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20 May 1999 (20.05.99)

(54) Title: MAMMALIAN CELL MEMBRANE PROTEINS; RELATED REAGENTS

(57) Abstract

The purification and isolation of various genes which encode mammalian cell surface polypeptides. Nucleic acids, proteins, antibodies, and other reagents useful in modulating development of cells, e.g., lymphoid and myeloid, are provided, along with methods for their use.

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INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 98/15316

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N15/62 C07K14/705 C07K16/28 C12Q1/68
A61K38/17 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q A61K G01N

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 39446 A (HUMAN GENOME SCIENCES, INC.) 11 September 1998 SEQ ID Nos: 80,133,203,256 (identical to human DAP-10); see claims 1-23 ---	1-20
E	WO 99 06554 A (GENSET) 11 February 1999 SEQ ID Nos: 40,308 (identical to human DAP-10); ---	1-4, 10-15
E	WO 99 06548 A (GENSET) 11 February 1999 SEQ ID Nos.122,376 (homolog to human DAP-12); --- -/--	1-4, 10-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
1 March 1999	17. 03. 99

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 49292 A (INST NAT SANTE RECH MED ;VELY FREDERIC (FR); VIVIER ERIC (FR); TOM) 5 November 1998 Seq ID Nos: 27,28 (homolog to human DAP-12); SEQ ID Nos.12,17 homolog to murine DAP-12, >99%);SEQ ID No. 31 (identical to human DAP-12); see page 1, line 1 - page 24, line 17; figures 17-23	1-20
X	R. STRAUSBERG: "nh52a05.r1 NCI_CGAP_Pr5 Homo sapiens cDNA clone IMAGE:955952." EMBL SEQUENCE DATABASE,15 July 1997, XP002095086 Heidelberg, FRG Accession no. AA516481;	10-18
X	M. MARRA ET AL.: "The WashU-HHMI Mouse EST Project" EMBL SEQUENCE DATABASE,30 April 1996, XP002095087 Heidleberg, FRG mb31f12.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 331055 5'; Acession no. W13188;	8-10
X	M. MARRA ET AL.: "The WashU-HHMI Mouse EST Project" EMBL SEQUENCE DATABASE,12 February 1997, XP002095088 Heidelberg, FRG mt35c02.r1 Soares mouse 3NbMS Mus musculus cDNA clone 623042 5' similar to SW:NK13_RAT P27471 Natural Killer Cell Surface Protein P1-3.2.3; Accession no. AA186015;	10-18
X	L HILLIER ET AL: "The WashU-Merck EST project 1997" EMBL NUCLEOTIDE SEQUENCE,23 June 1997, XP002084878 cited in the application zv41f05.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 756225 3' similar to TR:G498729 zinc finger protein; Accession no. AA480109;	12-15, 17,18

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	M. MARRA ET AL.: "The WashU-HHMI Mouse EST Project" NCBI NATIONAL LIBRARY OF MEDICINE,, 25 October 1996, XP002084879 Bethesda, MD, US cited in the application mo08f09.r1 Life Tech mouse embryo 10 5dpc 10665016 Mus Musculus cDNA clone 553001 5', Accession no. AA098506; ---	12-15
A	BLERY M ET AL: "RECONSTITUTED KILLER CELL INHIBITORY RECEPTORS FOR MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I MOLECULES CONTROL MAST CELL ACTIVATION INDUCED VIA IMMUNORECEPTOR TYROSINE-BASED ACTIVATION MOTIFS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 14, 4 April 1997, pages 8989-8996, XP002052877 see the whole document ---	1-20
A	OLCESE L ET AL: "HUMAN KILLER CELL ACTIVATORY RECEPTORS OF MHC CLASS I MOLECULES AREINCLUDED IN A MULTIMERIC COMPLEX EXPRESSED BY NATURAL KILLER CELLS" JOURNAL OF IMMUNOLOGY, vol. 158, no. 11, 1 June 1997, pages 5083-5086, XP002052878 see the whole document ---	1-20
A	K TAKASE ET AL: "A new 12-kilodalton dimer associated with pre-TCR complex and clonotype-independent CD3 complex on immature thymocytes" JOURNAL OF IMMUNOLOGY, vol. 159, no. 2, 15 July 1997, pages 741-747, XP002084880 see the whole document ---	1-20
A	WO 97 20046 A (SCHERING CORP) 5 June 1997 see the whole document ---	1-20
A	WO 96 26961 A (NAT JEWISH CENTER FOR IMMUNOLO ;CAMBIER JOHN C (US)) 6 September 1996 see the whole document ---	1-20
A	B L THOMAS: "Of ITAMs and ITIMs: Turning on and off the B cell antigene receptor" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 181, no. 6, 1 June 1995, pages 1953-1956, XP002084881 see the whole document --- -/--	1-20

