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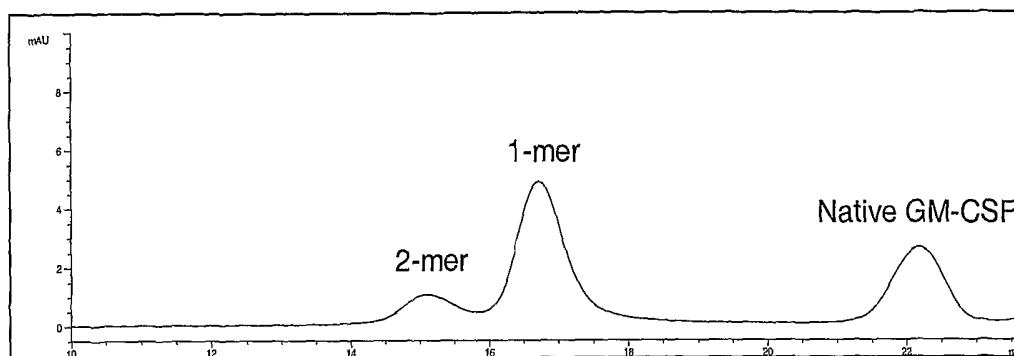
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONJUGATES OF A GM-CSF MOIETY AND A POLYMER



SEC-HPLC Analysis of mPEG2-NHS, 40kDa,-GM-CSF Conjugate Solution

(57) Abstract: Conjugates of a GM-CSF moiety and one or more water-soluble polymers are provided. Typically, the water-soluble polymer is poly(ethylene glycol) or a derivative thereof. Also provided are compositions comprising conjugates, methods of making conjugates, and methods of administering compositions comprising conjugates to a patient.

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INTERNATIONAL SEARCH REPORT

Int. application No
PCT/US2005/025052

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P35/00

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

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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAIFER M G P ET AL: "IMPROVED CONJUGATION OF CYTOKINES USING HIGH MOLECULAR WEIGHT POLY(ETHYLENE GLYCOL): PEG-GM-CSF AS A PROTOTYPE" POLYMER PREPRINTS, AMERICAN CHEMICAL SOCIETY, US, vol. 38, no. 1, 1997, pages 576-577, XP000884661 ISSN: 0032-3934 pag. 576, col. I last 2 par., column 2 last par., figure I and II	1,2,4,5, 13-22, 24-29, 31-42, 47,49, 50, 52-55, 57-63
Y	pag. 576, col. I last 2 par., column 2 last par., figure I and II ----- -/--	1-63

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/025052

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 02/02132 A (SMITHKLINE BEECHAM CORPORATION; BAM, NARENDRA; KING, ANDREW, G; YEHL, P) 10 January 2002 (2002-01-10) Example 2 pag. 16, example 3 pag. 19 claims 21,30	1,2, 13-24, 26,28, 29, 31-42, 47, 52-55, 57-59, 62,63
X	WO 2004/012773 A (F. HOFFMANN-LA ROCHE AG) 12 February 2004 (2004-02-12)	1-3,9, 13-17,23
Y	pag. 7 lines 8,9; pag. 19 line 8; formula example 2 pag. 38; Formula I-C1 claim 7	1-63
X	WO 03/040211 A (SHEARWATER CORPORATION; BENTLEY, MICHAEL, DAVID; ZHAO, XUAN; SHEN, XIA) 15 May 2003 (2003-05-15) pag. 28 example 3, pag. 23 line 31	1,2,9, 11-24
Y	WO 2004/018698 A (GENITRIX, LLC; SEGAL, ANDREW, H; YOUNG, ELIHU) 4 March 2004 (2004-03-04) page 96, lines 3,4	30,51
Y	US 5 629 384 A (VERONESE ET AL) 13 May 1997 (1997-05-13) abstract	13,32,35
Y	US 6 689 351 B1 (PIERCE GLENN ET AL) 10 February 2004 (2004-02-10) cited in the application Column 12 line 35-41 Column 13 line 5-58 abstract	1-63
P,X	WO 2005/000360 A (NEKTAR THERAPEUTICS AL, CORPORATION; HARRIS, J., MILTON; KOZLOWSKI, AN) 6 January 2005 (2005-01-06) first formula pag. 3; 5th formula pag. 37; par. 158	1,9,12
A	US 2003/114647 A1 (HARRIS J. MILTON ET AL) 19 June 2003 (2003-06-19) formula par. 45; par. 144; par. 178	1,2,9, 13-24
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/025052

