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(54) Title: HUMAN DICKKOPF-RELATED PROTEIN AND NUCLEIC ACID MOLECULES AND USES THEREFOR

(57) Abstract: Novel Dkk and Dkk-related polypeptides, proteins, and nucleic acid molecules are disclosed. In addition to isolated, full-length Dkk an Dkk-related proteins, the invention further provides isolated fusion proteins, antigenic peptides and antibodies. The invention also provides Dkk and Dkk-related nucleic acid molecules, recombinant expression vectors containing a nucleic acid molecule of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a Dkk and Dkk-related gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 C12N15/12 C07K16/18 G01N33/50 G01N33/53
C12Q1/68 A61K38/17

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 7 C07K C12N

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.
X	WO 98 46755 A (MCCARTHY SEAN A ;MILLENNIUM BIOTHERAPEUTICS INC (US)) 22 October 1998 (1998-10-22) Note: 100.0% nt seq identity of SEQ ID NO:1 (3) with SEQ ID NO:1 (3) in 2479 bp (1050 bp) overlap, 100.0% aa seq identity of SEQ ID NO:2 with SEQ ID NO:2 in 350 aa overlap. the whole document example 1 page 85, line 31 -page 86, line 7 page 89-95 claims 1-22 --- -/--	1-22

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2000	18. 10. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van de Kamp, M

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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.
X	WO 98 27932 A (HUMAN GENOME SCIENCES INC ;RUBEN STEVEN M (US); SOPPET DANIEL R (U) 2 July 1998 (1998-07-02) Note: 99.7% nt seq identity of SEQ ID NO:1 with SEQ ID NO:1 (3) in 2445 bp (1050 bp) overlap, 99.1% aa seq identity of SEQ ID NO:2 with SEQ ID NO:2 in 350 aa overlap. the whole document page 2, line 22 -page 3, line 12 page 4, line 8-12 examples 1-4 page 45-49 claims 1-4,8-20 figures 1,2	1-22

A	GLINKA ET AL: "Dickkopf-1 is a member of a new family of secreted proteins and functions in head induction" NATURE, vol. 391, no. 6665, 22 January 1998 (1998-01-22), pages 357-362, XP002140766 the whole document page 357, right-hand column, line 4-13; figure 1B	1-22

A	FINCH P W ET AL.: "Purification and molecular cloning of a secreted, Frizzled-related antagonist of Wnt action" PROC. NATL. ACAD. SCI. USA, vol. 94, no. 13, June 1997 (1997-06), pages 6770-6775, XP002140787 abstract; figure 2	1-22

P,X	KRUPNIK V E ET AL.: "Functional and structural diversity of the human Dickkopf gene family" GENE, vol. 238, no. 2, 1 October 1999 (1999-10-01), pages 301-313, XP002140768 Note: 99.9% (99.7%) nt seq identity of hdkk-3 with SEQ ID NO:1 (3) in 2479 bp (1050 bp) overlap, 99.1% aa seq identity of hDkk-3 with SEQ ID NO:2 in 350 aa overlap. the whole document page 304, left-hand column, line 21-34; figure 1	1-22

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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.
P,X	WO 99 22000 A (DEUTSCHES KREBSFORSCH ;GLINKA ANDREI (DE); NIEHRS CHRISTOF (DE)) 6 May 1999 (1999-05-06) Note: 67.6% nt seq identity of SEQ ID NO:7 with SEQ ID NO:3 in 873 bp overlap, 65.4% aa seq identity of translated SEQ ID NO:7 with SEQ ID NO:2 in 254 aa overlap. the whole document claim 4A; figure 2 ---	1-22
E	WO 00 18194 A (ARNOLD & RICHTER KG ;BRAUCKMANN WILFRIED (DE); STEGMAIER KLAUS DIE) 30 March 2000 (2000-03-30) Note: 99.7% nt seq identity of SEQ ID NO:2 with SEQ ID NO:1 (3) in 1053 bp (1050 bp) overlap, 99.1% aa seq identity of SEQ ID NO:9 with SEQ ID NO:2 in 350 aa overlap. the whole document figures 2,9; examples 2,10,11 claims 1-20 -----	1-22

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INTERNATIONAL SEARCH REPORT

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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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:

1. ☐ 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.:

1-22 all partially

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-22 (all partially)

An isolated nucleic acid molecule: a) comprising a nucleotide (nt) sequence which is at least 60% homologous to a nt sequence of SEQ ID NO:1 or 3, or of the DNA insert of the plasmid with ATCC Accession No. 98452, or a complement thereof; or b) comprising at least 1000 nts from said nt sequences; or c) encoding a polypeptide comprising an amino acid (aa) sequence at least about 60% homologous to the aa sequence of SEQ ID NO:2, or to the aa sequence encoded by the insert of said plasmid; or d) encoding a fragment of at least 15 contiguous aa residues of said aa sequence; or e) encoding a naturally occurring allelic variant of said polypeptide, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1 or 3 or the DNA insert of said plasmid, under stringent conditions. An isolated nucleic acid molecule: f) comprising the nt sequence of SEQ ID NO:1 or 3, or of the DNA insert of the plasmid with ATCC Accession No. 98452; or g) encoding a polypeptide comprising the aa sequence of SEQ ID NO:2, or encoded by the DNA insert of said plasmid. Vectors, host cells. Isolated polypeptides analogous to said isolated nucleic acid molecules (a,c,d,e,g). Fusion proteins. Antibodies. Methods for producing polypeptides. Methods for detecting the presence of said polypeptides. Methods for detecting the presence of said nucleic acid molecules. Methods for identifying compounds which bind to or modulate said polypeptides. Methods for modulating the activity of said polypeptides.

2. Claims: 1-22 (all partially)

As invention 1, but concerning SEQ ID NO:4-6, and the plasmid with ATCC Accession No. _____.

3. Claims: 1-22 (all partially)

As invention 1, but concerning SEQ ID NO:7-9, and the plasmid with ATCC Accession No. 98633.

4. Claims: 1-22 (all partially)

As invention 1, but concerning SEQ ID NO:13-15, and the plasmid with ATCC Accession No. _____.

5. Claims: 1-22 (all partially)

As invention 1, but concerning SEQ ID NO:20-22, and the plasmid with ATCC Accession No. _____.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/05452

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9846755 A	22-10-1998	AU 7137398 A	11-11-1998
		EP 0975755 A	02-02-2000
WO 9827932 A	02-07-1998	AU 5613498 A	17-07-1998
		EP 0954575 A	10-11-1999
WO 9922000 A	06-05-1999	DE 19747418 C	15-07-1999
		EP 1027440 A	16-08-2000
WO 0018194 A	30-03-2000	DE 19844293 A	30-03-2000