

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 May 2003 (30.05.2003)

PCT

(10) International Publication Number
WO 03/044056 A3

- (51) International Patent Classification⁷: C07K 14/61, A61K 47/48, 38/27
- (21) International Application Number: PCT/US02/37270
- (22) International Filing Date:
20 November 2002 (20.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/331,907 20 November 2001 (20.11.2001) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- (88) Date of publication of the international search report:
21 August 2003
- 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.



WO 03/044056 A3

(54) Title: CHEMICALLY-MODIFIED HUMAN GROWTH HORMONE CONJUGATES

(57) Abstract: The present invention provides a chemically modified human Growth Hormone (hGH) prepared by binding a water soluble polymer to the protein. The chemically-modified protein according to the present invention may have a much longer lasting hGH activity than that of the unmodified hGH, enabling reduced dose and scheduling opportunities.

INTERNATIONAL SEARCH REPORT

 International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K14/61 A61K47/48 A61K38/27

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 A61K

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, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 055532 A (CHRISTIANSEN JESPER ;MAXYGEN APS (DK); DRUSTRUP JOERN (DK); ANDERS) 18 July 2002 (2002-07-18) the whole document	1-79
Y	VERONESE FRANCESCO M: "Peptide and protein PEGylation: A review of problems and solutions." BIOMATERIALS, vol. 22, no. 5, March 2001 (2001-03), pages 405-417, XP002237938 ISSN: 0142-9612 the whole document	1-79

 Further documents are listed in the continuation of box C.

 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

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"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

10 April 2003

Date of mailing of the international search report

05.05.03

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INTERNATIONAL SEARCH REPORT

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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.
Y	WO 01 76639 A (FINN RORY ; QI HONG (US); SEDO KURT (US); GOKARN YATIN (US); HILLS) 18 October 2001 (2001-10-18) examples the whole document ---	1-79
X	US 4 179 337 A (DAVIS FRANK F ET AL) 18 December 1979 (1979-12-18) column 3 the whole document ---	1-35, 41-79
Y	the whole document ---	1-79
X	WO 97 11178 A (GENENTECH INC ; OLSON KENNETH (US); WELLS JAMES A (US); CLARK ROSS) 27 March 1997 (1997-03-27) cited in the application page 47 -page 51; examples VII-XIV ---	1-32, 41-79
Y	page 47 -page 51; examples VII-XIV ---	1-79
X	CLARK R ET AL: "Long-acting growth hormones produced by conjugation with polyethylene glycol" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 271, no. 36, 6 September 1996 (1996-09-06), pages 21969-21977, XP002216386 ISSN: 0021-9258 the whole document ---	1-32, 41-79
Y	the whole document ---	1-79
X	WO 93 00109 A (GENENTECH INC) 7 January 1993 (1993-01-07) cited in the application page 3 page 20 ---	1-32, 41-79
Y	page 3 page 20 ---	1-79
Y	WO 96 11953 A (AMGEN INC) 25 April 1996 (1996-04-25) page 7 ---	1-32, 41-79
Y	WO 00 44785 A (HOFFMANN LA ROCHE) 3 August 2000 (2000-08-03) page 26 ---	1-32, 41-79
Y	WO 89 05824 A (GENETICS INST) 29 June 1989 (1989-06-29) page 10 -page 11 ---	1-32, 41-79
X	WO 00 42175 A (COX GEORGE N ; BOLDER BIOTECHNOLOGY INC (US); DOHERTY DANIEL H (US)) 20 July 2000 (2000-07-20) cited in the application the whole document ---	36-40
Y	the whole document ---	1-79
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/37270

