et al. "Protection Des Phenols Par Le Groupement Azidomethylene Application A La Synthèse De Phenols Instables," *Tetrahedron*, 1998, 44(19): 6055 (English Abstract Only).
 Lu, G. and Burgess, K. (2006) "A Diversity Oriented Synthesis of 3'-O-Modified Nucleoside Triphosphates for DNA 'Sequencing by Synthesis'" *Bioorg. Med. Chem. Lett.*, 16:3902-3905.
 Lyamichev, V. et al. (1999) "Polymorphism Identification and Quantitative Detection of Genomic DNA by Invasive Cleavage of Oligonucleotide Probes," *Nat. Biotech* 17:292-296.
 Maier et al. (1995) "Synthesis and Properties of New Fluorescein-Labeled Oligonucleotides," *Nucleosides and Nucleotides*, 14:961-965.
 Margulies, M.; Egholm, M.; Altman, W. E. (2005) "Genome Sequencing in Microfabricated High-Density Picolitre Reactors." *Nature*, 437:376-380.
 Markiewicz et al. (1997) "A new method of synthesis of fluorescently
 Marquez et al. (2003) "Selective Fluorescence Quenching of 2,3-Diazabicyclo[2.2.2]oct-2-ene by Nucleotides," *Organic Letters*, 5:3911-3914.
 Mathews C.K. et al. (1985) "Chemical Synthesis of Oligonucleotides," *Biochemistry*, 2nd Edition, pp. 127-128.
 Meng et al. (2006) "Design and Synthesis of a Photocleavable Fluorescent Nucleotide 3'-O-Allyl-dGTP-PC-Biodipy-FL-510 as a Reversible Terminator for DNA Sequencing by Synthesis," *J. Org. Chem* 71:3248-3252.
 Metzker, M.L. et al. (1994) "Termination of DNA synthesis by novel 3' modified deoxyribonucleoside 5' triphosphates," *Nucleic Acids Res.* 22: 4259-4267.
 Metzker M.L. (2005) "Emerging Technologies in DNA Sequencing," *Genome Res.*, 15:1767-1776.
 Mitra, R. D.; Shendure J.; Olejnik, J.; et al. (2003) "Fluorescent in situ sequencing on polymerase colonies." *Anal. Biochem.* 320:55-65.
 Monforte, J.A. and Becker, C.H. (1997) "High-throughput DNA analysis by time-of-flight mass spectrometry," *Nat. Med.* 3(3):360-362.
 Nazarenko et al. (2002) "Effect of primary and secondary structure of oligodeoxyribonucleotides on the fluorescent properties of conjugated dyes," *Nucleic Acids Research*, 30:2089-2095.
 Nickel et al. (1992) "Interactions of Azidothymidine triphosphate with the Cellular DNA polymerases alpha, delta, and epsilon and with DNA Primase," *J. Biol. Chem.* 267(2):848-854.
 Nielsen, J. et al. (2004) "Multiplexed Sandwich Assays in Microarray Format," *Journal of Immunological Methods*, vol. 290, pp. 107-120.
 Nishino et al. (1991) "Efficient Deamination of Phosphoranilidates by the Use of Nitrites and Acetic Anhydride." *Heteroatom Chemistry*, vol. 2, pp. 187-196.
 Olejnik, J. et al. (1995) "Photocleavable biotin derivatives: a versatile approach for the isolation of biomolecules," *Proc. Natl. Acad. Sci. USA.* 92:7590-7594.
 Olejnik, J. et al. (1999) "Photocleavable peptide DNA conjugates: synthesis and applications to DNA analysis using MALDI MS," *Nucleic Acids Res.* 27:4626-4631.
 Pastinen et al. (1997) "Minisequencing: A Specific Tool for DNA Analysis and Diagnostics on Oligonucleotide Arrays," *Genomic Res.*, 7:606-614.
 Pelletier, H. et al. (1994) "Structures of ternary complexes of rat DNA polymerase β , a DNA template-primer, and ddCTP," *Science* 264:1891-1903.
 Prober, J.M. et al. (1987) "A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides," *Science* 238:336-341.
 Quaedflieg et al. (1992) "An Alternative Approach Toward the Synthesis of (3'→5') Methylene Acetal Linked Dinucleosides." *Tetrahedron Letters*, vol. 33, pp. 3081-3084.
 Rao et al. (2001) "Four Color FRET Dye Nucleotide Terminators For DNA Sequencing," *Nucleosides, Nucleotides and Nucleic Acids*, 20:673-676.
 Rasolonjatovo et al. (1998) "6-N-(N-Methylanthranilylamido)-4-Oxo-Hexanoic Acid: A New Fluorescent Protecting Group Applicable to a New DNA Sequencing Method," *Nucleosides and Nucleotides*, 17:2021-2025.
 Ronaghi, (1998) "PCR-Introduced Loop Structure as Primer in DNA Sequencing." *BioTechniques*, 25:876.
 Ronaghi, M., Uhlen, M., and Nyren, P. (1998) "A Sequencing Method Based on Real-time Pyrophosphate," *Science* 281:364-365.
 Rosenblum, B.B. et al. (1997) "New dye-labeled terminators for improved DNA sequencing patterns," *Nucleic Acids Res.* 25:4500-4504.
 Roskey, M.T., Juhasz, P., Smirnov, I.P., Takach, E.J., Martin, S.A., and Haff, L.A. (1996) "DNA sequencing by delayed extraction-matrix-assisted laser desorption/ionization time of flight mass spectrometry," *Proc. Natl. Acad. Sci. USA.* 93:4724-4729.
 Ross, P.L. et al. (1997) "Discrimination of Single-Nucleotide Polymorphism in Human DNA Using Peptide Nucleic Acid Probes Detected by MALDI-TOF Mass Spectrometry," *Anal. Chem.* 69:4197-4202.

