(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2014 (28.08.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/130879 A3

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/US2014/017810

(22) International Filing Date:
21 February 2014 (21.02.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/768,368 22 February 2013 (22.02.2013) 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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, 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))*

[Continued on next page]

(54) Title: NOVEL ANTIBODY CONJUGATES AND USES THEREOF

Biochemical Characteristics of Selected DLL3 Modulators

Clone	Bin	Domain	Affinity (nM)	Cyno XR	Mouse & Rat XR
SC16.4	F	EGF4	0.5[F]	N.D.	Yes
SC16.8	A	EGF5	0.5[F]	N.D.	Yes
SC16.10	E	EGF2	4.0[F]	N.D.	No
SC16.13	B	EGF2	2.0[B]	No[Y]	No
SC16.15	G	N-terminal	0.5[B]	Yes[B]	Yes
SC16.25	C	N-terminal	0.2[B]	Yes[B]	No
SC16.34	D	DSL	0.2[B]	Yes[B]	Yes
SC16.39	I	EGF6	1.0[F]	N.D.	Yes
SC16.46	A	EGF1	0.5[F]	No[Y]	Yes
SC16.51	H	N-terminal	2.0[F]	Yes[B]	Yes
SC16.56	D	DSL	1.0[B]	Yes[B]	Yes
SC16.65	B	EGF2	0.9[B]	No[B]	No
SC16.67	D	EGF3	0.5[F]	Yes[Y]	No

[B] Biacore; [F] ForteBio; [Y] Yeast Display

FIG. 5

(57) Abstract: Provided are novel antibody drug conjugates (ADCs), and methods of using such ADCs to treat proliferative disorders.

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— *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))*

— *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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
16 October 2014

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/17810

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28; C12P 21/08; A61K 39/00 (2014.01)
USPC - 530/391.7; 424/139.1, 178.1
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(8): C07K 16/00, 16/28, 16/30, 14/47; C12P 21/08; A61K 39/00, 47/48, 31/5517; A61P 35/00; C07D 519/00 (2014.01)
USPC: 530/391.7, 387.9, 386, 380, 350; 424/139.1, 130.1, 178.1; 540/561

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)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; ProQuest; PubMed; conjugate, antibody, pyrrolobenzodiazepine, 'DLL3,' 'SC16.3'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	WO 2011/130616 A1 (HOWARD, P et al.) October 20, 2011; abstract; page 7, lines 15-27; page 30, lines 24-30; page 50, lines 1-7; Claims 1, 63-66, 70, 71	1-5, 6/1-6/5, 7/1-7/5, 21/1-21/5, 22/1-22/5 ----- 33
Y --- A	US 2012/0328624 A1 (YOSHIDA, K et al.) December 27, 2012; abstract; paragraph [0016]	1-5, 6/1-6/5, 7/1-7/5, 21/1-21/5, 22/1-22/5 ----- 8/1-8/5, 9/1-9/5, 10/1-10/5, 27/1-27/5
Y --- A	WO 2004/035537 A2 (ALBONE, EF et al.) April 29, 2004; abstract; paragraph [0140]	6/1-6/5, 7/1-7/5 ----- 9/1-9/5
Y --- A	WO 2006/119062 A2 (LU, HS et al.) November 09, 2006; abstract; page 41, lines 1-9; page 107, Table 1	6/1-6/5, 7/1-7/5 ----- 9/1-9/5
P, X	WO 2013/126746 A2 (STULL, RA et al.) August 29, 2013; entire document	1-5, 6/1-6/5, 7/1-7/5, 8/1-8/5, 9/1-9/5, 10/1-10/5, 21/1-21/5, 22/1-22/5, 27/1-27/5, 33

☐ Further documents are listed in the continuation of Box C. ☐

* 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
18 July 2014 (18.07.2014)	11 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/17810

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.: 11-20, 28-32, 34-57
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.:
Claims 1-10, 21-27, 33, antibody-drug-conjugate ADC1, SC16.3 (anti-DLL3 antibody), SEQ ID NOs: 3 (eptiope of a DLL3 protein, Homo sapiens amino acid sequence), 21 (anti-DLL3 antibody light chain variable region, Mus musculus amino acid sequence), 23 (anti-DLL3 antibody heavy chain variable region, Mus musculus amino acid sequence), SC16.3-DL1 (the first antibody-drug-conjugate as set forth in figure 6)

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/US14/17810

-***-Continued from Box No. 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.

Group I+: Claims 1-10, 21-27 and 33 and antibody-drug-conjugate ADC1, SC16.3 (anti-DLL3 antibody), SEQ ID NOs: 3 (epitope of a DLL3 protein, Homo sapiens amino acid sequence), 21 (anti-DLL3 antibody light chain variable region, Mus musculus amino acid sequence), 23 (anti-DLL3 antibody heavy chain variable region, Mus musculus amino acid sequence) and SC16.3-DL1 (the first antibody drug conjugate as set forth in Figure 6) are directed toward a conjugate selected from the group consisting of ADC1, ADC2, ADC3, ADC4, and ADC5 wherein Ab comprises an anti-DLL3 antibody or immunoreactive fragment thereof; and a conjugate as set forth in FIG. 6.

