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(54) Title: ANTIBODY LOCKER FOR THE INACTIVATION OF PROTEIN DRUG

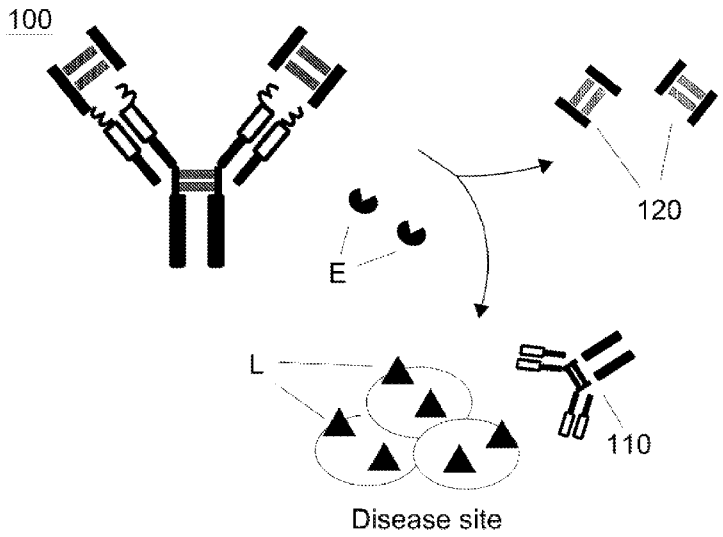


FIG. 2

(57) Abstract: Disclosed herein is a hinge antibody capable of being selectively activated in a target cell or tissue to treat a condition therein. The hinge antibody includes a functional antibody, two inhibitory domains and four cleavable linkers. The functional antibody is capable of treating the condition in an activated state, and has two light chains and two heavy chains. Each inhibitory domain includes a hinge domain of an immunoglobulin and consists of two peptide arms. Each cleavable linker includes a peptide substrate cleavable by an enzyme specifically or highly expressed in the target cell or tissue, and connects one of the peptide arms of the inhibitory domains to the N-terminal of one of the light chains and heavy chains of the functional antibody. Also disclosed herein are methods for preparing and using this hinge antibody.

WO 2014/193973 A3

— *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:
19 February 2015

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/39821

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395, A61K 39/00, C12P 21/08 (2014.01)
CPC - A61K 2039/505, A61K 38/00
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) - A61K 39/395, A61K 39/00, C12P 21/08 (2014.01)
CPC - A61K 2039/505, A61K 38/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/133.1, 424/134.1, 530/387.3, 530/391.7, 435/320.1, 435/69.7, 536/23.4

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST; PatBase; Google Scholar
search terms - Activatable antibody, Activatable antibodies, antibody hinge, cleavable linker, inhibitory domains, inhib*, mask, masking, domain, igg, igg1, iga, immunoglobul*, selectiv$, activ$, cleav*, linker, hinge, locker, tnf, RANKL, two, 2, more than, multip$, coupl$, pair,

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 2012/0244154 A1 (DAUGHERTY et al.) 27 September 2012 (27.09.2012) para [0008]; [0009]; [0017]; [0021]; [0030]-[0033]; [0122]; [0147]-[0149]; [0180]-[0181]; [0293]; Table 1.	1, 2, 8, (23-24)/(1,2,8) --- 3-7, 9, (23-24)/(3-7,9) --- 10, (23-24)/10
Y	US 2011/0287009 A1 (SCHEER et al.) 24 November 2011 (24.11.2011) para [0012]; [0047]; [0050]; [0104]; [0149]; [0183]; [0205].	4-7, (23-24)/(4-7)
Y --- A	US 2010/0248279 A1 (YAMAUCHI et al.) 30 September 2010 (30.09.2010) claims 21-23; SEQ ID NO: 1.	9, (23-24)/9 --- 10, (23-24)/10
Y	US 2010/0029497 A1 (HIMMLER et al.) 04 February 2010 (04.02.2010) para [0335]-[0340]; SEQ ID NO: 44.	3, (23-24)/3
Y --- A	US 2006/0018903 A1 (HELLENDOORN et al.) 26 January 2006 (26.01.2006) para [0024]; [0042]; SEQ ID NO: 161.	3, (23-24)/3 --- 10, (23-24)/10

☒ 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
04 December 2014 (04.12.2014)	17 DEC 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: Lee W. Young 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/US 14/39821

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:
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, 23 and 24, directed to a hinge antibody capable of being selectively activated in a target cell or tissue to treat a condition therein.
Group II, claims 11-22, directed to an expression system for producing a hinge antibody capable of being selectively activated in a target cell or tissue to treat a condition therein.

