(19) World Intellectual Property Organization

International Bureau



(43) International Publication Date 5 January 2006 (05.01.2006)

PCT

(10) International Publication Number WO 2006/000448 A3

(51) International Patent Classification:

C07K 14/565 (2006.01) A61K 39/395 (2006.01) C12N 15/62 (2006.01) A61K 38/21 (2006.01) C07K 19/00 (2006.01) C12N 15/22 (2006.01)

(21) International Application Number:

PCT/EP2005/006925

(22) International Filing Date: 28 June 2005 (28.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/583,389 28 June 2004 (28.06.2004)

(71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, 64293 Darmstadt (DE).

(72) Inventors; and

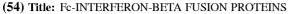
- (75) Inventors/Applicants (for US only): GILLIES, Stephen, D. [US/US]; 47 Swanson Lane, Carlisle, MA 01741 (US). WATKINS, Nigel, John [GB/GB]; 63 Cambridge Road, Girton, Cambridgeshire CB3 0PJ (GB). BAKER, Matthew, Paul [GB/GB]; The Holts, Sargents Yard, High Street, Horningsea, Cambridge CB5 9JG (GB). LO, King-Ming [US/US]; 6 Carol Lane, Lexington, MA 02420
- (74) Common Representative: MERCK PATENT GMBH; Frankfurter Strasse 250, 64293 Darmstadt (DE).

- (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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, 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, 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: 2 March 2006

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.



(57) Abstract: Disclosed are Fc-interferon-beta (Fc-IFN-β) fusion proteins and nucleic acid molecules encoding them. The Fc-IFN-β fusion proteins include variants of the interferon-beta (IFN-β) protein that are altered to achieve enhanced biological activity, prolonged circulating half-life and greater solubility. Also disclosed are methods of producing the fusion proteins and methods of using the fusion proteins and/or nucleic acid molecules for treating diseases and conditions alleviated by the administration of interferon-beta.



INTERNATIONAL SEARCH REPORT

Interactional Application No PCT/EP2005/006925

A. CLASSIFICATION OF SUBJECT MATTER C07K14/565 C12N15/62 C12N15/22

CO7K19/00

A61K39/395

A61K38/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ccc} \text{Minimum documentation searched} & \text{(classification system followed by classification symbols)} \\ & & \text{C07K} & \text{C12N} & \text{A61K} \end{array}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

	data base consulted during the international search (name of data	•	d)
EPO-In	ternal, BIOSIS, EMBASE, WPI Data,	, Sequence Search	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of t	the relevant passages	Relevant to claim No.
Y	WO 01/03737 A (BOLDER BIOTECH COX, GEORGE, N., III; DOHERTY 18 January 2001 (2001-01-18) see especially pages 42-43; the whole document		1-20
Υ	WO 00/23472 A (BIOGEN, INC; WH ADRIAN; RUNKEL, LAURA; BRICKEL MARGOT; HOCH) 27 April 2000 (2 see especially pages 47-53; the whole document	1-20	
Y	WO 00/69913 A (LEXIGEN PHARMA(CORP) 23 November 2000 (2000-: the whole document		1-20
χ Furt	ther documents are listed in the continuation of box C.	Patent family members are listed	in annex.
° Special ca	ategories of cited documents:	"T" later document published after the int	ternational filling date
consider con	ent which may throw doubts on priority claim(s) or its cited to establish the publication date of another on or other special reason (as specified) nent referring to an oral disclosure, use, exhibition or	or priority date and not in conflict wit clied to understand the principle or the invention 'X' document of particular relevance; the cannot be considered novel or cannot involve an inventive step when the document of particular relevance; the cannot be considered to involve an involve an invention to the combined with one or ments, such combination being obvi	h the application but heory underlying the claimed invention by the considered to ocument is taken alone claimed invention niventive step when the lore other such docu.
"P" docum	means ent published prior to the international filing date but han the priority date claimed	in the art. *&" document member of the same paten	•
Date of the	actual completion of the international search	Date of mailing of the international se	arch report
9	December 2005	19/12/2005	
Name and	mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Riiswiik	Authorized officer	
	Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giebeler, K	

