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(71) Applicant (for all designated States except US): WYETH
[US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CAO, Jingsong
[CN/US]; 169 Florence Street, Newton, MA 02467
(US). GIMENO, Ruth, E. [DE/US]; 65 Beverly Road,
Wellesley, MA 02481 (US). LI, Jian-Liang [US/US]; 110
Dartmouth Street, Medford, MA 02155 (US).

(74) Agents: CALNAN, William, H. et al.; Wyeth, Patent Law
Department, Five Giralda Farms, Madison, NJ 07940 (US).

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10 April 2008(54) Title: GPAT4 ENCODES A MAMMALIAN, MICROSOMAL ACYL-COA:GLYCEROL 3-PHOSPHATE ACYLTRANS-
FERASE

(57) Abstract: The present invention provides isolated and purified polynucleotides and polypeptides related to mouse and human microsomal acyl-CoA: glycerol 3-phosphate acyltransferase 4 (GP AT4) and their uses in modulating triacylglycerol (TAG) levels in a cell or sample of interest. The invention also provides GPAT4 agonists and antagonists, e.g., GPAT4 polynucleotides and polypeptides, antibodies to GPAT4 (agonistic and antagonistic antibodies), GPAT4 inhibitory polypeptides, and GPAT4 inhibitory polynucleotides. The present invention is also directed to novel methods for diagnosing, prognosing, monitoring, treating, ameliorating and/or preventing conditions related to GPAT4, TAG synthesis (or accumulation), or the synthesis (or accumulation) of TAG precursors (e.g., MAG, LPA, PA, and/or G3P). These GPAT4-associated conditions include, but are not limited to, dyslipidemia (e.g., hyperlipidemia, hypertriglyceridemia, Type III hyperlipidemia), obesity, hypercholesterolemia, hepatic steatosis, cancer, skin disorders associated with altered lipid metabolism (e.g., acne vulgaris, dry skin), adiposity, type 2 diabetes (and complications associated therewith, such as dermopathy, retinopathy, neuropathy, and nephropathy), insulin resistance, hyperinsulinemia, hypertension, cardiovascular disease, atherosclerosis, stroke, thrombosis, lipodystrophy, lipopenia, Reye's syndrome, Cushing's syndrome, metabolic syndrome (e.g., syndrome X), eating disorders (e.g., anorexia, bulimia), skin homeostasis, disorders related to energy storage, nutrient absorption, and lipid metabolism, reduced or absent lactation, and low preterm birth weight (and complications thereof, such as defects in neural development).

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/005112

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/00 C07K16/00 C12N15/00 C12Q1/00 A61P3/10 A61P9/00 A61P3/00		
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) A61K A61P C07K C12N C12Q 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, Sequence Search, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI D. ET AL.: "Cloning and identification of the human LPAAT-zeta gene, a novel member of the lysophosphatidic acid acyltransferase family" J. HUMAN. GENET., vol. 48, 2003, pages 438-442, XP002466955 see abstrcat, page 439 left col., fig.1 -----	10,15-19
Y	US 2003/175924 A1 (HILLMAN JENNIFER L [US] ET AL) 18 September 2003 (2003-09-18) see abstract, Seq. ID No.1-2, [0219]-[0227], [0115] -----	10,15-19
☐ 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		Date of mailing of the international search report
30 January 2008		22/02/2008
Name and mailing address of the ISA/ 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		Authorized officer MERCKLING-RUIZ, V

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-9,11-14

The present claims 1-9,11-14 encompass compounds defined only by their desired function (i.e. agonist or antagonist of GPAT4), contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, especially since neither the prior art nor the present application do disclose a single example of an agonist (or antagonist) of GPAT4. Undue experimentation would be required to screen compounds randomly. This is all the more true that, even in the application itself, a screening method for agonists/antagonists has been described in theory but has not been actually used, and has therefore not given any result (i.e. no agonist or antagonist found)

This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search for claims 1-9 and 11-14. Neither a compositions comprising an agonist/antagonist of GPAT4, nor the use of such a composition for the manufacture of a medicament or diagnostic agent are regarded as clearly disclose/sufficiently supported.

The search was therefore restricted to :

- methods for screening for modulators of GPAT4 activity (claim 10)
- antibodies against GPAT4 (claims 15-19)

These embodiments are regarded as sufficiently clear and disclosed by the application.

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, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/005112

Box No. 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:
2. ☒ Claims Nos.: 1-9, 11-14
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 No. 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:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/005112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003175924 A1	18-09-2003	NONE	