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 880 255 A (DELGADO ET AL) 9 March 1999 (1999-03-09) cited in the application</p> <p>Column 5 lines 20-21 Column 7 line 20- Column 8 line 18 Column 11 line 55-58 claims 1,2</p>	<p>4,5, 13-17, 24-29, 62,63</p>
X	<p>EP 0 727 437 A (POLYMASC PHARMACEUTICALS PLC) 21 August 1996 (1996-08-21)</p> <p>pag. 6 lines 16-23; pag. 7 lines 30-45, pag 9 lines 35-36</p>	<p>4,5, 13-17, 24-29, 62,63</p>
A	<p>EP 0 402 070 A (SCHERING CORPORATION) 12 December 1990 (1990-12-12) claim 2</p>	<p>47,48</p>
X	<p>EP 1 026 171 A (POLYMASC PHARMACEUTICALS PLC) 9 August 2000 (2000-08-09)</p> <p>pag. 25 line 17; par 83; par. 104-108; par. 110; par 130-131; tables pag 4, 6; claim 10</p>	<p>4,5, 13-17, 24-29, 52-56, 60,62,63</p>
X	<p>WO 2004/022630 A (NEKTAR THERAPEUTICS AL, CORPORATION; KOZLOWSKI, ANTONI) 18 March 2004 (2004-03-18)</p>	<p>4,5, 9-13, 17-24, 26-29, 31-45, 47,50, 52-55, 57,60-63</p>
Y	<p>pag. line 23; pag. 64 line 23; Claim 93; pag. 45 structure XV; pag. 65 line 1-pag. 67 line 29; pag. 75 example 5; pag. 83 Example 7;</p>	<p>6</p>
X	<p>MALIK F ET AL: "Polyethylene Glycol (PEG)- modified Granulocyte-Macrophage Colony- stimulating Factor (GM-CSF) with conserved Biological Activity" EXPERIMENTAL HEMATOLOGY, NEW YORK, NY, US, vol. 20, 1992, pages 1028-1035, XP002138685 ISSN: 0301-472X pag. 1029 . lines 19-46, V par..; pag. 1031 lines 1-7; pag. 1033 line 4 pag. 1033</p>	<p>4,5, 13-17, 24, 26-29, 52-55, 57,58, 60-63</p>

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INTERNATIONAL SEARCH REPORT

International application No
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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.
A	DELGADO C ET AL: "COUPLING OF POLY(ETHYLENE GLYCOL) TO ALBUMIN UNDER VERY MILD CONDITIONS BY ACTIVATION WITH TRESYL CHLORIDE: CHARACTERIZATION OF THE CONJUGATE BY PARTITIONING IN AQUEOUS TWO-PHASE SYSTEMS" BIOTECHNOLOGY AND APPLIED BIOCHEMISTRY, ACADEMIC PRESS, US, vol. 12, no. 2, 1990, pages 119-128, XP009010066 ISSN: 0885-4513 pag 120 lines 8-14; pag. 122 scheme 1	3,4, 13-17
X	WO 98/32466 A (POLYMASC PHARMACEUTICALS PLC; FRANCIS, GILLIAN, ELIZABETH; FISHER, DER) 30 July 1998 (1998-07-30) pag. 31 Example 7claim 10	4,5,13, 17,24, 52-55, 60,62,63
X	EP 0 400 472 A (SUMITOMO PHARMA; SEIKAGAKU KOGYO CO LTD; SUMITOMO PHARMACEUTICALS COMP) 5 December 1990 (1990-12-05) Pag. 7 lines 8-10, 46; pag. 36 lines 30-58.claim 2	31-37,47
P,X	WO 2004/060406 A (NEKTAR THERAPEUTICS AL, CORPORATION) 22 July 2004 (2004-07-22) formula pag. 42 line 9; pag. 89 lines 24-26; fig. 3	4,5
Y	WO 01/87925 A (BOLDER BIOTECHNOLOGY, INC; ROSENDAHL, MARY, S; COX, GEORGE, N; DOHERTY) 22 November 2001 (2001-11-22) page 59, line 17 - page 61, line 8	31-34
Y	DEMIROGLOU A ET AL: "A NOVEL REACTION SEQUENCE FOR THE COUPLING OF NUCLEOPHILES TO AGAROSE WITH 2,2,2-TRIFLUOROETHANESULFONYL CHLORIDE" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, WILEY VCH VERLAG, WEINHEIM, DE, vol. 33, no. 1, 1994, pages 120-123, XP000606513 ISSN: 1433-7851 pag. 120 first column equations a, b, c,	1-63
Y	EP 1 303 292 A (SMITHKLINE BEECHAM CORPORATION) 23 April 2003 (2003-04-23) pag. 24 last 9 lines; claim 21	4-63

INTERNATIONAL SEARCH REPORT

International application No.
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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 60, 61 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 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 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.:

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: 1-3 complete; claims 9-63 partially

Conjugates of GM-CSF and a water soluble polymer selected from poly(alkylene oxide), polyvinyl(pyrrolidone), poly(vinyl alcohol), polyoxazoline, polyacryloylmorpholine embraced under the general formula depicted on present claim 1, methods for making said conjugates, pharmaceutical compositions comprising said conjugates and methods for delivering said conjugates to a patient; except for the subject matter of inventions 2 and 3.