INTERNATIONAL SEARCH REPORT



		PCT/EP2005/006925		
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT			
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	LO K-M ET AL: "High level expression and secretion of Fc-X fusion proteins in mammalian cells" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 11, no. 6, June 1998 (1998-06), pages 495-500, XP002125745 ISSN: 0269-2139 cited in the application the whole document	1-20		
A	US 4 737 462 A (MARK ET AL) 12 April 1988 (1988-04-12) cited in the application the whole document	1-20		
Α	DAY C ET AL: "ENGINEERED DISULFIDE BOND GREATLY INCREASES SPECIFIC ACTIVITY OF RECOMBINANT MURINE INTERFERON- BETA" JOURNAL OF INTERFERON RESEARCH, MARY ANN LIEBERT, INC., NEW YORK, NY, US, vol. 12, no. 2, 1 April 1992 (1992-04-01), pages 139-143, XP000647532 ISSN: 0197-8357 the whole document	1-20		
Α	WO 02/074783 A (MERCK PATENT GMBH; CARR, FRANCIS, J; CARTER, GRAHAM; JONES, TIM; WATKI) 26 September 2002 (2002-09-26) the whole document	1-20		
Α	STEWART A G ET AL: "CHEMICAL MUTAGENESIS OF HUMAN INTERFERON-BETA: CONSTRUCTION, EXPRESSION IN E. COLI, AND BIOLOGICAL ACTIVITY OF SODIUM BISULFITE-INDUCED MUTATIONS" DNA, MARY ANN LIEBERT, NEW YORK, NY, US, vol. 6, no. 2, April 1987 (1987-04), pages 119-128, XP009004161 ISSN: 0198-0238 the whole document	1-20		
A	RUNKEL LAURA ET AL: "Systematic mutational mapping of sites on human interferon-beta-1a that are important for receptor binding and functional activity" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 39, no. 10, 14 March 2000 (2000-03-14), pages 2538-2551, XP002160244 ISSN: 0006-2960 the whole document	1-20		

INTERNATIONAL SEARCH REPORT

information on patent family members

Internal Application No PCT/EP2005/006925

Patent document cited in search repo	ort	Publication date		Patent family member(s)		Publication date
WO 0103737	A	18-01-2001	AU CA EP JP NZ	782496 6102200 2379388 1200124 2003508023 517184	A A1 A1 T	04-08-2005 30-01-2001 18-01-2001 02-05-2002 04-03-2003 27-02-2004
WO 0023472	A	27-04-2000	AU BR CCN CZ EE HU JP NO NZ PL SKR	766190 1315800 9915548 2343094 1333785 20011330 5005 200100223 1121382 0200414 2002527100 PA01003790 20011861 510559 347932 5102001 200101087	A A A A A B B A A A A A A A A A A A A A	09-10-2003 08-05-2000 14-08-2001 27-04-2000 30-01-2002 12-09-2001 28-10-2004 17-06-2002 08-08-2001 29-06-2002 27-08-2002 18-09-2002 13-06-2001 19-12-2003 22-04-2002 04-03-2003 21-09-2001
WO 0069913	A	23-11-2000	AU AU BR CA CZ EP HU JP MX NO PL ZA	777963 5031800 0010725 2372400 1361793 20014123 1187852 0201474 2003530070 PA01011845 20015587 352332 200109227	A A A1 A3 A1 A2 T A A	04-11-2004 05-12-2000 19-02-2002 23-11-2000 31-07-2002 12-06-2002 20-03-2002 28-08-2002 14-10-2003 21-06-2002 16-01-2002 11-08-2003 03-02-2003
US 4737462	Α	12-04-1988	NONE			
WO 02074783	A	26-09-2002	BR CA CN HU JP MX PL US ZA	0208041 2441095 1496369 0303534 2004529633 PA03008310 362870 2005054052 200307992	A1 A2 T A A1 A1	25-02-2004 26-09-2002 12-05-2004 28-01-2004 30-09-2004 11-12-2003 02-11-2004 10-03-2005 14-01-2005