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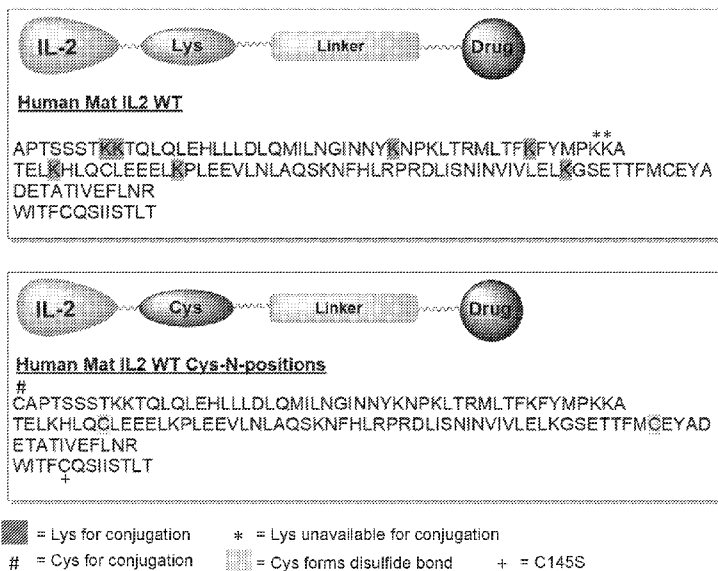


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HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

(54) Title: COMPOUNDS, COMPOSITIONS, METHODS, AND USES FOR TREATING CANCER AND IMMUNOLOGICAL DISORDERS

FIG. 1



(57) Abstract: The present disclosure provides novel polypeptide-therapeutic compound or hormone-therapeutic compound conjugates using cleavable or non-cleavable linkers, whereby the polypeptide or hormone serves to target specific cells using receptor expression on the targeted cell to bind the ligand (polypeptide or hormone) carrying the therapeutic compound unlike antibody drug conjugates. Upon binding, the ligand and the therapeutic compound (multiples of the therapeutic compound in some embodiments) enter the cell by receptor-mediated endocytosis, and release drugs conjugated to the ligand by linkers, to interact with intracellular components to enhance, restore, or block a signal transduction process. The ligands for the polypeptide-therapeutic compound or hormone-therapeutic compound conjugates include, but are not limited to: cytokines, growth factors and hormones among other proteins with corresponding cell surface specific receptors. The disorders targeted by such polypeptide-therapeutic compound or hormone-therapeutic compound



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SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
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- (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, 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))*
- *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))*
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 A61K A61P

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, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JAIN NARESHKUMAR ET AL: "Current ADC Linker Chemistry", PHARMACEUTICAL RESEARCH, SPRINGER NEW YORK LLC, US, vol. 32, no. 11, 11 March 2015 (2015-03-11), pages 3526-3540, XP035553874, ISSN: 0724-8741, DOI: 10.1007/S11095-015-1657-7 [retrieved on 2015-03-11] figures 5,6,8,9,10 ----- -/--	1-14, 20-22, 24-43, 49-51, 54-84, 87-105

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 23 October 2019	Date of mailing of the international search report 08/01/2020
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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 Villard, Anne-Laure
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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/107332 A1 (JEFFREY SCOTT [US]) 3 May 2012 (2012-05-03) paragraph [0164] pages 26-29 -----	1-6,8,9, 11-14, 20-22, 24-31, 34-43, 49-51, 54-84, 87-105
Y	T. LIST ET AL: "A Chemically Defined Trifunctional Antibody-Cytokine-Drug Conjugate with Potent Antitumor Activity", MOLECULAR CANCER THERAPEUTICS, vol. 13, no. 11, 9 September 2014 (2014-09-09), pages 2641-2652, XP055289329, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-14-0599 abstract page 2642, left-hand column, paragraph 2 figure 2C -----	24-43, 49-51, 54-84, 87-105
X	WO 2007/092213 A2 (MILLENNIUM PHARM INC [US]; LANGSTON STEVEN P [US] ET AL.) 16 August 2007 (2007-08-16)	1,4,6,7, 11-14, 104
Y	page 39; compounds I-13 page 46; compounds I-64 page 49; compounds I-80,I-83 -----	1-14, 20-22, 24-43, 49-51, 54-84, 87-105
Y	EP 3 103 802 A1 (TAIHO PHARMACEUTICAL CO LTD [JP]) 14 December 2016 (2016-12-14) paragraph [0004] page 84; example 55 page 85; example 64 -----	1-14, 20-22, 24-43, 49-51, 54-84, 87-105
Y	PENG LU ET AL: "Discovery of a novel NEDD8 Activating Enzyme Inhibitor with Piperidin-4-amine Scaffold by Structure-Based Virtual Screening", ACS CHEMICAL BIOLOGY, vol. 11, no. 7, 6 May 2016 (2016-05-06), pages 1901-1907, XP055634745, ISSN: 1554-8929, DOI: 10.1021/acscchembio.6b00159 abstract -----	1-13,20, 24-42, 49, 54-84, 87-96, 99, 101-103
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/041486