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 99 03887 A (BOLDER BIOTECHNOLOGY INC ;COX GEORGE N III (US)) 28 January 1999 (1999-01-28)	36-40
Y	the whole document ---	1-79
X	EP 0 458 064 A (AMERICAN CYANAMID CO) 27 November 1991 (1991-11-27)	36-40
Y	the whole document ---	1-79
X	WO 92 16555 A (ENZON INC) 1 October 1992 (1992-10-01) the whole document page 7, line 28 ---	33-35
Y	ZALIPSKY S: "FUNCTIONALIZED POLY(ETHYLENE GLYCOL) FOR PREPARATION OF BIOLOGICALLY RELEVANT CONJUGATES" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 6, no. 2, 1995, pages 150-165, XP002068523 ISSN: 1043-1802 the whole document page 153 ---	1-79
Y	MONFARDINI C ET AL: "A BRANCHED MONOMETHOXYPOLY(ETHYLENE GLYCOL) FOR PROTEIN MODIFICATION" BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 6, no. 1, 1995, pages 62-69, XP000494804 ISSN: 1043-1802 the whole document ---	1-32, 41-79
X	THORNER MICHAEL O ET AL: "Growth hormone (GH) receptor blockade with a PEG-modified GH (B2036-PEG) lowers serum insulin-like growth factor-I but does not acutely stimulate serum GH." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 84, no. 6, June 1999 (1999-06), pages 2098-2103, XP002237939 ISSN: 0021-972X	1-7, 62-67, 75-79
Y	the whole document ---	1-79
Y	EP 0 605 963 A (ORTHO PHARMA CORP) 13 July 1994 (1994-07-13) the whole document ---	1-79

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/37270

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>FELIX A M ET AL: "PEGYLATED PEPTIDES IV ENHANCED BIOLOGICAL ACTIVITY OF SITE-DIRECTED PEGYLATED GRF ANALOGS" INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, MUNKSGAARD, COPENHAGEN, DK, vol. 46, no. 3/4, 1 September 1995 (1995-09-01), pages 253-264, XP000526320 ISSN: 0367-8377 the whole document -----</p>	1-79

INTERNATIONAL SEARCH REPORT

International application No.
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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:

Although claims 63-67,69-73,75-79 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.:
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:

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.:

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: 8-32,41-61,68-74(all complete);1-7,62-67,75-79(all in part)

Human growth hormone-PEG conjugates wherein the hGH-PEG attachment is at an amino acid having a free amino group. Uses for treatment of growth or development disorders

2. Claims: 33-35(all complete);1-7,62-67,75-79(all in part)

Human growth hormone-PEG conjugates wherein the hGH-PEG attachment is at an amino acid having a free carboxyl group. Uses for treatment of growth or development disorders

3. Claims: 36-40(all complete);1-7,62-67,75-79(all in part)

Human growth hormone-PEG conjugates wherein the hGH-PEG attachment is at an amino acid having a free sulfhydryl group. Uses for treatment of growth or development disorders.

INTERNATIONAL SEARCH REPORT

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02055532	A	18-07-2002	WO 02055532 A2	18-07-2002
WO 0176639	A	18-10-2001	AU 8930701 A WO 0176639 A2	23-10-2001 18-10-2001
US 4179337	A	18-12-1979	CA 1033673 A1 CH 616942 A5 DE 2433883 A1 FR 2313939 A1 GB 1469472 A JP 1152589 C JP 50042087 A JP 56023587 B NL 7409770 A SE 441753 B SE 7409366 A	27-06-1978 30-04-1980 05-02-1976 07-01-1977 06-04-1977 30-06-1983 16-04-1975 01-06-1981 22-01-1975 04-11-1985 21-01-1975
WO 9711178	A	27-03-1997	AU 718439 B2 AU 7073396 A EP 0851925 A1 JP 11512298 T US 6057292 A US 6004931 A US 6136563 A WO 9711178 A1 US 5849535 A ZA 9607973 A	13-04-2000 09-04-1997 08-07-1998 26-10-1999 02-05-2000 21-12-1999 24-10-2000 27-03-1997 15-12-1998 23-06-1997
WO 9300109	A	07-01-1993	AU 2147192 A PT 100629 A WO 9300109 A1	25-01-1993 30-09-1993 07-01-1993
WO 9611953	A	25-04-1996	US 5824784 A AT 179991 T AU 706700 B2 AU 1841995 A AU 4887099 A CA 2178752 A1 CA 2307142 A1 CN 1313343 A CN 1139932 A ,B DE 69509628 D1 DE 69509628 T2 DK 733067 T3 EP 0733067 A1 EP 0822199 A2 ES 2131811 T3 GR 3030526 T3 HK 1008826 A1 IL 112585 A JP 11310600 A JP 3177449 B2 JP 9025298 A JP 9506116 T JP 3177251 B2 KR 248111 B1 KR 261030 B1 NZ 281469 A	20-10-1998 15-05-1999 24-06-1999 06-05-1996 11-11-1999 25-04-1996 25-04-1996 19-09-2001 08-01-1997 17-06-1999 16-09-1999 01-11-1999 25-09-1996 04-02-1998 01-08-1999 29-10-1999 31-03-2000 31-08-2000 09-11-1999 18-06-2001 28-01-1997 17-06-1997 18-06-2001 15-03-2000 15-06-2000 24-04-1997