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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 98/15316

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	L L LANIER ET AL: "Immunoreceptor DAP12 bearing a tyrosine-based activation motif is involved in activating NK cells" NATURE, vol. 391, 12 February 1998, pages 703-707, XP002084882 see the whole document ---	1-20
P,X	M COLONNA: "Unmasking the killer's accomplice" NATURE, vol. 391, 12 February 1998, page 642/643 XP002084914 see the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/15316

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 (as far as in vivo methods are concerned) is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (1-20)-partially

A substantially pure or recombinant polypeptide: exhibiting identity over a length of at least about 12 amino acids to the mature polypeptide from SEQ ID NOs: 2 or 6; said polypeptide: (i) is a mature natural sequence DAP12 from Table 1; (ii) comprises an ITAM motif; or (iii) comprises a charged residue in a transmembrane domain; said polypeptide which is a natural allelic variant of DAP12; a fusion protein comprises said polypeptide; a kit comprises said polypeptide; a binding compound comprises an antigen binding portion from an antibody, which specifically binds to said natural DAP12 polypeptide; a kit comprising said binding compound; an isolated recombinant nucleic acid encoding said polypeptide; wherein said nucleic acid encodes an antigenic peptide sequence of Table 1; a cell or tissue comprising said recombinant nucleic acid; a nucleic acid which hybridizes under stringent conditions to SEQ ID NOs: 1 or 5; a method of modulating phyiology or development of a cell or tissue culture cell comprising contacting said cell with an agonist or antagonist of a DAP12; a method for screening for a compound which blocks interaction of a DAP12 with KIR, ILT/MIR, or CD94/NGK2C receptor, comprising contacting said compound to said DAP12 in the presence of said receptor;

2. Claims: (1-20)-partially

A substantially pure or recombinant polypeptide: exhibiting identity over a length of at least about 12 amino acids to the mature polypeptide from SEQ ID NOs: 8 or 10; said polypeptide: (i) is a mature natural sequence DAP10 from Table 2; (ii) comprises an ITAM motif; or (iii) comprises a charged residue in a transmembrane domain; said polypeptide which is a natural allelic variant of DAP12; a fusion protein comprises said polypeptide; a kit comprises said polypeptide; a binding compound comprises an antigen binding portion from an antibody, which specifically binds to said natural DAP10 polypeptide; a kit comprising said binding compound; an isolated recombinant nucleic acid encoding said polypeptide; wherein said nucleic acid encodes an antigenic peptide sequence of Table 2; a cell or tissue comprising said recombinant nucleic acid; a nucleic acid which hybridizes under stringent conditions to SEQ ID NOs: 7 or 9; a method of modulating phyiology or development of a cell or tissue culture cell comprising contacting said cell with an agonist or antagonist of a DAP10; a method for screening for a compound which blocks interaction of a DAP10 with KIR, ILT/MIR, or CD94/NGK2C receptor, comprising contacting said compound to said DAP10 in the presence of said receptor;

3. Claims: (1-20)-partially

A substantially pure or recombinant polypeptide: exhibiting

identity over a length of at least about 12 amino acids to the mature polypeptide from SEQ ID NOs: 12 or 14; said polypeptide: (i) is a mature natural sequence MDL-1 from Table 3; (ii) comprises a charged residue in a transmembrane domain; said polypeptide which is a natural allelic variant of MDL-1; a fusion protein comprises said polypeptide; a kit comprises said polypeptide; a binding compound comprises an antigen binding portion from an antibody, which specifically binds to said natural MDL-1 polypeptide; a kit comprising said binding compound; an isolated recombinant nucleic acid encoding said polypeptide; wherein said nucleic acid encodes an antigenic peptide sequence of Table 3; a cell or tissue comprising said recombinant nucleic acid; a nucleic acid which hybridizes under stringent conditions to SEQ ID NOs: 11 or 13; a method of modulating phyiology or development of a cell or tissue culture cell comprising contacting said cell with an agonist or antagonist of a MDL-1;

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/US 98/15316

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9839446 A		NONE	
WO 9906554 A	11-02-1999	NONE	
WO 9906548 A	11-02-1999	NONE	
WO 9849292 A	05-11-1998	FR 2762844 A	06-11-1998
WO 9720046 A	05-06-1997	AU 7739696 A	19-06-1997
WO 9626961 A	06-09-1996	AU 5296796 A	18-09-1996
		CA 2247207 A	06-09-1996
		EP 0812330 A	17-12-1997