The conjugate comprising an anti-DLL3 antibody will be searched to the extent that encompasses antibody-drug-conjugate ADC1, SC16.3 (anti-DLL3 antibody), SEQ ID NOs: 3 (epitope of a DLL3 protein, Homo sapiens amino acid sequence), 21 (anti-DLL3 antibody light chain variable region, Mus musculus amino acid sequence), 23 (anti-DLL3 antibody heavy chain variable region, Mus musculus amino acid sequence), and SC16.3-DL1 (the first antibody-drug-conjugate as set forth in Figure 6). It is believed that Claims 1 (in-part), 2-5, 6 (in-part), 7 (in-part), 8 (in-part), 9 (in part), 10 (in-part), 21 (in-part), 22 (in-part), 27 (in-part) and 33 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass antibody-drug-conjugate ADC1, SC16.3 (anti-DLL3 antibody), SEQ ID NOs: 3 (epitope of a DLL3 protein, Homo sapiens amino acid sequence), 21 (anti-DLL3 antibody light chain variable region, Mus musculus amino acid sequence), 23 (anti-DLL3 antibody heavy chain variable region, Mus musculus amino acid sequence), and SC16.3-DL1 (the first antibody drug conjugate as set forth in Figure 6). Additional chemical structures or sequences will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected chemical structures or sequences. Applicants must further indicate, if applicable, the claims which encompass this first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" groups will result in only the first claimed invention to be searched/examined. An Exemplary Election would be: antibody-drug-conjguate ADC2, SC16.4 (anti-DLL3 antibody), SEQ ID NOs: 4 (epitope of a DLL3 protein, Homo sapiens amino acid sequence), 25 (anti-DLL3 antibody light chain variable region, Mus musculus amino acid sequence), 27 (anti-DLL3 antibody heavy chain variable region, Mus musculus amino acid sequence), SC16.4-DL1 (the second antibody-drug-conjugate as set forth in Figure 6).

Groups I+ share the technical features including an antibody-drug-conjugate (ADC) comprising an anti-DLL3 antibody or immunoreactive fragment thereof, wherein the ADCs share the common significant structural elements: a pyrrolobenzodiazepine (PBD) dimer and a drug-linker compound comprising a binding moiety connecting the drug-linker to the cell binding agent, a cleavable -NH-valine-alanine-CO-moiety, and a spacer unit.

However, these shared technical features are previously disclosed by US 2013/0028919 A1 to Howard, et al. (hereinafter 'Howard') in view of US 2012/0328624 A1 to Yoshida, et al. (hereinafter 'Yoshida').

Howard discloses an antibody drug conjugate (a conjugate consisting of an antibody and a drug unit; paragraphs [0007], [0008]) comprising an antibody or immunoreactive fragment thereof (the conjugate may contain an antibody or an antigen-binding (immunoreactive) fragment of an antibody; paragraph [0008]), wherein the drug unit consists of a pyrrolobenzodiazepine dimer (formula II of the Howard reference, where R(sup)(6), R(sup)(9), R(sup)(10), R(sup)(11), R(sup)(6'), R(sup)(9'), R(sup)(10') and R(sup)(11') are selected as H, Y and Y' are selected as O, R'' is selected as propylene, and R(sup)(7) and R(sup)(7') are selected as OR, where R is selected as a methyl group, is a PBD dimer similar to compound SG2000 and matches a significant structural element of ADC1, ADC2, ADC3, ADC4 and ADC5 of the instant PCT application; paragraphs [0004], [0009]-[0014]) and a drug linker compound (a compound of formula CBA-A(sup)(1)-L(sup)(1)-L(sup)(2), where CBA is a cell binding agent (antibody), A(sup)(1) is a stretcher unit, L(sup)(1) is a specificity unit, and L(sup)(2) is a spacer unit, which attaches to the drug unit (a drug linker compound); paragraphs [0143], [0176], [0177]) comprising a binding moiety connecting the drug-linker to the cell binding agent (A(sup)(1) is a stretcher unit connecting the cell binding agent to the remainder of the drug linker; paragraphs [0177], [0288], [0298-[0302]), a cleavable -NH-valine-alanine-CO- moiety (L(sup)(1) is the site of action for cathepsin-mediated cleavage and comprises -NH-X(sub)(1)-X(sub)(2)-CO-, where X(sub)(1)-X(sub)(2) is –Val-Ala-; paragraphs [0215], [0233], [0381]) and a spacer unit (L(sup)(2) is a spacer unit which is either merely a covalent bond, a self-immolative group, or part of a self-immolative group; paragraph [0177]). Howard does not disclose an anti-DLL3 antibody. Yoshida discloses an anti-DLL3 antibody (antibodies that bind to DLL3 protein that are used in conjugates; paragraphs [0015]-[0017], [0102]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the antibody-drug-conjugate, as previously disclosed by Howard, with an antibody that binds to DLL3, as previously disclosed by Yoshida, as the previous disclosure by Howard includes the use of antibody-drug-conjugates incorporating pyrrolobenzodiazepine that have potent cytotoxic activity against cancer cells (Howard; paragraphs [0007], [0008]), Yoshida discloses the use of anti-DLL3 antibodies that can be conjugated to substances having cytotoxic activity against cancer cells (Yoshida; paragraphs [0015], [0016]), and a combination of these references would have resulted in a novel antibody-drug-conjugate for effectively targeting DLL3 and delivering a pyrrolobenzodiazepine for cancer treatment.

Since none of the special technical features of the Group I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the combination of the Howard and Yoshida references, unity of invention is lacking.

-***-Continued Within the Next Supplemental Box-***-