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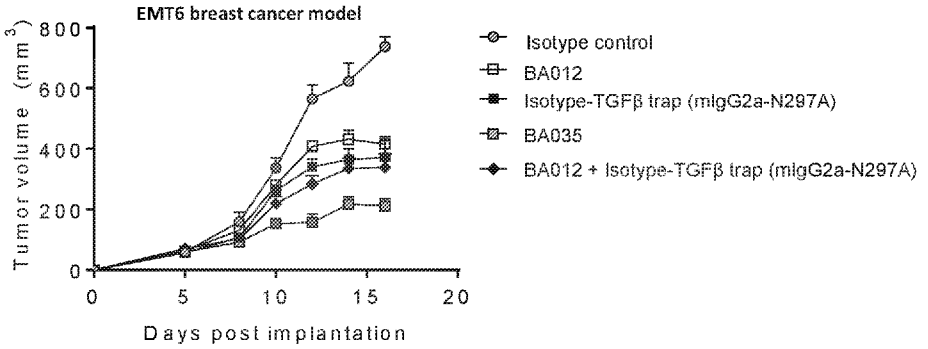
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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

(54) **Title:** ANTI-CD73 ANTIBODIES AND METHODS OF USE THEREOF

FIG. 12B



(57) **Abstract:** The instant disclosure provides antibodies that specifically bind to CD73 (*e.g.*, human CD73) and antagonize CD73 function. Also provided are anti-CD73 antibodies that further comprise a TGFβ-binding moiety or a VEGF-binding moiety. The instant disclosure additionally provides pharmaceutical compositions comprising these antibodies, nucleic acids encoding these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies.

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[Continued on next page]

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

International application No
PCT/US2019/021313

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61P35/00
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)
C07K 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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/118613 A1 (SYDDANSK UNIV [DK]) 13 July 2017 (2017-07-13) page 1, lines 22-30 page 11, lines 3-24 ----- -/--	1-67, 81-98, 112-129, 148-205

[X] Further documents are listed in the continuation of Box C.

[X] 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
12 August 2019	18/10/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Irion, Andrea

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/021313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. G. TERP ET AL: "Anti-Human CD73 Monoclonal Antibody Inhibits Metastasis Formation in Human Breast Cancer by Inducing Clustering and Internalization of CD73 Expressed on the Surface of Cancer Cells", THE JOURNAL OF IMMUNOLOGY, vol. 191, no. 8, 16 September 2013 (2013-09-16), pages 4165-4173, XP055245512, US ISSN: 0022-1767, DOI: 10.4049/jimmunol.1301274 page 4166, left-hand column, paragraph 4	1-67, 81-98, 112-129, 148-205
X	WO 2016/131950 A1 (INNATE PHARMA [FR]) 25 August 2016 (2016-08-25) page 3, lines 17-19 page 4, line 34 - page 5, line 13 page 4, line 20 page 76; table 2 claims 35-41	1-67, 81-98, 112-129, 148-205
X	WO 2017/064043 A1 (INNATE PHARMA [FR]; CENTRE LÉON BÉRARD [FR]) 20 April 2017 (2017-04-20) page 65, lines 6-7 page 67, lines 7-11 page 67, line 331 - page 69, line 29; example 6 page 71 - page 72; example 8	1-67, 81-98, 112-129, 148-205
X	WO 2016/081748 A2 (SQUIBB BRISTOL MYERS CO [US]) 26 May 2016 (2016-05-26) examples 1-9 page 2, paragraph 2 page 48, paragraph 2 - page 56, paragraph 4	1-67, 81-98, 112-129, 148-205
X	WO 2017/152085 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 8 September 2017 (2017-09-08) examples 1-25	1-67, 81-98, 112-129, 148-205

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/021313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/075099 A1 (MEDIMMUNE LTD [GB]) 19 May 2016 (2016-05-19) paragraph [0492] - paragraph [0538]; examples 1-8 paragraph [0539] - paragraph [0554]; examples 9-13 paragraph [0555] - paragraph [0562]; example 14	1-67, 81-98, 112-129, 148-205

