



(51) International Patent Classification:

A61K 31/7088 (2006.01) A61P 35/00 (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:

PCT/US2023/034227

(22) International Filing Date:

29 September 2023 (29.09.2023)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/411,988 30 September 2022 (30.09.2022) US

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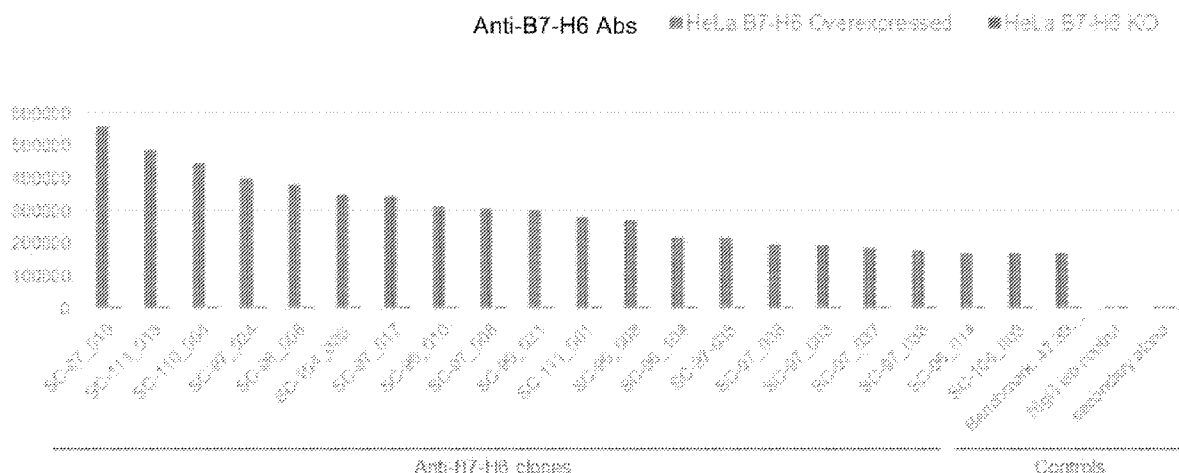
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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG,
KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY,
MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

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

(54) Title: AFFINITY BINDING ENTITIES DIRECTED TO B7H6 AND METHODS OF USE THEREOF

FIG. 1



(57) Abstract: Aspects of the disclosure include affinity-binding entities that target B7 homolog 6 (B7H6), chimeric antigen receptors (CARs) comprising the same, modified immune cells comprising said CARs, and compositions and methods comprising the same for the treatment of conditions associated with B7H6-expression. In embodiments, the modified immune cells are engineered $\gamma\delta$ T cells.

GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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))*

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

27 June 2024 (27.06.2024)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/034227

A. CLASSIFICATION OF SUBJECT MATTERIPC: A61K 31/7088 (2024.01); **A61K 39/395** (2024.01); A61P 35/00 (2024.01)CPC: **A61K 39/39558**; A61K 31/7088; A61P 35/00

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2021/0032658 A1 (BLUEBIRD BIO INC.) 04 February 2021 (04.02.2021) entire document	1-3, 5, 6, 32
A	Castellanos space space space space	1-3, 5, 6, 32
A	US 2021/0340258 A1 (TRUSTEES OF DARTMOUTH COLLEGE) 04 November 2021 (04.11.2021) entire document	1-3, 5, 6, 32
A	US 2020/0237927 A1 (FIVE PRIME THERAPEUTICS INC.) 30 July 2020 (30.07.2020) entire document	1-3, 5, 6, 32
A	US 2022/0125884 A1 (GILEAD SCIENCES INC.) 28 April 2022 (28.04.2022) entire document	1-3, 5, 6, 32
A	US 9,205,148 B2 (LANGERMANN et al.) 08 December 2015 (08.12.2015) entire document	1-3, 5, 6, 32



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

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

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“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

13 March 2024 (13.03.2024)

Date of mailing of the international search report

14 May 2024 (14.05.2024)

Name and mailing address of the ISA/US

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Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/034227**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first 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 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.:

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/US2023/034227

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/034227

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.: **7-31, 33-54**
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 need to be paid.