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:

--continued on first extra sheet attached hereto--

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.:
1-10, 23, 24

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/US 14/39821

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2013/0011394 A1 (KNOETGEN) 10 January 2013 (10:01.2013) para [0016]; [0082]; [0255]; SEQ ID NO: 24.	7, (23-24)/7 --- 10, (23-24)/10
A	US 2008/0292628 A1 (HUI) 27 November 2008 (27.11.2008) para [0004]-[0006]; SEQ ID NO: 14.	10, (23-24)/10

continuation of Box No. III:

Special technical features
Group I includes the special technical feature of a hinge antibody comprising two light chains and two heavy chains and four cleavable linkers, wherein each cleavable linker connects one of the two peptide arms of the two inhibitory domains to the N-terminals of one of the two light chains and two heavy chains of the functional antibody, which is not required by Group II.
Group II includes the special technical feature of an expression system for producing a hinge antibody comprising, a first nucleic acid sequence, comprising, from 5' to 3', a first inhibitory domain-encoding region encoding a first peptide arm of an inhibitory domain of the hinge antibody, wherein the inhibitory domain comprises a hinge domain of an immunoglobulin, or a fragment of the hinge domain, a first cleavable linker-encoding region encoding a cleavable linker of the hinge antibody, and a light chain-encoding region encoding a light chain of a functional antibody of the hinge antibody; and
a second nucleic acid sequence, comprising, from 5' to 3', a second inhibitory domain-encoding region encoding a second peptide arm of the inhibitory domain of the hinge antibody, a second cleavable linker-encoding region encoding the cleavable linker of the hinge antibody, and a heavy chain-encoding region encoding a heavy chain of the functional antibody of the hinge antibody, which is not required by Group I.

Common technical features:
Group I.(a hinge antibody) is related to Group II (an expression system for producing a hinge antibody), and share the common technical feature of a hinge antibody capable of being selectively activated in a target cell or tissue to treat a condition therein comprising a functional antibody capable of treating the condition in an activated state, comprising at least one light chain and at least one heavy chain; two inhibitory domains, and at least two cleavable linkers, wherein each cleavable linker comprises a peptide substrate cleavable by an enzyme that is specifically or highly expressed in the target cell or tissue, and a method for treating cancer or an autoimmune disease in a subject, comprising administering to the subject a therapeutically effective amount of the hinge antibody. However, these shared technical features do not represent a contribution over prior art, because these shared technical features are obviated by US 2011/0287009 A1 to Scheer et al., (hereinafter Scheer), in view of US 2012/0244154 A1 to Daugherty et al., (hereinafter Daugherty).

Scheer teaches a hinge antibody to treat a condition therein comprising a functional antibody capable of treating the condition in an activated state (para [0104], [0205]), comprising at least one light chain and at least one heavy chain (para [0029]); two inhibitory domains (para [0149] "The heteromultimer can comprise a "heterodimer" formed by the first and second hinge-containing polypeptides or can form higher order tertiary structures where polypeptides in addition to the first and second hinge-containing polypeptides are present"; [0151]; Note that para [0012] of the present application describes that each of the two inhibitory domains is a hinge domain of an immunoglobulin), and at least two cleavable linkers (para [0347] "an antibody is conjugated to one or more moieties (for example, drug moieties), e.g., about 1 to about 20 moieties per antibody, optionally through a linker"; each conjugation can have a linker; [0194] cleavable), wherein each cleavable linker comprises a peptide substrate cleavable by an enzyme that is specifically or highly expressed in the target cell or tissue (para [0349] 'Amino acid linker components can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzymes, for example, a tumor-associated protease, cathepsin B, C and D, or a plasmin protease').

Scheer does not specifically teach the antibody is capable of being selectively activated in a target cell or tissue.
Daugherty teaches an antibody capable of being selectively activated in a target cell or tissue (para [0006]). Since Daugherty teaches a cleavable moiety required for activation "may be selected based on a protease that is co-localized in tissue with the desired target of the TBM of the ABP. A variety of different conditions are known in which a target of interest is co-localized with a protease, where the substrate of the protease is known in the art. For example, the target tissue can be a cancerous tissue, particularly cancerous tissue of a solid tumor" (para [0180]), it would have been obvious to one of ordinary skill in the art to have incorporated the masking moiety elements taught by Daugherty for selective activation upon cleavage, into the antibodies taught by Scheer, in order to make the antibodies capable of being selectively activated in a target cancer cell upon cleavage by an enzyme that is specifically or highly expressed in the target cancer cells. As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

A further feature shared by Groups I and II is a method for treating cancer or an autoimmune disease in a subject, comprising administering to the subject a therapeutically effective amount of a hinge antibody. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by Scheer. Scheer further teaches a method for treating cancer or an autoimmune disease in a subject, comprising administering to the subject a therapeutically effective amount of the hinge antibody (para [0066]). As the technical feature was known in the art at the time of the invention, it cannot be considered a special technical feature that would otherwise unify the groups.

Therefore, Groups I and II lack unity of invention under PCT Rule 13.