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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 January 2016 (28.01.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/014839 A3

(51) International Patent Classification:
C07K 16/28 (2006.01) *G01N 33/574* (2006.01)
A61K 49/00 (2006.01)

(21) International Application Number:
PCT/US2015/041809

(22) International Filing Date:
23 July 2015 (23.07.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/028,003 23 July 2014 (23.07.2014) 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, 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, 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).

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:
10 March 2016

(54) Title: METHODS AND COMPOSITIONS RELATED TO ANTIBODY FRAGMENTS THAT BIND TO TUMOR-ASSOCIATED GLYCOPROTEIN 72 (TAG-72)

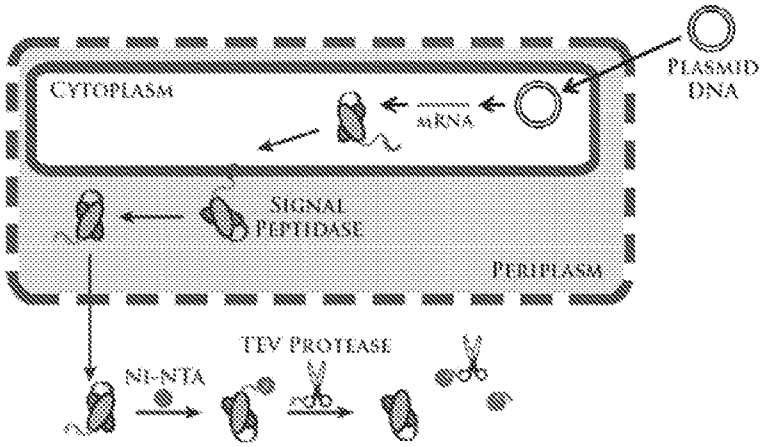

FIG.1

(57) Abstract: Disclosed herein are methods and compositions related to antibody fragments which specifically bind sialyl-Tn epitope of tumor-associated glycoprotein 72 (TAG-72).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/41809

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28; A61K 49/00; G01N 33/574 (2015.01)
CPC - A61K 51/1045; C07K 16/468, 16/30
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 16/28; A61K 49/00, 16/46; G01N 33/574; A61K 51/00 (2015.01)
CPC: A61K 51/1045; C07K 16/468, 16/30, 2317/31, 2317/55, 2319/00

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data), NCBI Blast, Lens.Org, PubMed, Google Scholar; 'TAG-72', 'sialyl', antibod*, fragment*, bind*, tumor*, cancer*, tissu*, administer*, antigen*, vector*, diabod*, therapeutic*, imag*, cell*, treat*, bind*, blood*, prob*, 'Ohio State Innovation Foundation', 'Thomas Magliery', 'Brandon Sullivan', 'Nicholas Long'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	US 2007/0244032 A1 (KIM, Y et al.) October 18, 2007; abstract; paragraphs [0001], [0012], [0032], [0038], [0039], [0041], [0043], [0044], [0054], [0061]-[0063], [0073]; Claim 10.	1, 7, 12, 14, 15, 22-24, 31 ----- 2,3, 6, 13, 16, 17-21, 25-30, 32-38 ----- 4, 8-11
Y	CHENG, K. 99mTc-Hydrazinonicotinamide-anti-TAG-72 CC49 Divalent Single Chain Fv Monoclonal Antibody. Molecular Imaging and Contrast Agent Database. 19 June 2007, pages 1-5; page 1, last paragraph; page 2, first paragraph; page 3, third paragraph.	2, 3, 6
Y	US 2010/0183504 A1 (CHEN, FF) July 22, 2010; paragraphs [0022], [0029], [0031], [0035], [0036], [0069], [0070]-[0072], [0074], [0123], [0124], [0135], [0136], [0174], [0192], [0199], [0202], [0203], [0206], [0229], [0235], [0302], [0305], [0306]; Claims 41, 51.	13, 17-21, 25-30, 34, 36,38
Y	US 2008/0279847 A1 (HONG, HJ et al.) November 13, 2008; paragraphs [0049], [0088]-[0090], [0102], [0112].	6, 16, 32-36, 38
Y	US 2011/0159525 A1 (KASHMIRI, S et al.) June 30, 2011; paragraphs [0138], [0139].	37
A	JULIEN, S. et al. Sialyl-Tn In Cancer: (How) Did We Miss The Target? Biomolecules. 2012, Vol. 2, pages 435-466; abstract, page 451, second paragraph. DOI: 10.3390/biom2040435.	2
A	WO 2005/121180 A1 (HONG, HJ et al.) December 22, 2005; paragraph [0124]; Claims 1, 3	5