Group I+: claims 1-6 and 32 are drawn to affinity-binding entities that target B7 homolog 6 (B7H6), chimeric antigen receptors (CARs) comprising the same, modified immune cells comprising said CARs, and compositions and methods comprising the same.

The first invention of Group I+ is restricted to an antigen binding domain comprising a heavy chain variable region (VH) and a light chain variable region (VL), where the VH is selected to be SEQ ID NO:1 and the VL is selected to be SEQ ID NO:2, and chimeric antigen receptors comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the VH and VL sequence pairs listed in instant claim 1. It is believed that claims 1-3, 5, 6, and 32 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs 1 and 2.

Applicant is invited to elect additional VH, VL, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an antigen binding domain comprising a heavy chain variable region (VH) and a light chain variable region (VL), where the VH is selected to be SEQ ID NO:3 and the VL is selected to be SEQ ID NO:4, and chimeric antigen receptors comprising the same. Additional VH, VL, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. 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.

The inventions listed in Groups I+ 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:

The Groups I+ formulas do not share a significant structural element responsible for treating disorders associated with B7H6, requiring the selection of alternative VH and VL where "An affinity binding entity

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

comprising an antigen binding domain that specifically binds to B7 homolog 6 (B7H6), wherein the antigen binding domain comprises: a heavy chain variable region/light chain variable region (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NOs: 1/2, 3/4, 5/6, 7/8, 9/10, 11/12, 13/14, 15/16, 17/18, 19/20, 21/22, 23/24, 25/26, 27/28, 29/30, 31/32, 33/34, 35/36, 37/38, and 39/40; or the six CDRs of a HCVR/LCVR sequence pair selected from the group consisting of SEQ ID NOs: 1/2, 3/4, 5/6, 7/8, 9/10, 11/12, 13/14, 15/16, 17/18, 19/20, 21/22, 23/24, 25/26, 27/28, 29/30, 31/32,

33/34, 35/36, 37/38, and 39/40.”

Additionally, even if Groups I+ were considered to share the technical features of an affinity binding entity comprising an antigen binding domain that specifically binds to B7 homolog 6 (B7H6), wherein the antigen binding domain comprises: a heavy chain variable region/light chain variable region (HCVR/LCVR) sequence pair; a gamma delta T cell comprising: (a) a nucleic acid sequence encoding a chimeric antigen receptor (CAR), said CAR comprising an antigen binding domain that specifically binds to B7 homolog 6 (B7H6); and/or (b) a polypeptide comprising a CAR comprising an amino acid sequence encoded by the nucleic acid of (a); wherein the gamma delta T cell functionally expresses the binding domain of the polypeptide or nucleic acid sequence encoded CAR on the surface of the gamma delta T cell. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2022/0125884 A1 to Gilead Sciences Inc. discloses an affinity binding entity comprising an antigen binding domain that specifically binds to B7 homolog 6 (B7H6) (the targeting moiety or domain comprises an antibody fragment, Para. [0162]; [a]ntigen targets useful in several therapeutic area contexts, including ...B7H6, Para. [0166]), wherein the antigen binding domain comprises: a heavy chain variable region/light chain variable region (HCVR/LCVR) sequence pair (antibody fragments comprise the heavy chain variable region (VH) and light chain variable region (VL) domains of antibody, Para. [0162]); a gamma delta T cell (gamma delta T cells, Para. [0979]) comprising: (a) a nucleic acid sequence encoding a chimeric antigen receptor (CAR), said CAR comprising an antigen binding domain that specifically binds to B7 homolog 6 (B7H6); and/or (b) a polypeptide comprising a CAR comprising an amino acid sequence encoded by the nucleic acid of (a); wherein the gamma delta T cell functionally expresses the binding domain of the polypeptide or nucleic acid sequence encoded CAR on the surface of the gamma delta T cell (the targeting moiety or domain comprises an antibody fragment, Para. [0162]; [a]ntigen targets useful in several therapeutic area contexts, including ...B7H6, Para. [0166]; the immune cell engineered to express chimeric antigen receptors (CARs), Para. [0980]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.