

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
25 June 2009 (25.06.2009)

PCT

(10) International Publication Number  
**WO 2009/077731 A3**

(51) International Patent Classification:

C07K 14/575 (2006.01) A61K 38/22 (2006.01)  
C07K 14/72 (2006.01) C07K 16/00 (2006.01)  
C12N 15/62 (2006.01) G01N 33/68 (2006.01)

(21) International Application Number:

PCT/GB2008/004120

(22) International Filing Date:

16 December 2008 (16.12.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0724656.4	19 December 2007 (19.12.2007)	GB
0724654.9	19 December 2007 (19.12.2007)	GB
60/015,424	20 December 2007 (20.12.2007)	US
61/015,419	20 December 2007 (20.12.2007)	US

(71) Applicant (for all designated States except US): **ASTERION LIMITED** [GB/GB]; Firth Court, Western Bank, Sheffield S10 2TN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ARTYMIUK, Peter** [GB/GB]; Asterion Limited, Firth Court, Western Bank, Sheffield S10 2TN (GB). **ROSS, Richard** [GB/GB]; Asterion Limited, Firth Court, Western Bank, Sheffield S10 2TN (GB).

(74) Agent: **GILHOLM, Harrison**; Marlborough House, Westminster Place, York Business Park, Nether Poppleton, York YO26 6RW (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

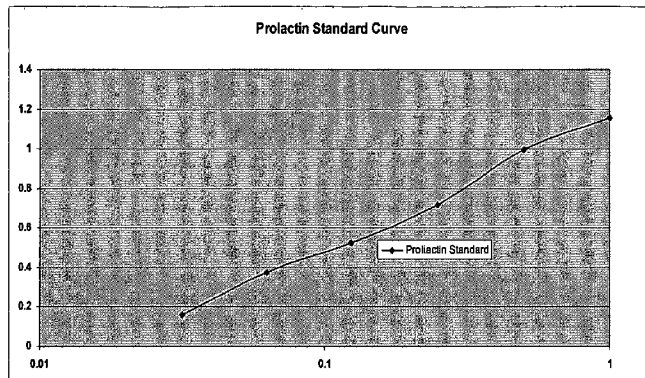
Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:  
17 September 2009

(54) Title: PROLACTIN FUSION PROTEINS

Figure 17



(57) Abstract: We disclose prolactin fusion proteins that have agonist or antagonist activity and their use in the treatment of conditions that would benefit from prolactin agonist or antagonist activity.

WO 2009/077731 A3

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2008/004120

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C07K14/575 C07K14/72 C12N15/62  
 ADD. A61K38/22 C07K16/00 G01N33/68

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, EMBASE, BIOSIS, WPI Data, 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 01/96565 A (ASTERION LTD [GB]; ROSS RICHARD [GB]; ARTYMIUK PETER [GB]; SAYERS JON) 20 December 2001 (2001-12-20)	1-27, 51-57, 73-76
Y	the whole document	70-72
X	WO 2007/128979 A (ASTERION LTD [GB]; PRADHANANGA SARBENDRA [GB]; SAYERS JOHN [GB]; ROSS) 15 November 2007 (2007-11-15)	1-32, 36-42, 49-69, 73-76
Y	page 8, line 14 - page 9, line 8; claims 28-37 page 14, line 15 - page 15, line 23	70-72
Y	WO 2007/036033 A (STEM CELL THERAPEUTICS CORP [CA]; GREGG CHRISTOPHER [CA]; WEISS SAMUEL) 5 April 2007 (2007-04-05) cited in the application	70-72
A	the whole document	73

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

9 July 2009

Date of mailing of the international search report

16/07/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040,  
 Fax: (+31-70) 340-3016

Authorized officer

Wiame, Ilse

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/004120

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>YASUKAWA KIYOSHI ET AL: "Fusion protein of interleukin-6 and interleukin-6 receptor without a polypeptide linker."            JOURNAL OF BIOSCIENCE AND BIOENGINEERING,            vol. 96, no. 1, July 2003 (2003-07), pages            38-46, XP002520258            ISSN: 1389-1723            abstract</p>	9,16-17, 23-25
A	<p>WILKINSON IAN R ET AL: "A ligand-receptor fusion of growth hormone forms a dimer and is a potent long-acting agonist"            NATURE MEDICINE, NATURE PUBLISHING GROUP,            NEW YORK, NY, US,            vol. 13, no. 9,            1 September 2007 (2007-09-01), pages            1108-1113, XP009089546            ISSN: 1078-8956            the whole document</p>	10,26
A	<p>LANGENHEIM J F ET AL: "Two wrongs can make a right: Dimers of prolactin and growth hormone receptor antagonists behave as agonists"            MOLECULAR ENDOCRINOLOGY, BALTIMORE, MD,            US,            vol. 20, no. 3,            1 January 2006 (2006-01-01), pages            661-674, XP009089441            ISSN: 0888-8809            abstract</p>	26
A	<p>DATABASE UniProt [Online]            21 July 1986 (1986-07-21), "RecName:            Full=Prolactin; Short=PRL; Flags:            Precursor;"            XP002520260            retrieved from EBI accession no.            UNIPROT:P01236            Database accession no. P01236            the whole document</p>	10
A	<p>DATABASE UniProt [Online]            1 August 1990 (1990-08-01), "RecName:            Full=Prolactin receptor; Short=PRL-R;            Flags: Precursor;"            XP002520261            retrieved from EBI accession no.            UNIPROT:P16471            Database accession no. P16471            the whole document</p>	11