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEUNG CHUNG-HANG ET AL: "A natural product-like inhibitor of NEDD8-activating enzyme", CHEMICAL COMMUNICATIONS, R S C PUBLICATIONS, GB, vol. 47, no. 9, 7 March 2011 (2011-03-07), pages 2511-2513, XP002784514, ISSN: 1364-548X abstract	1-13,20, 24-42, 49, 54-84, 87-96, 99, 101-103
Y	HAI-JING ZHONG ET AL: "Structure-based repurposing of FDA-approved drugs as inhibitors of NEDD8-activating enzyme", BIOCHIMIE, vol. 102, 1 July 2014 (2014-07-01), pages 211-215, XP055634756, FR ISSN: 0300-9084, DOI: 10.1016/j.biochi.2014.03.005 abstract; figure 1	1-13,20, 24-42, 49, 54-84, 87-96, 99, 101-103
Y	HAO MA ET AL: "Discovery of benzothiazole derivatives as novel non-sulfamide NEDD8 activating enzyme inhibitors by target-based virtual screening", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 133, 1 June 2017 (2017-06-01), pages 174-183, XP055634779, AMSTERDAM, NL ISSN: 0223-5234, DOI: 10.1016/j.ejmech.2017.03.076 abstract compound 7g	1-13,20, 24-42, 49, 54-84, 87-96, 99, 101-103
Y	HAI-JING ZHONG ET AL: "Discovery of deoxyvasicinone derivatives as inhibitors of NEDD8-activating enzyme", METHODS, vol. 71, 1 January 2015 (2015-01-01), pages 71-76, XP055634786, NL ISSN: 1046-2023, DOI: 10.1016/j.ymeth.2014.08.014 figures 1b,3	1-13,20, 24-42, 49, 54-84, 87-96, 99, 101-103
Y	WO 03/015697 A2 (UNIV SOUTHERN CALIFORNIA [US]; EPSTEIN ALAN L [US]; HU PEISHENG [US]) 27 February 2003 (2003-02-27) paragraphs [0043], [0047]	24-43, 49-51, 54-84, 87-105
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/041486

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 319 012 A2 (DU PONT [US]) 7 June 1989 (1989-06-07) claims 21,29 -----	24-43, 49-51, 54-84, 87-105
X,P	WO 2018/218119 A1 (UNIV LELAND STANFORD JUNIOR [US]) 29 November 2018 (2018-11-29) claims -----	1-14, 20-22, 24-43, 49-51, 54-84, 87-105

INTERNATIONAL SEARCH REPORT

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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.:
14, 21, 22, 43, 50, 51, 97, 98, 100, 104, 105(completely); 1-13, 20, 24-42
49, 54-84, 87-96, 99, 101-103(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: 14, 21, 22, 43, 50, 51, 97, 98, 100, 104, 105(completely); 1-13, 20, 24-42, 49, 54-84, 87-96, 99, 101-103(partially)

A compound of formula (I) wherein a therapeutic agent X3 is linked to a linker X2a and wherein X3 is a neddylation inhibitor and is selected from pevonedistat, TAS1, TAS2, TAK7243, piperacillin, M22, 6,6'-Biapigenin, ABPA3, Benzothiazole of claim 13, Deoxyvasicinone on page 203 of claim 13, TAS4464;

A conjugate thereof of formula (II) with a biologically active polypeptide or hormone;

A conjugate thereof of formula (III) with an IL-2 polypeptide or a bioactive homologue polypeptide of IL-2;

Pharmaceutical composition comprising such conjugates;

Said conjugates for use in the treatment of an immunological disorder or cancer.

2. claims: 1-13, 20, 24-42, 49, 54-84, 87-96, 99, 101-103(all partially)

A compound of formula (I) wherein a therapeutic agent X3 is linked to a linker X2a and wherein X3 is selected from an immunomodulating agent selected from thienopyridine of claim 13; imidazopyrimidine of claim 13; largazole; Pyr-41; phorbol-12 myristate 13-acetate, 2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one; Ofloxacin; Panepophenanthin; Himeic Acid A; Hyrtioreticulins A; Phytol; Coumarin A, Coumarin B; Deoxyvasicinone derivative on page 294 of claim 13; imidazolium-quinaxoline on page 294 of claim 13;

A conjugate thereof of formula (II) with a biologically active polypeptide or hormone;

A conjugate thereof of formula (III) with an IL-2 polypeptide or a bioactive homologue polypeptide of IL-2;

Pharmaceutical composition comprising such conjugates;

Said conjugates for use in the treatment of an immunological disorder or cancer.

3. claims: 17, 46(completely); 1-10, 15, 16, 18, 20, 24-39, 44, 45, 47, 52, 54-84, 87-96, 99, 101-103(partially)

A compound of formula (I) wherein a therapeutic agent X3 is linked to a linker X2a and wherein X3 is a chemotherapeutic agent selected from the classes of compounds claim 17 or docetaxel, etoposide, gemcitabine, vinblastine, paclitaxel, irinotecan, fluorouracil, methotrexate, carboplatin, oxaliplatin, cisplatin, doxorubicin.HCl, fulvestrant, isotretinoid, buserelin, evrolimus, carfilzomib, rifabutin, clindamycin, tubulysin A, indibulin, gefitinib, dasatinib;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A conjugate thereof of formula (II) with a biologically active polypeptide or hormone;
A conjugate thereof of formula (III) with an IL-2 polypeptide or a bioactive homologue polypeptide of IL-2;
Pharmaceutical composition comprising such conjugates;
Said conjugates for use in the treatment of an immunological disorder or cancer.

4. claims: 19, 23, 48, 53(completely); 1-10, 15, 16, 18, 20, 24-39, 44, 45, 47, 52, 54-84, 87-96, 99, 101-103(partially)

A compound of formula (I) wherein a therapeutic agent X3 is linked to a linker X2a and wherein X3 is the chemotherapeutic agent MMAE;
A conjugate thereof of formula (II) with a biologically active polypeptide or hormone;
A conjugate thereof of formula (III) with an IL-2 polypeptide or a bioactive homologue polypeptide of IL2;
Pharmaceutical composition comprising such conjugates;
Said conjugates for use in the treatment of an immunological disorder or cancer.

5. claims: 85, 86

IL2-polypeptide or a bio-active homologue polypeptide thereof comprising an amino acid sequence of table 4, or seq ID NO:1 or SEQ ID NO:2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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