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(71) Applicant: **INHIBRX, INC.** [US/US]; 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US).

(72) Inventors: **ECKELMAN, Brendan P.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, 92037 (US). **KAPLAN, Michael D.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US). **WILLIS, Katelyn M.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US). **PANDIT, Rajay A.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US).

SANABRIA, Angelica N.; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US). **BARNES, Sydney A.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US). **HAERR, Margaret E.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US). **TIMMER, John C.**; c/o Inhibrx, Inc., 11025 N. Torrey Pines Road, Suite 200, La Jolla, California 92037 (US).

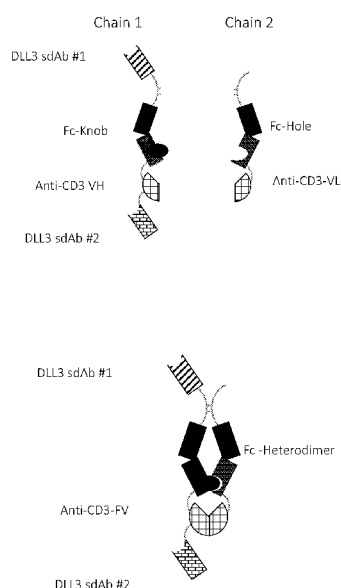
(74) Agent: **RICE, Rachel** et al.; Morrison & Foerster LLP, 12531 High Bluff Drive, Suite 100, San Diego, California 92130-2040 (US).

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

(54) Title: DLL3 SINGLE DOMAIN ANTIBODIES AND THERAPEUTIC COMPOSITIONS THEREOF

FIG. 3A



(57) Abstract: Provided herein are binding polypeptides that specifically bind DLL3. More specifically, provided herein are fusion proteins, including multivalent and/or multispecific constructs and chimeric antigen receptors, that bind DLL3. Also provided are pharmaceutical compositions containing the polypeptides, nucleic acid molecules encoding the polypeptides and vectors and cells thereof, and methods of use and uses of the provided DLL3 binding polypeptides for treating diseases and conditions, such as cancer.

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 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))*
- *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:

25 June 2020 (25.06.2020)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/055436

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.:
80-203, 252-255(completely); 1-79, 204-251, 256-281(partially)
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

International application No

PCT/US2019/055436

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, EMBASE, BIOSIS, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/134140 A1 (AMGEN RES GMBH [DE]) 10 August 2017 (2017-08-10)	1-79, 204-251, 256-281
Y	paragraph [0082]; claims 1, 10, 11	80-203, 252-255

X	WO 2017/021349 A1 (AMGEN RES GMBH [DE]) 9 February 2017 (2017-02-09)	1-79, 204-251, 256-281
Y	page 29 - page 30; claims 1,4	80-203, 252-255

X	WO 2009/124931 A2 (ABLYNX NV [BE]; SAUNDERS MICHAEL JOHN SCOTT [BE] ET AL.) 15 October 2009 (2009-10-15)	1-79, 204-251, 256-281
Y	claims 1,5	80-203, 252-255

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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

20 May 2020

Date of mailing of the international search report

28/05/2020

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

Saame, Tina

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/055436

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BUSHRA HUSAIN ET AL: "Expanding the Boundaries of Biotherapeutics with Bispecific Antibodies", BIODRUGS, vol. 32, no. 5, 21 August 2018 (2018-08-21), pages 441-464, XP055655206, NZ ISSN: 1173-8804, DOI: 10.1007/s40259-018-0299-9	1-79, 204-251, 256-281
Y	page 446 - page 447; table 1	80-203, 252-255
A	----- WO 2018/014260 A1 (NANJING LEGEND BIOTECH CO LTD [CN]) 25 January 2018 (2018-01-25) figure 4	1-281
A	----- US 2018/230225 A1 (FAN XIAOHU [CA] ET AL) 16 August 2018 (2018-08-16) the whole document	266-272
Y	----- KARIN TAYLOR ET AL: "Nanocell targeting using engineered bispecific antibodies", MABS, vol. 7, no. 1, 18 December 2014 (2014-12-18), pages 53-65, XP055469754, US ISSN: 1942-0862, DOI: 10.4161/19420862.2014.985952 table 1	80-203, 252-255, 257-265, 273-281
Y	----- ULRICH BRINKMANN ET AL: "The making of bispecific antibodies", MABS, vol. 9, no. 2, 10 January 2017 (2017-01-10), pages 182-212, XP055531122, US ISSN: 1942-0862, DOI: 10.1080/19420862.2016.1268307 page 191, left-hand column; figure 2 -----	80-203, 252-255, 257-265, 273-281

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/055436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-79, 204-251, 256-281(all partially)

A DLL3-binding polypeptide construct, comprising at least one heavy chain only variable domain (DLL3 VHH domain) that specifically binds DLL3 and optionally one or more additional binding domains that bind to a target other than DLL3 wherein the DLL3 VHH has the three CDR regions of clone L10D9 (SEQ ID Nos 319/336/354) or the three CDR regions of humanized variants of L10D9 (SEQ ID Nos 319-326/336-338/354).

2-14. claims: 1-79, 204-251, 256-281(all partially)

A DLL3-binding polypeptide construct, comprising at least one heavy chain only variable domain (DLL3 VHH domain) that specifically binds DLL3 and optionally one or more additional binding domains that bind to a target other than DLL3 wherein the DLL3 VHH has the three CDR regions of clone L10E5 (SEQ ID Nos 327/339/355) or the three CDR regions of humanized variants of L10E5 (SEQ ID Nos 327/339/355) (invention 2), wherein the wherein the DLL3 VHH has the three CDR regions of clone L8E7 (SEQ ID Nos 328/340/356) or the three CDR regions of humanized variants of L8E7 (SEQ ID Nos 328-329 and 456/340/356) (invention 3), or the three CDR regions of any of clones L3G3, L5A7, L5A8, L6C5, L6F1, 3B4, 6A1, 5H8, 3B12, 6B4 or 3C5 or the three CDR regions of humanized variants of these clones (inventions 4-14);

15. claims: 1-79, 204-251, 256-281(all partially)

A DLL3-binding polypeptide construct, comprising at least one heavy chain only variable domain (DLL3 VHH domain) that specifically binds DLL3 and optionally one or more additional binding domains that bind to a target other than DLL3 wherein the DLL3 VHH has a combination of three CDR regions as comprised within the scope of independent claim 1, but not covered by inventions 1-14;

16. claims: 80-203, 252-255(completely); 257-265, 273-281(partially)

A multispecific polypeptide construct, comprising: (a) a first component comprising a heterodimeric Fc region comprising a first Fc polypeptide and a second Fc polypeptide and (b) a second component comprising an anti-CD3 antibody or antigen-binding fragment comprising a variable heavy chain region (VH) and a variable light chain region (VL), wherein the VH and VL that comprise the anti-CD3 antibody or antigen binding fragment are linked to

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

opposite polypeptides of the heterodimeric Fc; the first and second components are coupled by a linker, wherein the heterodimeric Fc region is positioned N-terminal to the anti-CD3 antibody; and one or both of the first and second components comprises at least one antigen binding domain comprising a VHH domain that specifically binds DLL3 (DLL3 VHH domain).