☐ 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
04 January 2016 (04.01.2016)	12 JAN 2016
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

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/41809

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:

-***-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.:

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

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.:

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
Information on patent family members

International application No.
PCT/US15/41809

-***-Continued from Box No. III: Observations Where Unity of Invention Is Lacking:

Groups I+: Claims 1-38 are directed toward an antibody fragment which specifically binds tumor-associated glycoprotein 72 (TAG-72); a nucleic acid encoding the antibody; a vector comprising the nucleic acid; a cell that produces the antibody; compositions comprising the antibody; and methods of using the antibodies.

The antibody fragment will be searched to the extent that it encompasses SEQ ID NOs: 10 (VH domain amino acid sequence), 11 (VL domain amino acid sequence), 12 (3E8HL(GGGGS)his6.diabody DNA sequence), 13 (3E8HL(GGGGS)his6.diabody amino acid sequence). It is believed that Claims 1-3, 4 (in-part), 5, 6, 7 (in-part), 8, 9 (in-part) and 10-36 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 10 (VH domain amino acid sequence), 11 (VL domain amino acid sequence), 12 (3E8HL(GGGGS)his6.diabody DNA sequence), 13 (3E8HL(GGGGS)his6.diabody amino acid sequence). Applicant is invited to elect additional antibody fragment(s) with specified SEQ ID NO: for each, and accompanying encoding nucleic acid(s) with specified SEQ ID NO: for each, to be searched. Additional antibody fragment and encoding nucleic acid sequences will be searched upon the payment of additional fees. 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 lection would be: SEQ ID NOs: 14 (3E8LH(GGGGS)4.scFv DNA sequence), 15 (3E8LH(GGGGS)4.scFv amino acid sequence).

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

Groups I+ share the technical features including: an antibody fragment which specifically binds tumor-associated glycoprotein 72 (TAG-72); an isolated amino acid sequence comprising 90% identity to SEQ ID NO: 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, or 45; a nucleic acid encoding the antibody for expression; a vector comprising the nucleic acid; a cell that produces the antibody; a composition comprising the antibody and a pharmaceutically acceptable carrier; a composition suitable for the treatment of cancer comprising a therapeutically effective amount of the antibody fragment; a composition for the in vivo or in vitro detection of cancer comprising a diagnostically effective amount of an antibody fragment; a method for in vivo treatment of a mammal having a TAG-72-expressing cancer comprising a step of administering to the mammal a therapeutically effective amount of a composition; a method for in vitro immunodetection of TAG-72-expressing cancer cells comprising a step of contacting the cancer cells with a composition; a method of in vivo immunodetection of TAG-72-expressing cancer cells in a mammal comprising a step of administering to the mammal a diagnostically effective amount of a composition; a method of in vivo treatment of cancer comprising the steps of: (a) intravenously administering a radionuclide-labeled antibody fragment; (b) detecting tumor cells using a radionuclide activity probe: and (c) removing the detected tumor cells by surgical excision; a kit comprising the antibody fragment and instructions for use; a method of making an antibody fragment, comprising: (a) culturing the isolated cell under conditions such that said antibody fragment is expressed: and (b) recovering said antibody fragment from the cell; and a method of treating cancer comprising administering to a subject in need thereof a composition, wherein the effector moiety is a chemotherapeutic agent.

However, these shared technical features are previously disclosed by US 2007/0244032 A1 to Kim, et al. (hereinafter 'Kim') in view of US 2008/0279847 A1 to Hong, et al. (hereinafter 'Hong').

