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(54) Title: BINARY ENCODED SEQUENCE TAGS

(57) Abstract: Disclosed is a method for the comprehensive analysis of nucleic acid samples and a detector composition for use in the method. The method, referred to as Binary Encoded Sequence Tags (BEST), involves generation of a set of nucleic acid fragments; adding an adaptor to the ends containing recognition site for cleavage at a site offset from the recognition site; cleaving the fragment to generate fragments having a plurality of sticky ends; indexing of the fragments into sets based on the sequence of sticky ends. The fragments are indexed by adding an offset adaptor to newly generated ends. A different adaptor will be coupled to each different sticky end. The resulting fragments - which will have defined ends, be of equal lengths (in preferred embodiment), and a central sequence derived from the source nucleic acid molecule - are binary sequence tags. The binary sequence tags can be used and further analyzed in numerous ways. For example, the binary sequence tags can be captured by hybridization and coupling, preferably by ligation, to a probe. The probe is preferably immobilized in an array or on sortable beads. One form of the BEST method, referred to as modification assisted analysis of binary sequence tags (MAABST), assesses modification of sequences in nucleic acid molecules by detecting differential cleavage based on the presence or absence of modification in the molecules.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 710 000 A (GINGERAS THOMAS R ET AL) 20 January 1998 (1998-01-20) the whole document ---	1-126
X	WO 98 40518 A (GUILFOYLE RICHARD A ;GUO ZHEN (US); WISCONSIN ALUMNI RES FOUND (US) 17 September 1998 (1998-09-17) claims 40-46 ---	1-126
X	EP 0 735 144 A (JAPAN RES DEV CORP) 2 October 1996 (1996-10-02) claims 4,5 ---	1-126
X	US 5 858 656 A (DEUGAU KENNETH VICTOR ET AL) 12 January 1999 (1999-01-12) column 4, line 21 - line 45; claim 27 --- -/--	1-126

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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PCT/US 00/22164

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 46704 A (LYNX THERAPEUTICS INC) 11 December 1997 (1997-12-11) claims 1-27 ----	1-126
A	WO 98 30721 A (PIONEER HI BRED INT ;BIRO RONALD L (US); FEAZEL RHONDA (US); HELEN) 16 July 1998 (1998-07-16) claim 4; examples 1-3 ----	1-126
A	WO 93 17126 A (NEW YORK HEALTH RES INST) 2 September 1993 (1993-09-02) claims 1,36; examples 1-3 ----	1-126
A	WO 97 31256 A (BLOK HERMAN ;BARANY GEORGE (US); KEMPE MARIA (US); ZIRVI MONIB (US) 28 August 1997 (1997-08-28) claims 1,2 ----	1-126
A	WO 98 48047 A (BRAX GENOMICS LTD ;THOMPSON ANDREW HUGIN (GB); SCHMIDT GUENTER (GB) 29 October 1998 (1998-10-29) the whole document ----	1-126
A	US 5 658 736 A (WONG GORDON G) 19 August 1997 (1997-08-19) claim 1 ----	1-126
A	US 5 888 737 A (BRENNER SYDNEY ET AL) 30 March 1999 (1999-03-30) claims 1,2 -----	1-126

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/US 00/22164

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 5710000	A	20-01-1998	US 6027894 A	22-02-2000
			US 6291181 B1	18-09-2001
WO 9840518	A	17-09-1998	US 5994068 A	30-11-1999
			AU 7465198 A	29-09-1998
			EP 0970250 A1	12-01-2000
			WO 9840518 A2	17-09-1998
			US 6228999 B1	08-05-2001
			US 6280948 B1	28-08-2001
EP 0735144	A	02-10-1996	JP 2763277 B2	11-06-1998
			JP 9028399 A	04-02-1997
			JP 2763278 B2	11-06-1998
			JP 8322598 A	10-12-1996
			AU 692685 B2	11-06-1998
			AU 5031196 A	10-10-1996
			EP 0735144 A1	02-10-1996
			US 5707807 A	13-01-1998
US 5858656	A	12-01-1999	US 5508169 A	16-04-1996
			CA 2036946 A1	07-10-1991
WO 9746704	A	11-12-1997	US 5846719 A	08-12-1998
			AU 733782 B2	24-05-2001
			AU 3374097 A	05-01-1998
			CN 1230226 A	29-09-1999
			CZ 9803979 A3	14-07-1999
			EP 0923650 A1	23-06-1999
			HU 0003944 A2	28-03-2001
			JP 2000515006 T	14-11-2000
			NO 985698 A	08-02-1999
			PL 331513 A1	19-07-1999
			US 6138077 A	24-10-2000
			US 6172218 B1	09-01-2001
			WO 9746704 A1	11-12-1997
			US 6235475 B1	22-05-2001
US 6172214 B1	09-01-2001			
US 6150516 A	21-11-2000			
US 6013445 A	11-01-2000			
WO 9830721	A	16-07-1998	AU 6024598 A	03-08-1998
			US 6100030 A	08-08-2000
			WO 9830721 A1	16-07-1998
WO 9317126	A	02-09-1993	AU 3728093 A	13-09-1993
			CA 2130562 A1	02-09-1993
			EP 0675966 A1	11-10-1995
			WO 9317126 A1	02-09-1993
			US 6103463 A	15-08-2000
WO 9731256	A	28-08-1997	AU 735440 B2	05-07-2001
			AU 2799797 A	10-09-1997
			CA 2244891 A1	28-08-1997
			EP 0920440 A2	09-06-1999
			WO 9731256 A2	28-08-1997
WO 9848047	A	29-10-1998	AU 733924 B2	31-05-2001
			AU 7063898 A	13-11-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/22164

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9848047	A	CN 1252103 T EP 0981645 A1 WO 9848047 A2	03-05-2000 01-03-2000 29-10-1998
US 5658736	A	19-08-1997 NONE	
US 5888737	A	30-03-1999 AU 737331 B2 AU 7121398 A EP 0975655 A1 WO 9846621 A1 US 6175002 B1	16-08-2001 11-11-1998 02-02-2000 22-10-1998 16-01-2001