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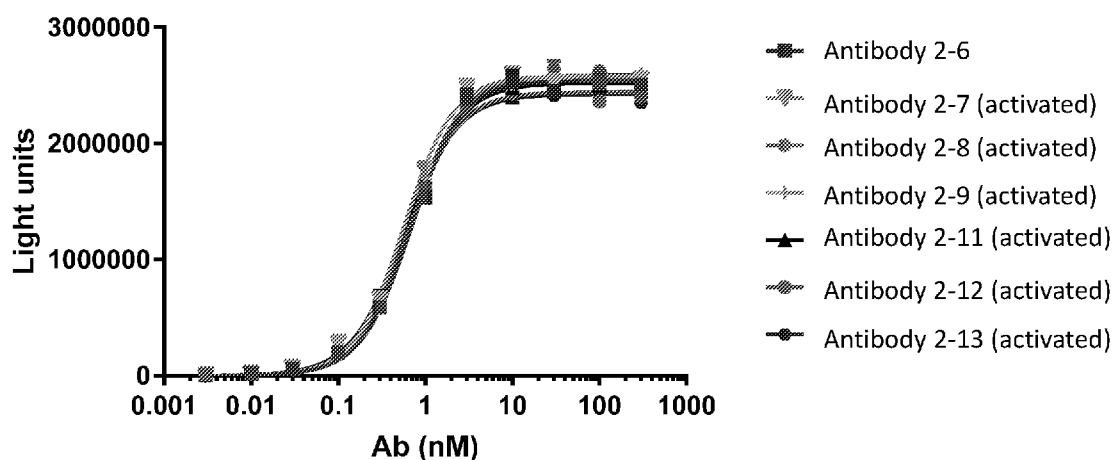
Declarations under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(54) Title: ACTIVATABLE MASKED ANTI-CTLA4 BINDING PROTEINS

FIG. 10B

Binding to human CTLA4



(57) Abstract: The invention provides activatable masked anti-CTLA4 binding proteins (e.g., antibodies, bispecific antibodies, and chimeric receptors) and their use in treating and preventing cancer, as well as compositions and kits comprising the activatable masked anti-CTLA4 binding proteins.



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:

06 August 2020 (06.08.2020)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/068538

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.: 5(completely); 9, 10, 14-18, 21-27(partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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.:
1-4, 6, 11-13, 30-38(all 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/US2019/068538

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P35/00 C07K14/705
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)
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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/081173 A2 (CYTOMX THERAPEUTICS LLC [US]; STAGLIANO NANCY E [US] ET AL.) 15 July 2010 (2010-07-15) the document, in particular examples 10-14 -----	1-4,6, 11-13, 30-38
Y	WO 2018/218076 A1 (JANUX THERAPEUTICS INC [US]) 29 November 2018 (2018-11-29) the whole document, in particular paragraph 7, figure 2, examples 15-20 -----	1-4,6, 11-13, 30-38
Y	WO 2018/106862 A1 (AGENUS INC [US]; LUDWIG INST FOR CANCER RES LTD [CH] ET AL.) 14 June 2018 (2018-06-14) the whole document, particular paragraphs 90, 158, 330-337, figure 9, SEQ ID NOs: 49, 52 ----- -/--	1-4,6, 11-13, 30-38



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

24 March 2020

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23/06/2020

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/068538

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KRISHNA R POLU ET AL: "Probody therapeutics for targeting antibodies to diseased tissue", EXPERT OPINION ON BIOLOGICAL THERAPY, vol. 14, no. 8, 1 August 2014 (2014-08-01) , pages 1049-1053, XP055228738, ASHLEY, LONDON; GB ISSN: 1471-2598, DOI: 10.1517/14712598.2014.920814 the whole document, in particular figure 1B, 2 and expert opinion -----	1-4,6, 11-13, 30-38
Y	JOSHUA M. DONALDSON ET AL: "Design and development of masked therapeutic antibodies to limit off-target effects: Application to anti-EGFR antibodies", CANCER BIOLOGY & THERAPY, vol. 8, no. 22, 15 November 2009 (2009-11-15), XP055274198, US ISSN: 1538-4047, DOI: 10.4161/cbt.8.22.9765 the whole document, in particular abstract, introduction and figure 1 -----	1-4,6, 11-13, 30-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/068538