Kim discloses an antibody fragment (a single-chain antibody (an antibody fragment); abstract) which specifically binds tumor-associated glycoprotein 72 (TAG-72) (which specifically binds tumor-associated glycoprotein 72 (TAG-72); abstract); an isolated amino acid sequence comprising 84.2% identity to SEQ ID NO: 13 (a fusion polypeptide having the amino acid sequence of SEQ ID NO: 11 (an isolated amino acid sequence comprising 84.2% identity to SEQ ID NO: 13); paragraph [0035], SEQ ID NO: 11, wherein SEQ ID NO: 11 is 84.2% identical to Applicants' SEQ ID NO: 13); a nucleic acid encoding the antibody (a nucleic acid encoding the antibody; paragraph [0035]) for expression (for expression; paragraph [0001]); a vector comprising the nucleic acid (a vector comprising the nucleic acid; paragraphs [0001], [0035]); a cell that produces the antibody (a cell that produces the antibody; paragraph [0001]); a composition comprising the antibody and a pharmaceutically acceptable carrier (a composition comprising the antibody and a pharmaceutically acceptable carrier; paragraph [0041]); a composition suitable for the treatment of cancer comprising a therapeutically effective amount of the antibody fragment (an anti-cancer agent composition comprising the chimeric ligd as an effective ingredient (a composition suitable for the treatment of cancer comprising a therapeutically effective amount of the antibody fragment; Claim 10); a method of making an antibody fragment (a method of producing an antibody fragment fusion protein (a method of making an antibody fragment (a method of producing an antibody fragment fusion protein (a method of making an antibody fragment); paragraph [0060]), comprising: (a) culturing the isolated cell under conditions such that said antibody fragment is expressed (culturing cells expressing the antibody fragment fusion ((a) culturing the isolated cell under conditions such that said antibody fragment is expressed); paragraph [0060]): and (b) recovering said antibody fragment from the cell (and recovering the antibody fusion protein from the culture medium ((b) recovering said antibody fragment from the cell); paragraph [0060]). Kim further discloses immunohistochemical analyses of the expression of TAG-72 in human cancer cell lines (immunohistochemical analyses of the expression of TAG-72 in human cancer cell lines; paragraph [0023]); wherein the fusion protein includes a linker comprising 5 amino acids of Gly4Ser (wherein the fusion protein includes a linker comprising 5 amino acids of Gly4Ser; paragraph [0035]), and a linker comprising 15 amino acids of (Gly4Ser)3 (a linker comprising 15 amino acids of (Gly4Ser)3; paragraph [0051]).

Kim does not disclose an isolated amino acid sequence comprising 90% identity to SEQ ID NO: 13; a composition for the in vivo or in vitro detection of cancer comprising a diagnostically effective amount of an antibody fragment; a method for in vivo treatment of a mammal having a TAG-72-expressing cancer comprising a step of administering to the mammal a therapeutically effective amount of a composition; a method for in vitro immunodetection of TAG-72-expressing cancer cells comprising a step of contacting the cancer cells with a composition; a method of in vivo immunodetection of TAG-72-expressing cancer cells in a mammal comprising a step of administering to the mammal a diagnostically effective amount of a composition; a method of in vivo treatment of cancer comprising the steps of: (a) intravenously administering a radionuclide-labeled antibody fragment; (b) detecting tumor cells using a radionuclide activity probe: and (c) removing the detected tumor cells by surgical excision; a kit comprising the antibody fragment and instructions for use; a method of treating cancer comprising administering to a subject in need thereof a composition, wherein the effector moiety is a chemotherapeutic agent.

-***-Continued Within the Next Supplemental Page:

