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[Continued on next page]

(54) Title: COMPOSITION OF ANTIBODY CONSTRUCT-AGONIST CONJUGATES AND METHODS OF USE THEREOF

(57) Abstract: Various antibody construct compositions are disclosed. The compositions of antibody construct-immune stimulatory compound conjugates are also provided. Additionally provided are themethods of preparation and used of the antibody construct-immune stimulatory compoundconjugates. This includes methods for treating disorders, such as cancer. A genus of STING agonist compounds and method of synthesis is also disclosed.

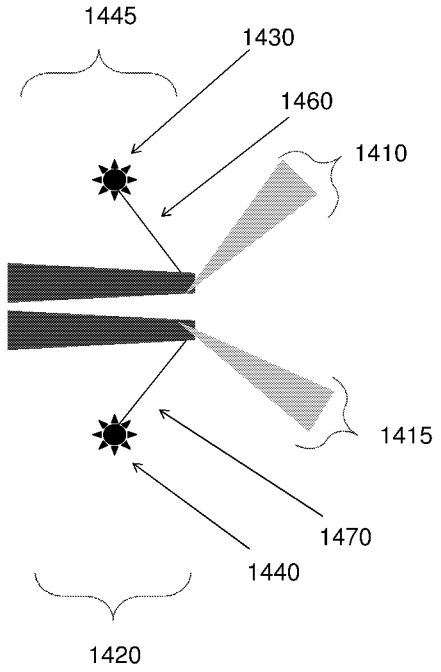

FIGURE 14

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

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
20 July 2017

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/65353

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/00, 39/39, 39/395 (2017.01)
CPC - A61K 9/0019, 31/404, 39/0011, 39/39, 39/3955, 31/7088

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/0295110 A1 (PFIZER INC.) November 7, 2013; paragraph [0255]	74-75
Y	WO 2003/040170 A2 (PFIZER PRODUCTS INC., et al.) May 15, 2003; paragraphs [0072], [0125], [0189], [0191], [0192], [0196], [0210], [0241]	1-2, 3/1-2, 4/1-2
Y	WO 1992/14842 A1 (GILEAD SCIENCES, INC.) September 3, 1992; page 35, lines 34-35; claim 57	1-2, 3/1-2, 4/1-2
A	US 2003/0211100 A1 (BEDIAN, V et al.) November 13, 2003; claim 46	76
A	US 2009/0074771 A1 (KOENIG, S et al.) March 19, 2009; abstract	76

☐ 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	Date of mailing of the international search report
20 March 2017 (20.03.2017)	31 MAY 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/65353

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.: 5-73, 83-99, 107-125
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:

-***-Please See Supplemental Page-***-

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 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.:
1-2, 3/1-2, 4/1-2, 74-76; SEQ ID NOs: 4, 15, 16

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.

-***-Continued from Box III Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-4, 74-76 and SEQ ID NOs: 4, 16 and 15 are directed toward a conjugate comprising: a) an immune-stimulatory compound; b) an antibody construct comprising an antigen binding domain and an Fc domain; and a composition comprising said antibody construct.

The antibody construct will be searched to the extent it encompasses a light chain encompassing SEQ ID NO: 4 (first exemplary light chain) and a heavy chain encompassing SEQ ID NO: 16 (first exemplary heavy chain); and binds to an Fc receptor with greater affinity than an antibody comprising a heavy chain encompassing SEQ ID NO: 15 (first exemplary comparative heavy chain). Applicant is invited to elect additional light and/or heavy chain sequence(s), with specified SEQ ID NO: for each; and/or comparative heavy chain sequence (s), with specified SEQ ID NO: for each, to be searched. Additional light and/or heavy chain sequence(s) and/or comparative heavy chain sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-4, 74, 75 (in-part) and 76 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 4 (light chain), SEQ ID NO: 16 (heavy chain), and SEQ ID NO: 15 (comparative heavy chain). Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a light chain encompassing SEQ ID NO: 26 (first exemplary elected light chain).

Group II, Claims 77-82, 100-106 and 126-152 are directed toward a compound represented by the structure of Formula (II).