(56)

References Cited

OTHER PUBLICATIONS

- Ruparel et al. (2005) "Design and Synthesis of a 3'-O-Allyl Photocleavable Fluorescent Nucleotide as a Reversible Terminator for DNA Sequencing by Synthesis," PNAS 102(17):5932-5937.
- Sarfati et al., (1995) "Synthesis of fluorescent derivatives of 3'-O-(6-aminohexanoyl)-pyrimidine nucleosides 5'-triphosphates that act as DNA polymerase substrates reversibly tagged at C-3," JCS Perkin Trans, 1163-1171.
- Saxon, E. and Bertozzi, C.R. (2000) "Cell surface engineering by a modified Staudinger reaction," Science 287:2007-2010.
- Schena, M., Shalon, D. and Davis, R. Brown P.O. (1995) "Quantitative monitoring of gene expression patterns with a cDNA microarray," Science 270: 467-470.
- Seeger (1998) "Single Molecule Fluorescence: High-Performance Molecular Diagnosis and Screening," Bioforum, Git Verlag, Darmstadt, DE vol. 21, (German text).
- Seo et al. (2003) "Click Chemistry to Construct Fluorescent Oligonucleotides for DNA Sequencing," J. Org. Chem. 68:609-612.
- Seo et al. (2004) "Photocleavable Fluorescent Nucleotides for DNA Sequencing on a Chip Constructed by Site-Specific Coupling Chemistry," PNAS 101(15):5488-5493.
- Seo et al. (2005) "Four-Color DNA Sequencing by Synthesis on a Chip Using Photocleavable Fluorescent Nucleotides," PNAS 102(17):5926-593.
- Shendure, J.; Porreca, G. J.; Reppas, N.B.; et al. (2005) "Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome." Science 309:1728-1732.
- Smith, L.M., Sanders, J.Z., Kaiser, R.J., et al. (1986) "Fluorescence Detection in Automated DNA Sequence Analysis," Nature 321:674-679.
- Speicher, M.R., Ballard, S.G., and Ward, D.C. (1996) "Karyotyping human chromosomes by combinatorial multi-fluor FISH," Nature Genetics 12: 368-375.
- Stoerker, J. et al. (2000) "Rapid Genotyping by MALDI-monitored nuclease selection from probe Libraries," Nat. Biotech 18:1213-1216.
- Tang, K., Fu, D.J., Julien, D., Braun, A., Cantor, C.R., and Koster, H. (1999) "Chip-based genotyping by mass spectrometry," Proc. Natl. Acad. Sci. USA. 96:10016-10020.
- Tong, X. and Smith, L.M. (1992) "Solid-Phase Method for the Purification of DNA Sequencing Reactions," Anal. Chem. 64:2672-2677.
- Torimura et al. (2001) "Fluorescence-Quenching Phenomenon by Photoinduced Electron Transfer between a Fluorescent Dye and Nucleotide Base," Analytical Sciences, 17:155-160.
- Tuncel et al. (1999) "Catalytically Self-Threading Polyrotaxanes," Chem. Comm. 1509-1510.
- Veeneman et al. (1991) "An Efficient Approach to the Synthesis of Thymidine Derivatives containing Phosphate-Isoteric Methylene Acetyl Linkages," Tetrahedron, 47:1547-1562.
- Wada et al. (2001) "2-(Azidomethyl)benzoyl as a new protecting group in nucleosides," Tetrahedron Letters, 42:1069-1072.
- Weiss (1999) "Fluorescent Spectroscopy of Single Biomolecules." Science, 283:1676.
- Welch et al. (1999) "Synthesis of Nucleosides Designed for Combinatorial DNA Sequencing," Chemistry, European Journal, 5:951-960.
- Welch MB, Burgess K, (1999) "Synthesis of fluorescent, photolabile 3'-O-protected nucleoside triphosphates for the base addition sequencing scheme," Nucleosides and Nucleotides 18:197-201.
- Wendy, Jen. Et al. (2000) "New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition," J. Am. Chem. Soc. 122:9874-9875.
- Woolley, A. T. et al. (1997) "High-Speed DNA Genotyping Using Microfabricated Capillary Array Electrophoresis Chips," Anal. Chem. 69:2181-2186.
- Yamashita et al. (1987) "Studies on Antitumor Agents VII. Antitumor Activities of O-Alkoxyalkyl Derivatives of 2'Deoxy-5-Zavgorodny, S. et al. (1991) "1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its synthetic Applications: A New Versatile Method in Nucleoside Chemistry," Tetrahedron Letters, 32(51): 7593-7596.