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Hong discloses humanized anti-TAG72 monoclonal antibodies (humanized anti-TAG72 monoclonal antibodies; abstract); comprising a single-chain antibody (comprising a single-chain antibody; paragraph [0049]) comprising a heavy chain variable region and light chain variable region (comprising a heavy chain variable region and light chain variable region; paragraph [0049]) that are linked to each other by a peptide linker (that are linked to each other by a peptide linker; paragraph [0049]); wherein the heavy chain variable region comprises SEQ ID NO: 4 (wherein the heavy chain variable region comprises SEQ ID NO: 4; paragraph [0042]) and a light chain variable region comprising SEQ ID NO: 21 (and a light chain variable region comprising SEQ ID NO: 21; paragraph [0042]); a composition (a composition; paragraph [0078]) for the in vivo or in vitro detection of cancer comprising a diagnostically effective amount of an antibody fragment (for the in vitro or in vivo detection and diagnosis of cancer, comprising the antibody (comprising a diagnostically effective amount of an antibody fragment); paragraphs [0080], [0081]); a method for in vivo treatment of a mammal having a TAG-72-expressing cancer (a method of treating cancer in a human, where the cancer expresses TAG-72 (a method for in vivo treatment of a mammal having a TAG-72-expressing cancer); paragraphs [0002], [0016]) comprising a step of administering to the mammal a therapeutically effective amount of a composition (comprising a step of administering to the mammal a therapeutically effective amount of a composition comprising the antibody; paragraphs [0016], [0084]); a method for in vitro immunodetection (a method for immunohistochemical detection (in vitro detection); paragraph [0080]) of TAG-72-expressing cancer cells (of TAG-72-expressing cancer cells; paragraphs [0002], [0080]) comprising a step of contacting the cancer cells with a composition (comprising contacting the cells with a composition comprising an antbody that binds to TAG-72 (comprising a step of contacting the cancer cells with a composition); paragraphs [0078], [0080]); a method of in vivo immunodetection (a method of in vivo immunodetection; paragraph [0081]) of TAG-72-expressing cancer cells (of TAG-72-expressing cancer cells; paragraphs [0002], [0081]) in a mammal (in a patient (mammal); paragraph [0081]) comprising a step of administering to the mammal a diagnostically effective amount of a composition (comprising administering to the patient (mammal) a composition comprising antibodies conjugated to a detectable imaging marker (comprising a step of administering to the mammal a diagnostically effective amount of a composition); paragraph [0081]); a method of in vivo treatment of cancer (a method of in vivo treatment of cancer; paragraph [0016]) comprising the steps of: (a) intravenously administering (intravenously administering; paragraphs [0081], [0093]) a radionuclide-labeled (a radionuclide-labeled; paragraphs [0081], [0083]) antibody fragment (antibody fragment; paragraph [0081]); (b) detecting tumor cells using a radionuclide activity probe (and detecting tumor cells using an imaging detector for the radioactivity (detecting tumor cells using a radionuclide activity probe); paragraphs [0002], [0081]-[0083]); a method of treating cancer (a method of treating cancer; paragraph [0016]) comprising administering to a subject in need thereof a composition (comprising administering to a subject in need thereof a composition; paragraphs [0016], [0084]), wherein the effector moiety is a chemotherapeutic agent (including an antibody linked to a chemotherapeutic agent; paragraphs [0088], [0089]). Hong further discloses wherein the imaging agent is present in an amount to enable effectively visualizing tumor sites distinct from normal tissues (wherein the imaging agent is present in an amount to enable effectively visualizing tumor sites distinct from normal tissues; paragraph [0081]).

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Kim, for utilizing any number of Gly4Ser repeats in the antibody fragment, as previously disclosed by Kim, such as a single Gly4Ser linker sequence, as disclosed by Kim. Additionally, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previously disclosure of Kim, for providing the single-chain antibodies as a non-fused, isolated antibody fragment; and to have provided said fragment in a kit with instructions for use, such as immunohistochemical detection of TAG-72 on cancer cell lines, or on samples from a subject, as previously disclosed by Kim. Furthermore, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Kim, for utilizing light and heavy chain variable sequences, as previously disclosed by Hong, with a linker sequence comprising Gly4Ser, as disclosed by Kim, for producing a single-chain antibody fragment, as disclosed by Hong, wherein the sequence of said fragment comprises 90.7% identity to SEQ ID NO: 13 of the instant PCT application, based on SEQ ID NOs: 4 and 21, as disclosed by Hong, joined by a linker comprising Gly4Ser, as disclosed by Kim. Also, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the disclosure of Kim, for providing methods of in vitro and in vivo detection of cancer cells for detecting and diagnosing cancer utilziing a radioactive label and probe detector, as disclosed by Hong, and treatment of cancer, including administration of an antibody fragment linked to a chemotherapeutic agent, as disclosed by Hong, for providing an effective means of diagnosing and treating a cancer; or by imaging a cancer in such a manner as to enable distinguishing tumor cells from normal cells, as disclosed by Hong, for enabling a surgeon to remove the tumor cells as an effective method of treatment.

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