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include an antibody construct, not present in Group II; the special technical features of Group II include a compound represented by the structure of Formula (II), not present in any of Groups I+.

No technical features are shared between Groups I+ and II, and, accordingly, these groups lack unity a priori. No technical features are shared between the antibody sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a conjugate comprising: a) an immune-stimulatory compound; b) an antibody construct comprising an antigen binding domain and an Fc domain, wherein said antigen binding domain binds to a first antigen and wherein a Kd for binding of said Fc domain to an Fc receptor in the presence of said immune-stimulatory compound is no greater than about 100 times a Kd for binding of said Fc domain to said Fc receptor in the absence of the immune stimulatory compound; and c) a linker, wherein said linker attaches said antibody construct to said immune-stimulatory compound; a composition comprising a light chain sequence that is at least 80% homologous to SEQ ID NO: 4 and heavy chain sequence that is at least 80% homologous to SEQ ID NO: 16.

However, these shared technical features are previously disclosed by WO 03/040170 A2 to Pfizer Products Inc. et al. (hereinafter 'Pfizer').

Pfizer discloses a conjugate (an anti-CD40 antibody linked to another molecule (a conjugate); paragraph [0196]) comprising: a) an immune-stimulatory compound (a protein including CD40L or a CD40-activating compound (an immune-stimulatory compound); paragraphs [0196], [0210], [0241]); b) an antibody construct comprising an antigen binding domain (an anti-CD40 antibody (b) an antibody construct comprising an antigen binding domain); paragraph [0196]) and an Fc domain (and a domain that binds to FcR (and an Fc domain); paragraph [0189]), wherein said antigen binding domain binds to a first antigen (wherein said antigen binding domain binds to a first antigen; abstract; paragraph [0196]) and wherein a Kd for binding of said Fc domain to an Fc receptor in the presence of said immune-stimulatory compound is no greater than about 100 times a Kd for binding of said Fc domain to said Fc receptor in the absence of the immune stimulatory compound (wherein mutations in the framework can be made to alter FcR binding (wherein a Kd for binding of said Fc domain to an Fc receptor in the presence of said immune-stimulatory compound is no greater than about 100 times a Kd for binding of said Fc domain to said Fc receptor in the absence of the immune stimulatory compound); paragraph [0189]; Pfizer is silent as to any effects of the presence of the immune-stimulatory compound on the affinity of the antibody for FcR, therefore, absent evidence to the contrary, the presence of the immune-stimulatory compound does not affect the affinity of the antibody for FcR); and c) a linker (a linker; paragraphs [0068], [0191]); a composition (a composition; abstract) comprising a light chain sequence comprising SEQ ID NO: 4 (comprising a light chain sequence comprising SEQ ID NO: 36 (comprising a light chain sequence comprising SEQ ID NO: 4); Table 8, antibody 21.2.1; paragraphs [0103], [0110]; SEQ ID NO: 36, wherein SEQ ID NO: 36 is 100% identical to Applicants' SEQ ID NO: 4) and a heavy chain sequence that is at least 80% homologous to SEQ ID NO: 16 (and a heavy chain comprising SEQ ID NO: 34 (and a heavy chain sequence that is at least 95% (80%) homologous to SEQ ID NO: 16); Table 8, antibody 21.2.1; paragraphs [0103], [0110]; SEQ ID NO: 34, wherein SEQ ID NO: 34 is 95% identical to Applicants' SEQ ID NO: 16).

Pfizer does not disclose wherein said linker attaches said antibody construct to said immune-stimulatory compound.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Pfizer to have used a linker, as disclosed by Pfizer to attach an immune-stimulatory compound, such as CD40L, or a CD40-activating compound, as disclosed by Pfizer, to an antibody to said same target, as disclosed by Pfizer, in order to enable the production of a conjugate, as disclosed by Pfizer, using a desired residue or functional group of the antibody, and, correspondingly, an appropriate functional group of the agent in order to preserve the functional activity of both the antibody and agent.

Since none of the special technical features of the Groups I+ and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Pfizer reference, unity of invention is lacking.