



(51) International Patent Classification:

C07K 14/54 (2006.01) A61K 38/20 (2006.01)

(21) International Application Number:

PCT/US2019/054570

(22) International Filing Date:

03 October 2019 (03.10.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/740,813	03 October 2018 (03.10.2018)	US
62/810,038	25 February 2019 (25.02.2019)	US
62/848,512	15 May 2019 (15.05.2019)	US

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(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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: IL-12 HETERODIMERIC FC-FUSION PROTEINS

Figure 8A

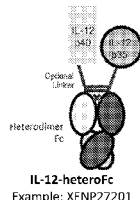


Figure 8B

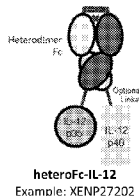


Figure 8C

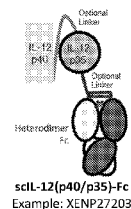


Figure 8D

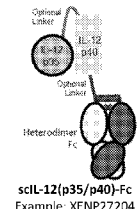


Figure 8E

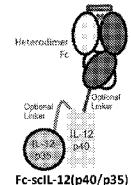
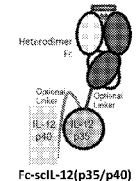


Figure 8F



(57) Abstract: The present invention provides novel IL-12 Fc fusion proteins, methods of making and using the same. The IL-12 Fc fusion proteins are useful for treatment of cancer and can be used in combination with checkpoint blockade.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:

18 June 2020 (18.06.2020)

(15) Information about Correction:

see Notice of 22 May 2020 (22.05.2020)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/054570

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/54 A61K38/20
ADD.

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 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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/030806 A1 (UNIV AJOU IND ACAD COOP FOUND) 15 February 2018 (2018-02-15) paragraphs [00164]-[00179] claims 1-17	1
X	US 2007/154453 A1 (WEBSTER GORDON D [US] ET AL) 5 July 2007 (2007-07-05) Examples and claims, [0113], [0054], [0080], [0085], [0097]	1,5, 223-237
X	WO 99/29732 A2 (LEXIGEN PHARM CORP [US]) 17 June 1999 (1999-06-17) Figure 1, Figure 2	1
X	KR 100 827 757 B1 (MERE LEXIGEN PHARM COR) 7 May 2008 (2008-05-07) Examples and claims	1
	-/-	



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 application or patent 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

16 January 2020

Date of mailing of the international search report

01/04/2020

Name and mailing address of the ISA/

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Authorized officer

Gómez Ortiz, Mariola

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/054570

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☐ forming part of the international application as filed:
- ☐ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
- ☒ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/054570

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 all searchable 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.:
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.:

2-5, 19(completely); 1, 7, 18, 20-24, 223-237(partially)

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/054570

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HÖLSCHER C: "The power of combinatorial immunology: IL-12 and IL-12-related dimeric cytokines in infectious diseases", MEDICAL MICROBIOLOGY AND IMMUNOLOGY, SPRINGER, BERLIN, DE, vol. 193, no. 1, 27 June 2003 (2003-06-27), pages 1-17, XP002411766, ISSN: 1432-1831, DOI: 10.1007/S00430-003-0186-X -----	1
A	JI-HEE HA ET AL: "Immunoglobulin Fc Heterodimer Platform Technology: From Design to Applications in Therapeutic Antibodies and Proteins", FRONTIERS IN IMMUNOLOGY, vol. 7, 6 October 2016 (2016-10-06), pages 1-16, XP055377975, DOI: 10.3389/fimmu.2016.00394 the whole document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/054570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/054570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 2-5, 19(completely); 1, 7, 18, 20-24, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains,
wherein the IL-12p40 subunit has one or more amino acids substitutions as in claim 2

2. claims: 6, 8-10(completely); 1, 7, 18, 20-24, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains,
wherein the IL-12p35 subunit is a variant

3. claims: 11-17(completely); 1, 18, 20-24, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains

4. claims: 26-31(completely); 25, 41-47, 223-237(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains,

5. claims: 32, 34-37(completely); 25, 33, 41-47, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains, wherein the subunit IL12p40 is as well modified

6. claims: 38-40(completely); 25, 33, 41-47, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a first fusion protein comprising a variant IL-12p40 subunit domain and a first Fc domain, wherein said IL-12p40 subunit domain is covalently attached to the N-terminus of said first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain and a second Fc domain, wherein said IL-12p35 subunit domain is covalently attached to the N-terminus of said Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains, wherein the IL12-p35 subunit is as well modified

7. claims: 49-52(completely); 48, 65-72, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain; and

b) a second Fc domain;

wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit,

8. claims: 53-60(completely); 48, 65-72, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain; and

b) a second Fc domain;

wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit, wherein the IL-12p40 subunit is as well modified.

