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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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[Continued on next page]



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(54) Title: GENE DISRUPTIONS, COMPOSITIONS AND METHODS RELATING THERETO

(57) Abstract: The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising disruptions in PRO179, PRO181, PRO244, PRO247, PRO269, PRO293, PRO298, PRO339, PRO341, PRO347, PRO531, PRO537, PRO718, PRO773, PRO860, PRO871, PRO872, PRO813, PRO828, PRO1100, PRO1114, PRO1115, PRO1126, PRO1133, PRO1154, PRO1185, PRO1194, PRO1287, PRO1291, PRO1293, PRO1310, PRO1312, PRO1335, PRO1339, PRO2155, PRO1356, PRO1385, PRO1412, PRO1487, PRO1758, PRO1779, PRO1785, PRO1889, PRO90318, PRO3434, PRO3579, PRO4322, PRO4343, PRO4347, PRO4403, PRO4976, PRO260, PRO6014, PRO6027, PRO6181, PRO6714, PRO9922, PRO7179, PRO7476, PRO9824, PRO19814, PRO19836, PRO20088, PRO70789, PRO50298, PRO51592, PRO1757, PRO4421, PRO9903, PRO1106, PRO1411, PRO1486, PRO1565, PRO4399 or PRO4404 genes. Such in vivo studies and characterizations may provide valuable identification and discovery of therapeutics and/or treatments useful in the prevention, amelioration or correction of diseases or dysfunctions associated with gene disruptions such as neurological disorders; cardiovascular, endothelial or angiogenic disorders; eye abnormalities; immunological disorders; oncological disorders; bone metabolic abnormalities or disorders; lipid metabolic disorders; or developmental abnormalities.



**Published:**

— with international search report

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9 August 2007

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2006/007353

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A01K67/027 C07K14/47 C07K14/515 C07K16/18 G01N33/50  
C12N5/10 A61K39/395

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)  
A01K C07K G01N A61K 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)

EPO-Internal, BIOSIS, Sequence Search, WPI Data, PAJ, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.

See patent family 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

26 January 2007

Date of mailing of the international search report

25/05/2007

Name and mailing address of the ISA/

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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       Y	INABA TOSHIMORI ET AL: "Angiopoietin-like protein 3 mediates hypertriglyceridemia induced by the liver X receptor." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 24, 13 June 2003 (2003-06-13), pages 21344-21351, XP002416869 ISSN: 0021-9258  the whole document	1-3, 18, 21, 26, 27, 42, 45, 50, 51, 67, 82, 85, 91, 96, 121, 136 4-17, 19, 20, 22-25, 28-41, 43, 44, 56-62, 68-81, 83, 84, 97, 122-135, 137, 138
X	----- KOISHI RYUTA ET AL: "Angpt13 regulates lipid metabolism in mice" NATURE GENETICS, vol. 30, no. 2, February 2002 (2002-02), pages 151-157, XP002321851 ISSN: 1061-4036 cited in the application  the whole document	1-3, 18, 21, 26, 27, 42, 45, 50, 51, 67, 82, 85, 91, 96, 121, 136
Y	----- WO 02/40662 A (DELTA GEN INC) 23 May 2002 (2002-05-23)  the whole document	4-17, 19, 20, 22-25, 28-41, 43, 44, 56-62, 68-81, 83, 84, 97, 122-135, 137, 138
X	----- WO 00/53757 A2 (GENENTECH INC) 14 September 2000 (2000-09-14)  page 82, line 8 - page 90, line 15 page 96, line 29 - page 99, line 38 page 101, line 20 - page 104, line 5 examples 2-4 claims 1-80  -----	1, 2, 22-26, 50, 67, 91, 96, 121
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/007353