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 02/37270

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9611953	A		WO 9611953 A1 US 5985265 A ZA 9501008 A	25-04-1996 16-11-1999 18-10-1996
WO 0044785	A	03-08-2000	AU 2618500 A BG 105851 A BR 0007781 A CN 1376164 T CZ 20012654 A3 EP 1157037 A1 JP 2002540065 T SK 10352001 A3 WO 0044785 A1	18-08-2000 28-06-2002 05-02-2002 23-10-2002 15-05-2002 28-11-2001 26-11-2002 04-06-2002 03-08-2000
WO 8905824	A	29-06-1989	US 4904584 A AU 2911189 A EP 0355142 A1 JP 2502646 T WO 8905824 A1	27-02-1990 19-07-1989 28-02-1990 23-08-1990 29-06-1989
WO 0042175	A	20-07-2000	AU 2413300 A BR 0008759 A CA 2359345 A1 CN 1355842 T EP 1144613 A1 JP 2002534119 T WO 0042175 A1	01-08-2000 06-08-2002 20-07-2000 26-06-2002 17-10-2001 15-10-2002 20-07-2000
WO 9903887	A	28-01-1999	AU 751898 B2 AU 8300098 A BR 9812267 A CN 1269805 T EP 1012184 A1 JP 2001510033 T NZ 502375 A WO 9903887 A1	29-08-2002 10-02-1999 18-12-2001 11-10-2000 28-06-2000 31-07-2001 30-11-2001 28-01-1999
EP 0458064	A	27-11-1991	AT 163431 T AU 639324 B2 AU 7607591 A CA 2041742 A1 DE 69128944 D1 DE 69128944 T2 DK 458064 T3 EP 0458064 A2 ES 2113354 T3 FI 912144 A GR 3026436 T3 IE 911511 A1 IL 97932 A JP 6009696 A KR 213455 B1 NO 911752 A NZ 237959 A PT 97539 A ,B US 5951972 A US 6010999 A ZA 9103359 A	15-03-1998 22-07-1993 07-11-1991 05-11-1991 02-04-1998 25-06-1998 27-04-1998 27-11-1991 01-05-1998 05-11-1991 30-06-1998 06-11-1991 22-02-1998 18-01-1994 02-08-1999 05-11-1991 26-05-1994 28-02-1992 14-09-1999 04-01-2000 25-03-1992

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/37270

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9216555	A	01-10-1992	AU	1676992 A		21-10-1992
			CA	2101918 A1		19-09-1992
			EP	0576589 A1		05-01-1994
			JP	6506217 T		14-07-1994
			WO	9216555 A1		01-10-1992

EP 0605963	A	13-07-1994	AU	5238393 A		23-06-1994
			EP	0605963 A2		13-07-1994
			FI	935485 A		10-06-1994
			JP	7196925 A		01-08-1995
			KR	254650 B1		01-05-2000
			KR	257643 B1		15-05-2000
			NO	934477 A		10-06-1994
			NZ	250375 A		26-07-1995
			CA	2110543 A1		10-06-1994
			ZA	9309214 A		08-06-1995
