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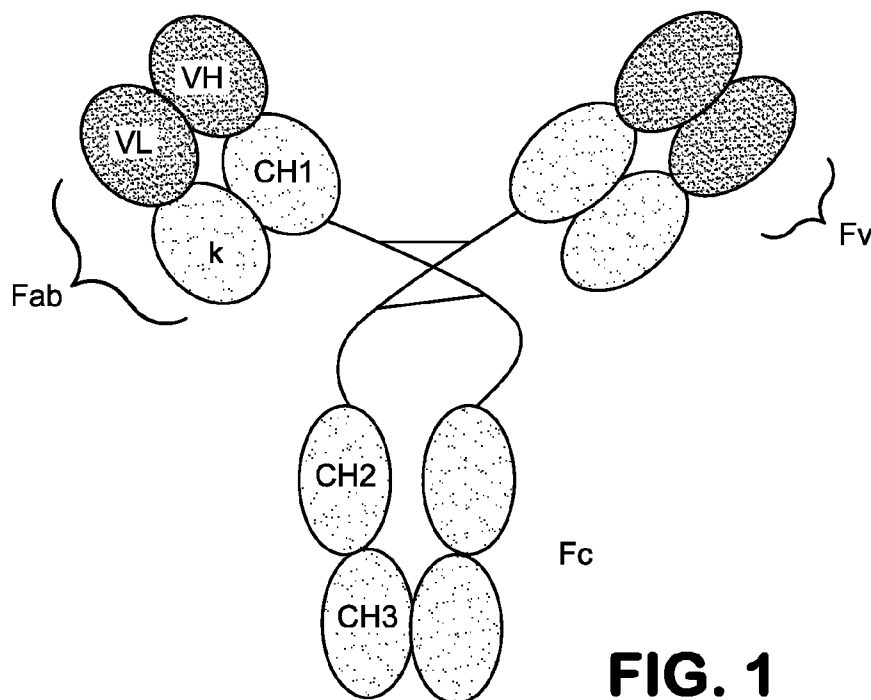
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[Continued on next page]

(54) Title: IL-17A/F IL-23 BISPECIFIC ANTIBODIES AND THEIR USES



(57) Abstract: The present invention relates to antagonizing the activity of IL-17A, IL-17F and IL-23 using bispecific antibodies that comprise a binding entity that is cross-reactive for IL-17A and IL-17F and a binding entity that binds IL-23p19. The present invention relates to novel bispecific antibody formats and methods of using the same.

FIG. 1



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— *of inventorship (Rule 4.17(iv))*

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/041928

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/24 A61K39/00 C07K16/46
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, BIOSIS, EMBASE, 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	MABRY R ET AL: "Engineering of stable bispecific antibodies targeting IL-17A and IL-23", PROTEIN ENGINEERING, DESIGN AND SELECTION, OXFORD JOURNAL, LONDON, GB, vol. 23, no. 3, March 2010 (2010-03), pages 115-127, XP002616663, ISSN: 1741-0126, DOI: 10.1093/PROTEIN/GZP073 [retrieved on 2009-12-18] the whole document ----- -/--	1,3,4, 14,60, 62-67, 110, 118-124, 167-182

☒ 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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/041928

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 2009/082624 A2 (ZYMOGENETICS INC [US]; LEWIS KATHERINE E [US]; BRENDER TY M [US]; YI E) 2 July 2009 (2009-07-02) Examples 6,13-18,20-41,claims 1-75 -----	1,3,4,6, 10,12, 14,17, 23,60, 62-67, 110, 118-124, 167-182
X	WO 2007/147019 A2 (ZYMOGENETICS INC [US]; LEWIS KATHERINE E [US]; PRESNELL SCOTT R [US];) 21 December 2007 (2007-12-21) 133-258, examples 26-27, claims 1-72 -----	1,3,4, 60, 62-67, 110, 118-124, 167-182
X	WO 2008/134659 A2 (ZYMOGENETICS INC [US]; LEWIS KATHERINE E [US]; PRESNELL SCOTT R [US];) 6 November 2008 (2008-11-06) examples 3-9, 219-273, claims 1-28 -----	1,3,4, 10,60, 62-67, 110, 118-124, 167-175
X	WO 2009/149189 A2 (ABBOTT LAB [US]; GHAYUR TARIQ [US]; ISAKSON PETER C [US]; OLSON LISA M) 10 December 2009 (2009-12-10) Page 6, line 26 - page 7, line 14; page 22, lines 5-23, page 24, line 14 -page 31, line 23, page 96, line 8-16, claims 1-76 -----	1,3,4, 7-9,19, 60, 62-67, 110, 118-124, 167-182

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041928

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.:
1, 14, 23, 62-67, 110, 118-124(completely); 3, 4, 6-10, 12, 17, 19, 60
167-182(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.