9. claims: 61-64(completely); 48, 65-72, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain; and

b) a second Fc domain;

wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit, wherein the IL-12p35 subunit is as well modified

10. claims: 74-77(completely); 73, 90-96, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

domain; and
 b) a second Fc domain;
 wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit.

11. claims: 78-85(completely); 73, 90-96, 223-237(partially)

A heterodimeric Fc fusion protein comprising:
 a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain; and
 b) a second Fc domain;
 wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit, with modified IL-12p40 subunit

12. claims: 86-89(completely); 73, 90-96, 223-237(partially)

A heterodimeric Fc fusion protein comprising:
 a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is covalently attached to said second protein domain, and wherein said second protein domain is covalently attached to the N-terminus of said first Fc domain; and
 b) a second Fc domain;
 wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit, wherein the IL-12p35 subunit is modified

13. claims: 98-101, 103(completely); 97, 114-118, 223-237(partially)

A heterodimeric Fc fusion protein comprising:
 a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 b) a second Fc domain;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit.

14. claims: 104-109(completely); 97, 102, 114-118, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 - b) a second Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit, wherein the IL-12p40 is modified

15. claims: 110-113(completely); 97, 102, 114-118, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 - b) a second Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p40 subunit and said second protein domain comprises an IL-12p35 subunit, wherein the IL-12p35 is modified

16. claims: 120-123, 238(completely); 135-139, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 - b) a second Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit.

17. claims: 124-130(completely); 119, 135-139, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 - b) a second Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit, wherein the IL-12p40 subunit is modified

18. claims: 131-134(completely); 119, 135-139, 223-237(partially)

A heterodimeric Fc fusion protein comprising:

- a) a fusion protein comprising a first protein domain, a second protein domain and a first Fc domain, wherein said first protein domain is attached to the C-terminus of said first Fc domain, and wherein said second protein domain is covalently attached to said first protein domain; and
 - b) a second Fc domain;
- wherein said first and said second Fc domains comprise modifications promoting heterodimerization of said first and said second Fc domains and wherein said first protein domain comprises an IL-12p35 subunit and said second protein domain comprises an IL-12p40 subunit, wherein the IL-12p35 subunit is modified

19. claims: 146-149(completely); 140-145, 223-237(partially)

A heterodimeric complex comprising:

- a) an IL-12p40 subunit, and
 - b) an IL-12p35 subunit,
- wherein the IL-12p40 subunit is modified

20. claims: 150-157(completely); 140-145, 223-237(partially)

A heterodimeric complex comprising:

- a) an IL-12p40 subunit, and
 - b) an IL-12p35 subunit,
- wherein the IL-12p35 subunit is modified

21. claims: 158-166

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A variant IL-12p40 subunit having altered affinity for IL-12 receptor

22. claims: 167-176

A variant IL-12p35 subunit haing altered affinity for IL-12 receptor

23. claims: 178-183(completely); 177, 189-191, 223-237(partially)

A heterodimeric protein comprising:

- a) a first fusion protein comprising an IL-12p40 subunit domain covalently attached to a first Fc domain; and
 - b) a second fusion protein comprising an IL-12p35 subunit domain covalent attached to a second Fc domain;
- wherein said first and second Fc domains a set of amino acid substitutions selected from the group consisting of
 L368D/K370S and S364K; L368D/K370S and S364K/E357L;
 L368D/K370S and S364K/E357Q; T411E/K360E/Q362E and D401K;
 L368E/K370S and S364K; K370S and S364K/E357Q;
 T366S/L368A/Y407V and T366W; and T366S/L368A/Y407V/Y349C and T366W/S354C; according to EU numbering.

24. claims: 184-188(completely); 177, 189-191, 223-237(partially)

A heterodimeric protein comprising:

- a) a first Fc domain; and
 - b) a fusion protein comprising:
 - i) a second Fc domain;
 - ii) an IL-12p40 subunit domain; and
 - iii) an IL-12p35 subunit domain;
- wherein said first and second Fc domains a set of amino acid substitutions selected from the group consisting of
 L368D/K370S and S364K; L368D/K370S and S364K/E357L;
 L368D/K370S and S364K/E357Q; T411E/K360E/Q362E and D401K;
 L368E/K370S and S364K; K370S and S364K/E357Q;
 T366S/L368A/Y407V and T366W; and T366S/L368A/Y407V/Y349C and T366W/S354C; according to EU numbering.

25. claims: 192-222(completely); 223-237(partially)

Several homodimeric Fc fusion proteins with modified Fc domains, IL12p40 modified and IL12p35 modified. Probalby each of them constituting a different invention.
