



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07K 19/00, A61K 38/20, 47/48 //</b> <b>C07K 14/54, 16/30</b></p>	<p><b>A3</b></p>	<p>(11) International Publication Number: <b>WO 99/29732</b></p> <p>(43) International Publication Date: 17 June 1999 (17.06.99)</p>
<p>(21) International Application Number: PCT/US98/25978</p> <p>(22) International Filing Date: 8 December 1998 (08.12.98)</p> <p>(30) Priority Data: 08/986,997 8 December 1997 (08.12.97) US</p> <p>(71) Applicant: LEXIGEN PHARMACEUTICALS CORPORATION [US/US]; 125 Hartwell Avenue, Lexington, MA 02173 (US).</p> <p>(72) Inventors: GILLIES, Stephen, D.; 159 Sunset Road, Carlisle, MA 01741 (US). LO, Kin-Ming; 6 Carol Lane, Lexington, MA 02173 (US). LAN, Yan; 21 Newton Street, Belmont, MA 02178 (US).</p> <p>(74) Agent: WALLER, Patrick, R., H.; Testa, Hurwitz &amp; Thibault, LLP, High Street Tower, 125 High Street, Boston, MA 02110 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 26 August 1999 (26.08.99)</p>	
<p>(54) Title: HETERODIMERIC FUSION PROTEINS USEFUL FOR TARGETED IMMUNE THERAPY AND GENERAL IMMUNE STIMULATION</p>		
<p>(57) Abstract</p> <p>Disclosed are methods for producing fusion proteins with the heterodimeric cytokine, interleukin-12. In order to insure that the proper ration of fused and non-fused subunits are obtained in the fusion protein, a specific stepwise approach to genetic engineering is used. This consists of first expressing the non-fused p40 IL-12 subunit in a production cell line, followed by or simultaneously expressing in the same cell, a second recombinant fusion protein consisting of the fused polypeptide linked by a peptide bond to the p35 subunit of IL-12. Molecules containing the p35 fusion protein cannot be secreted from the transfected mammalian cell without first complexing in a one to ratio with the p40 subunit, thus ensuring the production of active heterodimeric fusion proteins.</p>	<p>Legend: ● p35      ◐ p40 ▭ Fc      ▭▭ Fc-dimer</p> <p>●◐ Fc-p35 (NOT SECRETED) ◐◐ Fc-p40 (SECRETED) ●◐ Fc-p35/Fc-p40 (SECRETED) ●◐◐ Fc-p35/p40 (SECRETED) ◐◐◐ Fc-p40/p35 (SECRETED)</p>	

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25978

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07K19/00 A61K38/20 A61K47/48 //C07K14/54,C07K16/30

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 6 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)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>T. KIM ET AL.: "An ovalbumin-IL-12 fusion protein is more effective than ovalbumin plus free recombinant IL-12 in inducing a T helper cell type 1-dominated immune response and inhibiting antigen-specific IgE production."                      THE JOURNAL OF IMMUNOLOGY,                      vol. 158, no. 9, 1 May 1997, pages                      4137-4144, XP002106573                      Baltimore, MD, USA                      see abstract                      see figure 1                      see page 4143, left-hand column, line 7 -                      line 12</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>2,5-13,                      15,18,                      21,22</p>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

<sup>2</sup> 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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- "P" document published prior to the international filing date but later than the priority date claimed

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- "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.
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Date of the actual completion of the international search

18 June 1999

Date of mailing of the international search report

06/07/1999

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

Nooij, F

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25978

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 95 05468 A (LYNXVALE LTD.) 23 February 1995  see claims  ---	1,6-13, 18,19, 21,22
X	WO 96 18412 A (BETH ISRAEL HOSPITAL ASSOCIATION) 20 June 1996  see page 9, line 4 - line 26 see claims  ---	1,6-13, 18,19, 21,22
A	G. LIESCHKE ET AL.: "Bioactive murine and human interleukin-12 fusion proteins which retain antitumor activity in vivo." NATURE BIOTECHNOLOGY, vol. 15, no. 1, January 1997, pages 35-40, XP002106574 New York, NY, USA see abstract  ---	1-24
A	M. MARK ET AL.: "Expression and characterization of hepatocyte growth factor receptor-IgG fusion proteins." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 36, 25 December 1992, pages 26166-26171, XP002106575 Baltimore, MD, USA see abstract  ---	1-24
A	WO 92 08495 A (ABBOTT BIOTECH, INC.) 29 May 1992 see examples see claims  ---	1-24
A	WO 97 20062 A (UNIVERSITY OF MASSACHUSETTS & BETH ISRAEL HOSPITAL) 5 June 1997 see the whole document  ---	1-24
P,X	S. GILLIES ET AL.: "Antibody-IL-12 fusion proteins are effective in SCID mouse models of prostate and colon carcinoma metastases." THE JOURNAL OF IMMUNOLOGY, vol. 160, no. 12, 15 June 1998, pages 6195-6203, XP002106576 Baltimore, MD, USA see the whole document  -----	1-24

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/25978

## 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 18-20 (all partially, as far as an in vivo method is concerned) 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:

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.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/25978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505468 A	23-02-1995	NONE	
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WO 9618412 A	20-06-1996	EP 0793504 A	10-09-1997
		JP 11501506 T	09-02-1999
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WO 9208495 A	29-05-1992	AU 660297 B	22-06-1995
		AU 9059691 A	11-06-1992
		CA 2095836 A	10-05-1992
		EP 0574395 A	22-12-1993
		JP 9506761 T	08-07-1997
		US 5650150 A	22-07-1997
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WO 9720062 A	05-06-1997	AU 1407997 A	19-06-1997
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