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 02/45495 A (DELTAGEN INC.) 13 June 2002 (2002-06-13) the whole document	1-149
A	CAPECCHI M R: "TARGETED GENE REPLACEMENT" SCIENTIFIC AMERICAN, March 1994 (1994-03), pages 52-59, XP002940139 ISSN: 0036-8733 the whole document	1-149
A	SHIMAMURA M ET AL: "Leptin and insulin down-regulate angiopoietin-like protein 3, a plasma triglyceride-increasing factor" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 322, no. 3, 24 September 2004 (2004-09-24), pages 1080-1085, XP004536498 ISSN: 0006-291X the whole document	1-149
A	INUKAI K ET AL: "ANGPTL3 is increased in both insulin-deficient and -resistant diabetic states" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 317, no. 4, 14 May 2004 (2004-05-14), pages 1075-1079, XP004502878 ISSN: 0006-291X the whole document	1-149
A	ANDO Y ET AL: "A DECREASED EXPRESSION OF ANGIOPOIETIN-LIKE 3 IS PROTECTIVE AGAINST ATHEROSCLEROSIS IN APOE-DEFICIENT MICE" JOURNAL OF LIPID RESEARCH, vol. 44, no. 6, 2 April 2003 (2003-04-02), pages 1216-1223, XP008038574 ISSN: 0022-2275 abstract	1-149
A	CONKLIN D ET AL: "IDENTIFICATION OF A MAMMALIAN ANGIOPOIETIN-RELATED PROTEIN EXPRESSED SPECIFICALLY IN LIVER" GENOMICS, vol. 62, 1999, pages 477-482, XP002937815 ISSN: 0888-7543 cited in the application the whole document	1-149
T	LI CAI: "Genetics and regulation of angiopoietin-like proteins 3 and 4." CURRENT OPINION IN LIPIDOLOGY APR 2006, vol. 17, no. 2, April 2006 (2006-04), pages 152-156, XP009077842 ISSN: 0957-9672 the whole document	1-149

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box II.1

Although claims 26-45, 50, 51, 56-62, 67-85, 96, 97, 103-120 and 144-149 are 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.

## Continuation of Box II.2

Claims Nos.: 46-49, 52-55, 63-66, 86-90, 92-95, 98-120, 139-149

Present claims 46-49, 52-55, 63-66, 86-90, 92-95, 98-120, 139-149 relate to compounds/methods defined by reference to a desirable characteristic or property. Claims 46-49, 52-55, 63-66, 86-90, 92-95, 98-102, 139-143 relate to agents identified by certain methods and claims 103-120 and 144-149 relate to the use of these agents. The claims cover all compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for none of such compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/007353

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:  
  
Although claims 26-45, 50, 51, 56-62, 67-85, 96, 97, 103-120 and 144- 149 are 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.: 46-49, 52-55, 63-66, 86-90, 92-95, 98-120, 139-149  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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.:  
  
1-149 (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

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-149 (all partially)

A method of identifying a phenotype associated with a disruption of a gene which encodes for a PR0179 polypeptide; and subject-matter related thereto.

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Invention 2 - Invention 75: claims 1-149 (all partially)

A method of identifying a phenotype associated with a disruption of a gene which encodes for PR0181, PR0244, PR0247, PR0269, PR0293, PR0298, PR0339, PR0341, PR0347, PR0531, PR0537, PR0718, PR0773, PR0860, PR0871, PR0872, PR0813, PR0828, PR01100, PR01114, PR01115, PR01126, PR01133, PR01154, PR01185, PR01194, PR01287, PR01291, PR01293, PR01310, PR01312, PR01335, PR01339, PR02155, PR01356, PR01385, PR01412, PR01487, PR01758, PR01779, PR01785, PR01889, PR090318, PR03434, PR03579, PR04322, PR04343, PR04347, PR04403, PR04976, PR0260, PR06014, PR06027, PR06181, PR06714, PR09922, PR07179, PR07476, PR09824, PR019814, PR019836, PR020088, PR070789, PR050298, PR051592, PR01757, PR04421, PR09903, PR01106, PR01411, PR01486, PR01565, PR04399 or PR04404 polypeptide, respectively; and subject-matter related thereto.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/007353

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0240662	A	23-05-2002	AU	1798902 A		27-05-2002
WO 0053757	A2	14-09-2000	NONE			
WO 0245495	A	13-06-2002	AU	3953902 A		18-06-2002