- Zavgorodny et al. (2000) "S,X-Acetals in Nucleoside Chemistry. III. Synthesis of 2'- and 3'-O-Azidomethyl Derivatives of Ribonucleosides" Nucleosides, Nucleotides and Nucleic Acids, 19(10-12):1977-1991.
- Zhang et al. (2002) "Synthesis of Releasable Electrophore Tags for Applications in Mass Spectrometry," Bioconjugate Chem., vol. 13, pp. 1002-1012.
- Zhu, Z., Chao, J., Yu, H, et al. (1994) "Directly Labeled DNA Probes Using Fluorescent Nucleotides with Different Length Linkers," Nucleic Acids Res., 22:3418-3422.
- Jun. 4, 2013 Petition for Inter Partes Review of U.S. Pat. No. 7,057,026.
- J. Meinwald, An Approach to the Synthesis of Pederin, 49 Pure and Appl. Chem. 1275 (1977) (Exhibit 1004, filed Jun. 4, 2013 in connection with IPR2013-00324).
- Takeshi Matsumoto et al., A Revised Structure of Pederin, 60 Tetrahedron Letters 6297 (1968) (Exhibit 1005, filed Jun. 4, 2013 in connection with IPR2013-00324).
- Jun. 4, 2013 Declaration of Dr. Bruce Branchaud (Exhibit 1009, filed Jun. 4, 2013 in connection with IPR2013-00324).
- Excerpts from the '026 Patent File History (Exhibit 1010, filed Jun. 4, 2013 in connection with IPR2013-00324).
- Excerpts from the file history of European Patent Application No. 02781434.2 (Exhibit 1011, filed Jun. 4, 2013 in connection with IPR2013-00324).
- Nov. 21, 2013 Decision Denying Institution of Inter Partes Review of U.S. Pat. No. 7,057,026 in connection with IPR2013-00324.
- Trustees of Columbia University in the City of New York v. Illumina, Inc.*, Nos. 2014-1547, 2014-1548, and 2014-1550 (Fed. Cir. Jul. 17, 2015).
- Illumina Cambridge Ltd. v. Intelligent Bio-Systems, Inc.*, Nos. 167. 2015-1123 and 2015-1243 (Fed. Cir. Jan. 29, 2016).
- Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, No. 2015-1693 (Fed. Cir. May 9, 2016).
- Declaration of Michael Metzker in Opposition to Plaintiffs' Motion for Preliminary Injunction, *Illumina, Inc. v. Qiagen, N. V.*, No. 3:16-cv-02788-WHA (N.D. Cal. Jul. 25, 2016) (Doc. 76), first made publicly available Aug. 25, 2016.
- Notice of Motion to Stay Injunction Pending Appeal or, Alternatively, Pending Decision by the Federal Circuit on Stay Pending Appeal, *Illumina, Inc. v. Qiagen, N.V.*, No. 3:16-cv-02788-WHA (N.D. Cal. Sep. 15, 2016)(Doc. 122) (Redacted Version of Document Sought to be Sealed), first made publicly available Sep. 22, 2016.
- Sep. 23, 2016 Response to May 24, 2016 Communication Pursuant to Article 94 (3) EPC filed with the European Patent Office in connection with European Patent Application No. 15195765.1.
- Patent Owner Preliminary Response filed by The Trustees of Columbia University in the City of New York Mar. 27, 2018, in connection with Case No. IPR2018-00291.
- Patent Owner Preliminary Response filed by The Trustees of Columbia University in the City of New York Apr. 9, 2018, in connection with Case No. IPR2018-00318.
- Patent Owner Preliminary Response filed by The Trustees of Columbia University in the City of New York Apr. 9, 2018, in connection with Case No. IPR2018-00322.
- Patent Owner Preliminary Response filed by The Trustees of Columbia University in the City of New York May 4, 2018, in connection with Case No. IPR2018-00385.
- Patent Owner Preliminary Response filed by The Trustees of Columbia University in the City of New York Jul. 6, 2018, in connection with Case No. IPR2018-00797.
- Excerpts from the Prosecution History of U.S. Pat. No. 9,718,852 not included in Ex-1009 (Exhibit 2005 filed by The Trustees of Columbia University in the City of New York with the Patent Owner Preliminary Response, in connection with Case No. IPR2018-00291).

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