2. claims: 4-8 complete; claims 9-63 partially

Conjugates of GM-CSF and a water soluble polymer selected from poly(alkylene oxide), polyvinyl(pyrrolidone), poly(vinyl alcohol), polyoxazoline, polyacryloylmorpholine embraced under the general formula depicted on present claim 4, methods for making said conjugates, pharmaceutical compositions comprising said conjugates and methods for delivering said conjugates to a patient; except for the subject matter of inventions 2 and 3.

3. claims: Claims 31-61 partially

A pharmaceutical compositions comprising:
i) a human GM-CSF covalently attached, either directly or through a spacer moiety comprised of one or more atoms, to a water-soluble polymer, wherein the water-soluble polymer has a weight-average molecular weight of greater than 5,000 Daltons; and
ii) a pharmaceutically acceptable excipient, wherein at least about 85% of the conjugates in the composition have from one to two polymers attached to the human GM-CSF; except for the subject matter of inventions 2 and 3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/025052

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0202132	A	10-01-2002	AU 1674902 A EP 1303292 A1 JP 2004501975 T	14-01-2002 23-04-2003 22-01-2004
WO 2004012773	A	12-02-2004	AU 2003258518 A1 BR 0313212 A CA 2492775 A1 CN 1671422 A EP 1526872 A1 JP 2006502250 T MX PA05000796 A	23-02-2004 28-06-2005 12-02-2004 21-09-2005 04-05-2005 19-01-2006 19-04-2005
WO 03040211	A	15-05-2003	CA 2466027 A1 EP 1446438 A2 JP 2005508421 T MX PA04004336 A	15-05-2003 18-08-2004 31-03-2005 16-05-2005
WO 2004018698	A	04-03-2004	AU 2003265523 A1 CA 2496384 A1 EP 1573047 A2 MX PA05001953 A	11-03-2004 04-03-2004 14-09-2005 22-06-2005
US 5629384	A	13-05-1997	US 5631322 A	20-05-1997
US 6689351	B1	10-02-2004	AU 1462392 A CA 2081104 A1 EP 0526630 A1 IE 920560 A1 JP 5506673 T PT 100152 A WO 9214480 A1	15-09-1992 23-08-1992 10-02-1993 26-08-1992 30-09-1993 31-05-1993 03-09-1992
WO 2005000360	A	06-01-2005	AU 2004251602 A1 CA 2510040 A1 CN 1747748 A EP 1626741 A2 MX PA05007628 A	06-01-2005 06-01-2005 15-03-2006 22-02-2006 19-10-2005
US 2003114647	A1	19-06-2003	NONE	
US 5880255	A	09-03-1999	NONE	
EP 0727437	A	21-08-1996	NONE	
EP 0402070	A	12-12-1990	AT 110113 T AU 644083 B2 AU 5834890 A CA 2058441 A1 DE 69011586 D1 DE 69011586 T2 DK 402070 T3 EP 0476022 A1 EP 0561429 A1 HK 184996 A HU 58822 A2 JP 2572160 B2 JP 4502014 T KR 9604454 B1	15-09-1994 02-12-1993 07-01-1991 07-12-1990 22-09-1994 02-03-1995 12-09-1994 25-03-1992 22-09-1993 11-10-1996 30-03-1992 16-01-1997 09-04-1992 06-04-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/025052

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0402070	A		WO 9015151 A1 US 5109119 A	13-12-1990 28-04-1992
EP 1026171	A	09-08-2000	NONE	
WO 2004022630	A	18-03-2004	AU 2003270454 A1 BR 0314172 A CA 2498167 A1 EP 1546235 A2 JP 2005538224 T JP 2005350470 A MA 27401 A1 MX PA05002620 A	29-03-2004 26-07-2005 18-03-2004 29-06-2005 15-12-2005 22-12-2005 01-06-2005 05-05-2005
WO 9832466	A	30-07-1998	AT 200030 T AU 5773798 A DE 69800640 D1 DE 69800640 T2 EP 0921817 A1 JP 2001508783 T	15-04-2001 18-08-1998 03-05-2001 05-07-2001 16-06-1999 03-07-2001
EP 0400472	A	05-12-1990	AT 136315 T CA 2017543 A1 DE 69026306 D1 DE 69026306 T2 DK 400472 T3 ES 2085297 T3 GR 3019991 T3	15-04-1996 27-11-1990 09-05-1996 17-10-1996 13-05-1996 01-06-1996 31-08-1996
WO 2004060406	A	22-07-2004	AU 2003303519 A1 CA 2509248 A1 CN 1744918 A EP 1581260 A2 MX PA05007165 A	29-07-2004 22-07-2004 08-03-2006 05-10-2005 21-09-2005
WO 0187925	A	22-11-2001	AU 7485301 A CA 2408851 A1 CN 1443194 A EP 1284987 A2 JP 2004508014 T NZ 522847 A	26-11-2001 22-11-2001 17-09-2003 26-02-2003 18-03-2004 26-11-2004
EP 1303292	A	23-04-2003	AU 1674902 A JP 2004501975 T WO 0202132 A1	14-01-2002 22-01-2004 10-01-2002