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[Continued on next page]

(54) Title: ANTIBODY-DRUG CONJUGATES, THEIR PREPARATION AND THEIR THERAPEUTIC USE

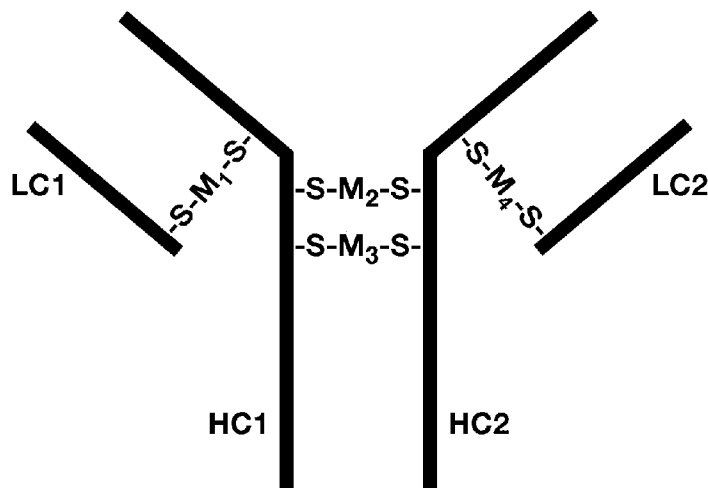


FIG. 1

(57) Abstract: The present disclosure relates to conjugates comprising biologically active molecules linked to a multimeric antigen-binding compound or a multimeric immunoglobulin via a linker. The disclosure further provides reagents and methods of manufacturing the conjugates and the linkers. The disclosure also provides compositions comprising the conjugates, methods of modifying abnormal cell growth and methods of treatment using the conjugates or the compositions.



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:

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- *as to the identity of the inventor (Rule 4.17(i))*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *of inventorship (Rule 4.17(iv))*

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25 February 2016

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K47/48 A61P35/00 A61P43/00 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) A61K 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 practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, DISSERTATION ABS, PASCAL		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/064424 A1 (POLYTHERICS LTD [GB]) 1 May 2014 (2014-05-01) examples 1-2 claims	1,2, 4-10,17, 22,26-29
X	WO 2013/190292 A2 (POLYTHERICS LTD [GB]) 27 December 2013 (2013-12-27) examples ----- -/--	1,2, 4-10,17, 22,26-29
☒ 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 7 October 2015		Date of mailing of the international search report 21/12/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Dullaart, Anwyn

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/033618

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.:

6-8(completely); 1, 2, 4, 5, 9, 10, 17, 22, 26-29(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/US2015/033618

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GEORGE BADESCU ET AL: "Bridging Disulfides for Stable and Defined Antibody Drug Conjugates", BIOCONJUGATE CHEMISTRY, vol. 25, no. 6, 3 May 2014 (2014-05-03), pages 1124-1136, XP055165403, ISSN: 1043-1802, DOI: 10.1021/bc500148x abstract page 1125 - page 1126 -----	1,2, 4-10,17, 22,26-29
X	DEL ROSARIO R B ET AL: "SULFHYDRYL SITE-SPECIFIC CROSS-LINKING AND LABELING OF MONOCLONAL ANTIBODIES BY A FLUORESCENT EQUILIBRIUM TRANSFER ALKYLATION CROSS-LINK REAGENT", BIOCONJUGATE CHEMISTRY, vol. 1, no. 1, 1990, pages 51-59, XP002313938, ISSN: 1043-1802, DOI: 10.1021/BC00001A006 abstract page 51, right-hand column page 52; figure 1 page 53 -----	1,2, 4-10,17, 22,26-29
X	WO 2013/085925 A1 (IGENICA INC [US]; JACKSON DAVID Y [US]; HA EDWARD [US]) 13 June 2013 (2013-06-13) example 7 -----	1,2, 4-10,17, 22,26-29
X	WO 2005/010151 A2 (ABGENIX INC [US]; WEBER RICHARD [US]; FENG XIAO [US]; FOORD ORIT [US];) 3 February 2005 (2005-02-03) example 10 -----	1,2, 4-10,17, 22,26-29
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/033618

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WO 2014064424 A1	01-05-2014	AU 2013336410 A1 CA 2884359 A1 CN 104755106 A EP 2911696 A1 IL 237673 A KR 20150085808 A US 2015283259 A1 WO 2014064424 A1	09-04-2015 01-05-2014 01-07-2015 02-09-2015 30-04-2015 24-07-2015 08-10-2015 01-05-2014
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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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: 6-8(completely); 1, 2, 4, 5, 9, 10, 17, 22, 26-29(partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is a maytansinoid or an auristatin; a pharmaceutical composition containing it, and a method of treatment using it.

- 1.1. claims: 6-8(completely); 1, 2, 4, 5, 10, 17, 22, 26-29(partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is a maytansinoid; a pharmaceutical composition containing it, and a method of treatment using it.

- 1.2. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is an auristatin; a pharmaceutical composition containing it, and a method of treatment using it.

2. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is a duocarmycin; a pharmaceutical composition containing it, and a method of treatment using it.

3. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is dolastatin 10; a pharmaceutical composition containing it, and a method of treatment using it.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

it.

4. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is a pyrrolobenzodiazepine; a pharmaceutical composition containing it, and a method of treatment using it.

5. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is spliceostatin; a pharmaceutical composition containing it, and a method of treatment using it.

6. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is amanatin; a pharmaceutical composition containing it, and a method of treatment using it.

7. claims: 1, 2, 4, 5, 9, 10, 17, 22, 26-29(all partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a first heavy chain of an antibody or antigen-binding portion thereof; and IC2 is a second heavy chain of the antibody or antigen-binding portion thereof, and where the drug is calicheamicin; a pharmaceutical composition containing it, and a method of treatment using it.

8. claims: 3(completely); 1, 4, 5, 9, 10, 17, 22, 26-29(partially)

Multimeric antigen-binding compound-conjugate of formula (I), wherein IC1 is a heavy chain of an antibody or antigen-binding portion thereof; and the IC2 is a light chain of the antibody or antigen-binding portion thereof; a pharmaceutical composition containing it, and a method of treatment using it.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. claims: 11-13, 18-20(completely); 22, 26-29(partially)

Multimeric immunoglobulin conjugate of figure (1), a method for its preparation, a pharmaceutical composition containing it, and a method of treatment using it.

10. claims: 14-16, 21(completely); 22, 26-29(partially)

A reagent of formula (III), a pharmaceutical composition containing it, and a method of treatment using it.

11. claim: 23

A method of reducing, retarding or stopping an abnormal cell growth comprising contacting the abnormal cell with a compound of any one of the claims 1 to 17, in an amount sufficient to retard, reduce or stop the abnormal cell growth, and wherein the abnormal cell growth is retarded, reduced or stopped.

12. claims: 24, 25

A method of killing a cell, comprising contacting the cell with a compound of any one the claims 1 to 17, in an amount sufficient to kill the cell, and wherein the cell is killed.

13. claim: 30

The use of a compound according to any one of the claims 1 to 17, for the manufacture of a medicament for the treatment of cancer.

14. claims: 31-56

An antibody-drug conjugate comprising an antibody, or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof is conjugated to at least one moiety of Formula (A)

15. claims: 57-80

A compound of Formula (L1)
