

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 July 2006 (13.07.2006)

PCT

(10) International Publication Number
WO 2006/074390 A3

(51) International Patent Classification:

C07K 14/65 (2006.01) A61P 21/00 (2006.01)
C07K 19/00 (2006.01) A61P 3/10 (2006.01)
A61K 38/29 (2006.01)

(21) International Application Number:

PCT/US2006/000495

(22) International Filing Date: 6 January 2006 (06.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/642,329 7 January 2005 (07.01.2005) US
60/656,583 25 February 2005 (25.02.2005) US

(71) Applicant (for all designated States except US): **REGENERON PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GLASS, David, J.** [US/US]; 341 Furnace Dock Road, Apt. 30, Cortlandt Manor, NY 10567 (US). **YANCOPOULOS, George, D.** [US/US]; 1519 Baptist Church Road, Yorktown Heights, NY 10598 (US). **DALY, Thomas, J.** [US/US]; 4 Dolphin Road, New City, NY 10956 (US). **PAPADOPOULOS, Nicholas, J.** [US/US]; 59 Heritage Lane, LaGrangeville, NY 12540 (US).

(74) Agent: **GREGG, Valeta**; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(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.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

11 January 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.

(54) Title: METHODS OF TREATING OBESITY WITH COMBINATION THERAPEUTICS OF IGF-I FUSION POLYPEPTIDES

(57) Abstract: A fusion protein comprising at least one IGF1 variant component and a fusion component (F), and, optionally, a signal sequence, exhibiting improved stability relative to the native IGF1 or IGF2 polypeptide. The fusion component (F) may be a multimerizing component, a targeting ligand, or another active or therapeutic compound. IGF1 variants were shown to have improved ability to induce skeletal muscle hypertrophy relative to native IGF1.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/65 C07K19/00

A61K38/29

A61P21/00

A61P3/10

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)
C07K

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, EMBASE, WPI Data, PAJ, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90/15142 A (GROPEP PTY. LTD) 13 December 1990 (1990-12-13) abstract	1,8-16, 18
Y	page 1, lines 4-19 page 2, lines 2-8 page 5, line 10 page 6, lines 1-12 page 10, paragraph 7 - page 11, paragraph 8 page 12, paragraph 1 page 13, paragraph 3-5 page 15, paragraph 1-4 examples 7,8	2-4,17, 19,20

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

28 June 2006

Date of mailing of the international search report

07. 11. 2006

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

Montrone, Marco

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/000495

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>EP 0 742 228 A (ELI LILLY AND COMPANY) 13 November 1996 (1996-11-13) abstract page 2, lines 1-42 page 5, lines 26-55 page 6, lines 1,2 page 7, line 1 - page 8, line 52 page 10, lines 1-19</p>	17,19,20
Y	<p>JANSSON ET AL: "Structural Changes in Insulin-like Growth Factor (IGF) I Mutant Proteins Affecting Binding Kinetic Rates to IGF Binding Protein 1 and IGF-I Receptor" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 36, 8 April 1997 (1997-04-08), pages 4108-4117, XP002134490 ISSN: 0006-2960 abstract</p>	2-4
A	<p>FRANCIS G L ET AL: "NOVEL RECOMBINANT FUSION PROTEIN ANALOGUES OF INSULIN-LIKE GROWTH FACTOR (IGF)-I INDICATE THE RELATIVE IMPORTANCE OF IGF-BINDING PROTEIN AND RECEPTOR BINDING FOR ENHANCED BIOLOGICAL POTENCY" JOURNAL OF MOLECULAR ENDOCRINOLOGY, vol. 8, no. 3, 1992, pages 213-223, XP000891905 ISSN: 0952-5041 abstract page 217, column 1, paragraph 3 - column 2, paragraph 2</p>	1,2,8-13
A	<p>FRANCIS G L ET AL: "INSULIN-LIKE GROWTH FACTOR (IGF)-II BINDING TO IGF-BINDING PROTEINS AND IGF RECEPTORS IS MODIFIED BY DELETION OF THE N-TERMINAL HEXAPEPTIDE OR SUBSTITUTION OF ARGININE FOR GLUTAMATE-6 IN IGF-II" BIOCHEMICAL JOURNAL, PORTLAND PRESS, LONDON, GB, vol. 293, no. 3, 1993, pages 713-719, XP008048625 ISSN: 0264-6021 abstract</p>	1-4,7-20

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material
 - on paper
 - in electronic form
 - c. time of filing/furnishing
 - contained in the international application as filed
 - filed together with the international application in electronic form
 - furnished subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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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 14 to 20 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.
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 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.:

1-4, 7-20 (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:

1. claims: 1-4,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a N-terminal deletion of amino acids
1-3.

2. claims: 1-4,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion or substitution of amino
acid Lys65.

3. claims: 1-4,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion or substitution of amino
acid Lys68.

4. claims: 1-4,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a C-terminal deletion of amino acids
65-70.

5. claims: 1-4,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion or substitution of amino
acid Arg36.

6. claims: 1-4,7-20(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion or substitution of amino
acid Arg37.

7. claims: 1-5,7-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion of amino acids at
positions 1-3 and 37.

8. claims: 1-20(all partially)

A fusion protein comprising:
a, at least one IGF-1 variant polypeptide component and
b, a fusion component (F),
wherein the IGF variant is a human IGF-1 protein of
SEQ.ID.NO.:1 comprising a deletion of amino acids at
positions 1-3, 37 and 68-70.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2006/000495

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 9015142	A	13-12-1990	AT 125869 T	15-08-1995
			AU 5667590 A	07-01-1991
			CA 2033176 A1	10-12-1990
			DE 69021335 D1	07-09-1995
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			JP 8301899 A	19-11-1996
			US 5622932 A	22-04-1997