X	WO 2017/100670 A1 (CORVUS PHARMACEUTICALS INC [US]; BIOATLA LLC [US]) 15 June 2017 (2017-06-15) paragraph [0210] - paragraph [0225] examples 1-2	1-67, 81-98, 112-129, 148-205

X	WO 2018/013611 A1 (CORVUS PHARMACEUTICALS INC [US]) 18 January 2018 (2018-01-18) paragraph [0142] - paragraph [0151] claim 44	1-67, 81-98, 112-129, 148-205

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/021313

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.: 112-129, 148-205(all 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.:
1-67, 81-98(completely); 112-129, 148-205(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: 1-67, 81-98(completely); 112-129, 148-205(partially)

Claims 1-12: Anti-CD73 antibodies comprising the CDRs referred to as SEQ ID NO. 13 (CDRH1), 14 (CDRH2), 7 (CDRH3), 16 (CDRL1), 10 (CDRL2), and 17 (CDRL3);
Claim 13: Anti-CD73 antibodies comprising the CDRH3 referred to as SEQ ID NO. 7 or the CDRL3 referred to as SEQ ID NO. 12 or 11;
and subject-matter related thereto (claims 43-67, 81-98).

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2. claims: 68-80(completely); 112-129, 148-205(partially)

An isolated antibody that specifically binds to huCD73 (not being part of 1.), the antibody comprising a TGFbeta-binding moiety and subject-matter related thereto.

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3. claims: 99-111(completely); 112-129, 148-205(partially)

An isolated antibody that specifically binds to huCD73 (not being part of 1.), the antibody comprising a VEGF-binding moiety and subject-matter related thereto.

4-20. claims: 130-146(completely); 148-205(partially)

An isolated antibody that specifically binds huCD73 (not being part of 1.), defined in claims 130-146 and subject-matter related thereto.

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21. claim: 147

A compound/molecule comprising a CD73-binding moiety (not being part of 1., 2.) (not limited to human CD73) and a TGFbeta-binding moiety and subject-matter related thereto.

Continuation of Box II.2

Claims Nos.: 112-129, 148-205(all partially)

The application comprises 24 independent product claims referring to CD73-binding compounds/molecules, 22 of which are anti-CD73 antibodies defined by various technical features.

1. Claim 1: Anti-CD73 antibody comprising the CDRs referred to as SEQ ID NO. 13 (CDRH1), 14 (CDRH2), 7 (CDRH3), 16 (CDRL1), 10 (CDRL2), and 17 (CDRL3).

2. Claim 13: Anti-CD73 antibodies comprising the CDRH3 referred to as SEQ ID NO. 7 or the CDRL3 referred to as SEQ ID NO. 12 or 11.

3. Claim 43: Anti-CD73 antibody binding the same epitope of huCD73 as the antibody of claims 1-42.

4. Claim 68: Antibody that binds to huCD73 and comprises a TGFbeta-binding moiety.

5. Claim 99: Antibody that binds to huCD73 and comprises a VEGF-binding moiety.

6. Claim 130: Anti-huCD73 antibody defined by bound epitope (SEQ ID NO. 90 (aa144-170: 27mer peptide) or SEQ ID NO. 91 (aa195-213: 19mer peptide))