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, 14, 23, 62-67, 110, 118-124(completely); 3, 4, 6-10, 12, 17, 19, 60, 167-182(partially)

A bispecific antibody comprising :

- + an IL-17A/F binding entity, comprising two pairs of immunoglobulin chains, each pair having one light and one heavy chain, and
- + an IL-23 binding entity comprising two Fab fragments each comprising a light chain and the CHI and variable regions of a heavy chain, and the Fab fragments of the IL-23 binding entity are linked to the C-termini of the heavy chains of the IL-17A/F binding entity, or to the N-termini of the light chains and the heavy chains of the IL-17A/F binding entity.
- + eventually a peptide linker, specific variable and/or constant domain sequences, CDR sequences
- + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

2. claims: 2, 15, 21, 68-73, 111, 125-138(completely); 3, 4, 6-10, 12, 17, 19, 60, 167-182(partially)

A bispecific antibody comprising

- + an IL-23 binding entity, comprising two pairs of immunoglobulin chains, each pair having one light and one heavy chain
- + an IL-17A/F binding entity, and the IL-17A/F binding entity comprises two Fab fragments each comprising a light chain and the CHI and variable regions of a heavy chain, and the Fab fragments of the IL-17A/F binding entity are linked to the C-termini of the heavy chains of the IL-23 binding entity, or to the N-termini of the light chains and the heavy chains of the IL-23 binding entity.
- + eventually a peptide linker, specific variable and/or constant domain sequences, CDR sequences
- + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

3. claims: 5, 11, 13, 16, 18, 20, 22, 26, 74-79, 112, 139-145(completely); 6-9, 60, 167-182(partially)

A bispecific antibody comprising

- + an IL-17A/F binding entity, comprising a light chain and an IL-17A/F heavy chain, eventually defined by the sequence of its light and heavy chain
- + an IL-23 binding entity comprising a light chain and an IL-23 heavy chain, defined by the sequence of its light and heavy chain
- + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

4. claims: 24, 25, 38, 80-85, 113, 146-152(completely); 60, 167-175(partially)

A bispecific antibody comprising a combination of
 + a pair of sequence defined heavy chains defined by their sequences and
 + a pair of light chains defined by their sequences
 + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

5. claims: 27-37, 86-91, 114, 153-159, 183-185(completely); 60, 167-175(partially)

A bispecific antibody comprising
 + a first binding entity that is an antibody comprising two pairs of immunoglobulin chains; and
 + a second binding entity being a Fv unit comprising a heavy chain variable domain and a light chain variable domain;
 * the Fv unit of the second binding entity is positioned between the Fab region and the hinge region of the antibody of the first binding entity; and
 * the Fv unit of the second binding entity is linked to the Fab region of the antibody of the first binding entity.
 + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

6. claims: 39-46, 54, 98-103, 116(completely); 61, 167-175(partially)

An IL17A/F monoclonal antibody or antigen-binding fragment thereof comprising
 + a heavy chain variable domain and defined by their sequences and
 + a light chain variable domain defined by their sequences

7. claims: 47-53, 104-109, 117, 186-188(completely); 61, 167-175(partially)

An IL23p19 monoclonal antibody or antigen-binding fragment thereof comprising
 + a heavy chain variable domain and defined by their sequences and
 + a light chain variable domain defined by their sequences

8. claims: 55-59, 92-97, 115, 160-166(completely); 60, 167-175(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An isolated bispecific antibody comprising a first binding entity and a second binding entity wherein

- + the first binding entity is
 - * an antibody comprising two pairs of immunoglobulin chains
 - * a lymphocyte antigen, cytokine, cytokine receptor, growth factor, growth factor receptor, interleukin or interleukin receptor and
- + the second binding entity
 - * comprises a single domain antibody, wherein the single domain antibody of the second binding entity is positioned between the CHI region of the Fab fragment and the hinge of the first binding entity, or .
 - * is a lymphocyte antigen, cytokine, cytokine receptor, growth factor, growth factor receptor, interleukin or interleukin receptor
- + eventually a peptide linker
- + Sequences, expression vector, host cell, method of production, composition and use in a method of treatment

9. claims: 189-206

An isolated antibody or antigen-binding fragment thereof which specifically binds IL-23p19, wherein the antibody or antigen-binding fragment binds a discontinuous epitope on IL-23p19

10. claims: 207-215

An isolated IL-17A/F binding entity which specifically binds IL-17A at an epitope comprising at least amino acid residue 108 (Tyr) of SEQ ID NO:2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/041928

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