-/--

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/004120

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LABRIOLA ET AL: "Beneficial effects of prolactin and laminin on human pancreatic islet-cell cultures" MOLECULAR AND CELLULAR ENDOCRINOLOGY, ELSEVIER IRELAND LTD, IE, vol. 263, no. 1-2, 2 December 2006 (2006-12-02), pages 120-133, XP005792583 ISSN: 0303-7207 abstract	74-75
A	SPANGELO B L ET AL: "Stimulation of in vivo antibody production and concanavalin-A-induced mouse spleen cell mitogenesis by prolactin" IMMUNOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 14, no. 1, 1 September 1987 (1987-09-01), pages 11-20, XP023816265 ISSN: 0162-3109 [retrieved on 1987-09-01] abstract	76
A	JOMAIN JEAN-BAPTISTE ET AL: "Structural and thermodynamic bases for the design of pure prolactin receptor antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 282, no. 45, November 2007 (2007-11), pages 33118-33131, XP002520259 ISSN: 0021-9258 abstract page 33122, column 2, line 14 - page 33123, column 1, line 3	28-32, 37-42
X	WO 2006/010891 A2 (ASTERION LTD [GB]; ARTYMIUK PETER [GB]; PRADHANANGA SARBENDRA [GB]; SA) 2 February 2006 (2006-02-02)	1-10,12, 26-32, 36-42, 49-69, 73-76
Y	the whole document page 7, line 30 - page 8, line 8 page 3, line 12 - line 17 page 9, line 8 - line 11 page 17, line 5 - line 14	70-72
X	WO 03/070765 A2 (ASTERION LTD [GB]; ROSS RICHARD [GB]; SAYERS JON [GB]; ARTYMIUK PETER) 28 August 2003 (2003-08-28)	1-10,12, 26-32, 36-42, 49-69, 73-76
Y	the whole document	70-72
	----- -/--	

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/004120

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BERNICHEIN SOPHIE ET AL: "Development of pure prolactin receptor antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM, US, vol. 278, no. 38, 19 September 2003 (2003-09-19), pages 35988-35999, XP002469191 ISSN: 0021-9258 page 35991, left-hand column, paragraph 1; figure 1 page 35989, left-hand column, line 1 - line 22  -----	29-32, 37-42

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2008/004120

## 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.:  
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 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:

see additional sheet

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.:  
  
11, 13-25, 29-32, 37-42(completely); 1-10, 12, 26-28, 36, 49-76(partially)
  
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.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 11, 13-25(completely); 1-10, 12, 26-27, 51-57, 70-76(partially)

A fusion polypeptide comprising the amino acid sequence of prolactin, or active binding part thereof, linked directly or indirectly, to the prolactin binding domain of the prolactin receptor; polynucleotide encoding said polypeptide and use thereof.

---

2. claims: 29-32, 37-42(completely); 1-10, 12, 26-28, 36, 49-76(partially)

A fusion polypeptide comprising the amino acid sequence of prolactin mutant G129R, or active binding part thereof, linked directly or indirectly, to the prolactin binding domain of the prolactin receptor; polynucleotide encoding said polypeptide and use thereof.

---

3. claims: 33-35, 43-48(completely); 1-10, 12, 26-28, 36, 49-76(partially)

A fusion polypeptide comprising the amino acid sequence of prolactin mutant delta1-9/C11S/G129R, or active binding part thereof, linked directly or indirectly, to the prolactin binding domain of the prolactin receptor; polynucleotide encoding said polypeptide and use thereof.

---

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/004120

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0196565	A	20-12-2001	AU 7423401 A	24-12-2001
			CA 2447632 A1	20-12-2001
			EP 1290170 A2	12-03-2003
			JP 2004503243 T	05-02-2004
			US 2009054336 A1	26-02-2009
			US 2004071655 A1	15-04-2004
			-----	
WO 2007128979	A	15-11-2007	AU 2007246913 A1	15-11-2007
			CA 2648487 A1	15-11-2007
			CN 101389649 A	18-03-2009
			EP 2004681 A1	24-12-2008
			KR 20080109814 A	17-12-2008
			-----	
WO 2007036033	A	05-04-2007	AU 2006297041 A1	05-04-2007
			CA 2664629 A1	05-04-2007
			EP 1928488 A1	11-06-2008
			JP 2009509943 T	12-03-2009
			KR 20080074108 A	12-08-2008
			-----	
WO 2006010891	A2	02-02-2006	AU 2005266184 A1	02-02-2006
			CA 2575441 A1	02-02-2006
			EP 1771467 A2	11-04-2007
			JP 2008507292 T	13-03-2008
			KR 20070067678 A	28-06-2007
			KR 20090006221 A	14-01-2009
			NZ 553224 A	31-05-2009
-----				
WO 03070765	A2	28-08-2003	AU 2002366325 A1	09-09-2003
			CA 2468439 A1	28-08-2003
			CN 1604965 A	06-04-2005
			EP 1456385 A2	15-09-2004
			GB 2384001 A	16-07-2003
			GB 2389115 A	03-12-2003
			HU 0402496 A2	29-03-2005
			JP 2005525106 T	25-08-2005
			KR 20060106862 A	12-10-2006
			KR 20070108254 A	08-11-2007
			MX PA04005675 A	19-04-2005
			NZ 533550 A	24-02-2006
			RU 2346047 C2	10-02-2009
			US 2005123558 A1	09-06-2005
			ZA 200404488 A	29-03-2006
			ZA 200600149 A	25-10-2006
			-----	