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010081173	A2	15-07-2010	
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		US 2018185481 A1	05-07-2018
		WO 2018106862 A1	14-06-2018

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 6, 11-13, 30-38(all partially)

A masked antibody comprising:

- a) an anti-CTLA4 antibody or antigen-binding fragment thereof which is the antibody designated 9D9 characterized by its structural features;
- b) a masking peptide comprising the amino acid sequence of SEQ ID NO:1: wherein the masking peptide is linked via a linker comprising a cleavable peptide to an amino-terminus or carbox-terminus of the VL or the VH domain of antibody 9D9; and related subject-matter.

2. claims: 1-4, 6, 11-13, 30-38(all partially)

A masked antibody comprising:

- a) an anti-CTLA4 antibody or antigen-binding fragment thereof which is the antibody designated 1005 characterized by its structural features;
- b) a masking peptide comprising the amino acid sequence of SEQ ID NO:1: wherein the masking peptide is linked via a linker comprising a cleavable peptide to an amino-terminus or carbox-terminus of the VL or the VH domain of antibody 1005; and related subject-matter.

3. claims: 1-4, 6-9, 11-13, 19-21, 28-38(all partially)

A masked antibody comprising:

- a) an anti-CTLA4 antibody or antigen-binding fragment thereof which is the antibody designated antibody A1 characterized by its structural features;
- b) a masking peptide comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 5 or 19; wherein the masking peptide is linked via a linker comprising a cleavable peptide to an amino-terminus or carbox-terminus of the VL or the VH domain of antibody antibody A1; and related subject-matter.

4. claims: 10, 14-18, 22-27, 39, 40(completely); 1-4, 6-9, 11-13, 19-21, 28-38(partially)

A masked antibody comprising:

- a) an anti-CTLA4 antibody or antigen-binding fragment thereof which is the antibody designated antibody A2 characterized by its structural features;
- b) a masking peptide comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 5 or

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19;
wherein the masking peptide is linked via a linker
comprising a cleavable peptide to an amino-terminus or
carbox-terminus of the VL or the VH domain of antibody
antibody A2; and related subject-matter.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 5(completely); 9, 10, 14-18, 21-27(partially)

Present claims 1-29, 39 and 40 relate to an extremely large number of possible antibodies/constructs comprising the antibodies directed to CTLA-4 which are characterized in that they are masked.

These claims further relate to (partial) structural features, i.e. sequences of the masked antibodies/antibody constructs or sequences of parts thereof. However, there is no sequence identifier in the present application clearly indicating which sequences are related to which antibody/antibody construct. The information provided in the sequence listing does not solve this issue for the reason that the sequence listing listing only indicates that all of the 508 sequences are artificial synthetic constructs. The only clear indications are provided in the examples of the present application relating to specific anti-CTLA4 antibodies and masking constructs derived therefrom. Thus, support and disclosure in the sense of Article 6 and 5 PCT is to be found for only a very small proportion of the antibodies/antibody construct claimed, i.e. the specific antibodies and masked antibody constructs disclosed in the examples which are based on the antibodies designated 9D9, 1005, antibody 1 and antibody 2.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of these claims (PCT Guidelines 9.19 and 9.23). The search of claims 1-29, 39 and 40 was restricted to those disclosed masked antibodies which appear to be supported (see examples of the present application). Moreover, only the subject-matter which is supported by the description has been taken as a basis for defining the number of inventions, as the applicant is not invited to pay additional search fees for inventions which prima facie lack sufficiency of disclosure. This in particular applies to the alternative masking peptides claimed.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.