7. Claim 131: Anti-huCD73 antibody binding to at least one residue of the peptides referred to as SEQ ID NO. 90/91.

8. Claim 132: Anti-huCD73 antibody binding to at least one residue of Y158, Y161, P165, D168.

9. Claim 133: Anti-huCD73 antibody defined by relative binding affinity to sequence referred to as SEQ ID NO. 133/141.

10. Claim 134: Anti-huCD73 antibody defined by relative binding affinity to sequence referred to as SEQ ID NO. 134/141.

11. Claim 135: Anti-huCD73 antibody binding to the residue Y158.

12. Claim 136: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 59/141.

13. Claim 137: Anti-huCD73 antibody binding to the residue Y161.

14. Claim 138: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 60/141.

15. Claim 139: Anti-huCD73 antibody binding to the residue Y165.

16. Claim 140: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 139/141.

17. Claim 141: Anti-huCD73 antibody binding to the residue Y168.

18. Claim 142: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 140/141.

19. Claim 143: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID

NO. 135/141.
20. Claim 144: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 136/141.
22. Claim 145: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 142/141 and SEQ ID NO. 137/141.
23. Claim 146: Anti-huCD73 antibody defined by relative binding affinity to sequences referred to as SEQ ID NO. 142/141 and SEQ ID NO. 138/141.
24. Claim 147: A compound or molecule comprising a CD73(not limited to human CD73)-binding moiety and a TGFbeta-binding moiety.
According to Rule 6.1(a) PCT, the number of claims shall be reasonable in consideration of the nature of the invention claimed, which is not the case here. The functional features claimed in claims 130-146 cannot be searched without undue burden.
The subject-matter referring to the subject-matter of claims 1 and 13 (and subject-matter related thereto, e.g. claims 1-67, 81-98, 112-129, 148-205) is clear and sufficiently disclosed in the application as filed. Hence the subject-matter of claims 1-67, 81-98, 112-129, and 148-205 is searchable.

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/021313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017118613 A1	13-07-2017	NONE	
WO 2016131950 A1	25-08-2016	EP 3259288 A1	27-12-2017
		WO 2016131950 A1	25-08-2016
WO 2017064043 A1	20-04-2017	EP 3362475 A1	22-08-2018
		US 2019225703 A1	25-07-2019
		WO 2017064043 A1	20-04-2017
WO 2016081748 A2	26-05-2016	AR 102698 A1	15-03-2017
		AU 2015349878 A1	25-05-2017
		BR 112017010110 A2	30-01-2018
		CA 2968357 A1	26-05-2016
		CL 2017001296 A1	16-02-2018
		CL 2018001414 A1	24-08-2018
		CN 107001474 A	01-08-2017
		EA 201790986 A1	31-10-2017
		EP 3221363 A2	27-09-2017
		JP 2017537620 A	21-12-2017
		KR 20170080699 A	10-07-2017
		MA 40309 A1	31-01-2018
		PE 07822017 A1	04-07-2017
		PH 12017500918 A1	20-11-2017
		SG 11201703192S A	30-05-2017
		TN 2017000203 A1	19-10-2018
		TW 201625693 A	16-07-2016
		US 2018127513 A1	10-05-2018
		US 2019055320 A1	21-02-2019
		UY 36404 A	01-06-2016
		WO 2016081748 A2	26-05-2016
WO 2017152085 A1	08-09-2017	AU 2017228470 A1	30-08-2018
		BR 112018067368 A2	15-01-2019
		CA 3016187 A1	08-09-2017
		CN 109476740 A	15-03-2019
		EA 201891983 A1	28-02-2019
		EP 3423494 A1	09-01-2019
		JP 2019514844 A	06-06-2019
		KR 20180118725 A	31-10-2018
		SG 11201806861S A	27-09-2018
		US 2019284293 A1	19-09-2019
		WO 2017152085 A1	08-09-2017
WO 2016075099 A1	19-05-2016	AU 2015345202 A1	18-05-2017
		BR 112017009398 A2	15-05-2018
		CA 2967118 A1	19-05-2016
		CL 2017001154 A1	12-01-2018
		CN 107001472 A	01-08-2017
		EP 3218406 A1	20-09-2017
		GB 2537445 A	19-10-2016
		JP 2018501197 A	18-01-2018
		KR 20170080607 A	10-07-2017
		RU 2017117596 A	17-12-2018
		SG 11201703332S A	30-05-2017
		TW 201632555 A	16-09-2016
		US 2016194407 A1	07-07-2016
		US 2018194858 A1	12-07-2018
		US 2019292274 A1	26-09-2019

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/021313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2016075099 A1	19-05-2016
WO 2017100670 A1	15-06-2017	AU 2016366548 A1	28-06-2018
		CA 3007646 A1	15-06-2017
		CL 2018001512 A1	08-03-2019
		CN 109154611 A	04-01-2019
		EA 201891366 A1	28-12-2018
		EP 3387442 A1	17-10-2018
		JP 2019503709 A	14-02-2019
		KR 20180134837 A	19-12-2018
		US 2019077873 A1	14-03-2019
		WO 2017100670 A1	15-06-2017
WO 2018013611 A1	18-01-2018	EP 3481869 A1	15-05-2019
		US 2018009899 A1	11-01-2018
		WO 2018013611 A1	18-01-2018