(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2024 (12.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/254515 A3

(51) International Patent Classification:
A61K 35/17 (2025.01) *A61K 48/00* (2006.01)
C07K 16/28 (2006.01) *C07K 16/30* (2006.01)
C12N 5/0783 (2010.01) *C12Q 1/6886* (2018.01)
A61P 35/00 (2006.01) *C12N 15/85* (2006.01)

(21) International Application Number:
PCT/US2024/033096

(22) International Filing Date:
07 June 2024 (07.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/506,634 07 June 2023 (07.06.2023) US

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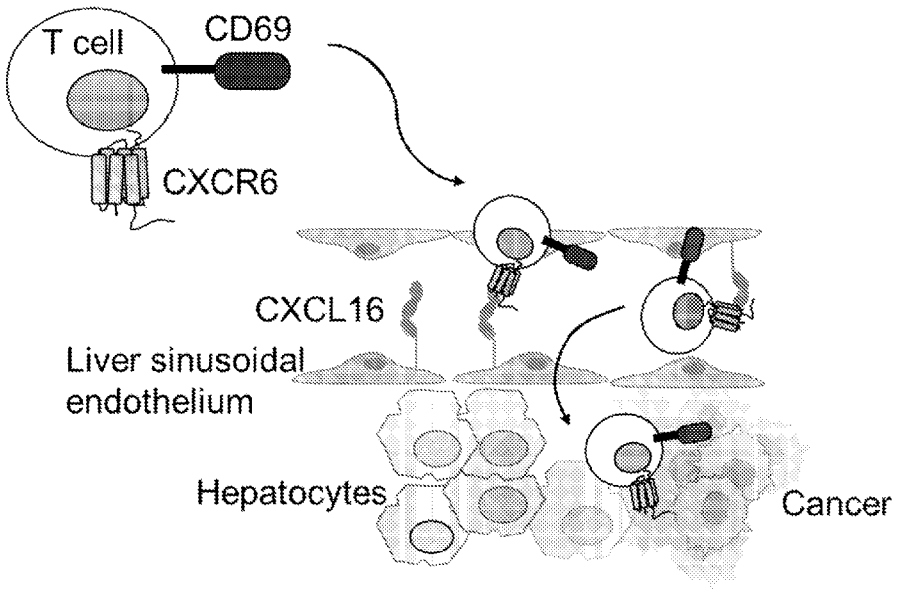
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, 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, 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,

(54) Title: SYSTEMS AND METHODS TO DIRECT CELLULAR THERAPIES IN VIVO TO AN ORGAN

FIG. 4B



(57) Abstract: Systems and methods to direct cellular therapies *in vivo* are provided. Systems and methods described herein include cells genetically modified to achieve at least two of: expression of a recombinant receptor, modulated expression of a trafficking signal, or modulated expression of a retention signal. The genetic constructs can be used to facilitate localized action of cellular therapies.

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[Continued on next page]

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 applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *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))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
01 May 2025 (01.05.2025)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 24/33096

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 35/17, C07K 16/28, C12N 5/0783, A61P 35/00, A61K 48/00, C07K 16/30 (2024.01)
ADD. C12Q 1/6886, C12N 15/85 (2024.01)

CPC - INV. A61K 35/17, C07K 16/28, C12N 5/0636, A61P 35/00, A61K 48/00, C07K 16/3007, C07K 14/70596
ADD. C12Q 2600/156, C12Q 1/6886, C12N 15/85

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.
X	US 2021/0213063 A1 (NOVARTIS AG et al.) 15 July 2021 (15.07.2021); para [0005], [0015], [0119], [0291], [0485], [0516], [0754], [0802], [1115], [1188], [1204]	1-5, 14-16, 168-170, 173, 178, 183, 189, 192, 195, 197-199
A	WO 2022/225981 A2 (IOVANCE BIOTHERAPEUTICS, INC.) 27 October 2022 (27.10.2022); entire document	1-5, 14-16, 168-170, 173, 178, 183, 189, 192, 195, 197-199

☐ 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
"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
09 October 2024	NOV 01 2024
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. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
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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 fi led.

   b. ☐ furnished subsequent to the international fi ling 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/US 24/33096

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.: 162-167
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 Supplemental Box ---

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.:
1-5, 14-16, 168-170, 173, 178, 183, 189, 192, 195, and 197-199, limited to colorectal cancer, liver, CEA, CXCR6, CD69

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 24/33096

Box No. III Observations where unity of invention is lacking

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-17 and 168-199, directed to a method of treating a subject in need thereof. The method of treating a subject will be searched to the extent that the method encompasses the primary cancer is colorectal cancer, the second location is liver, the target antigen
is CEA, and the trafficking signal comprises CXCR6, and the retention signal comprises CD69. The first named invention was determined based on first claim modulator compound (claims 1, 3). This 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. It is believed that claims 1-5, 14-16, 168-170, 173, 178, 183, 189, 192, 195, and 197-199, encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a method of treating a subject comprising the primary cancer is colorectal cancer, the second location is liver, the target antigen is CEA, and the trafficking signal comprises CXCR6, and the retention signal comprises CD69. Additional methods of treating a subject comprising additional target antigens, trafficking signals, and retention signals will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected methods of treating a subject in need thereof. Applicants must further indicate, if applicable, the claims which encompass 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. An exemplary election would be method of treating a subject in need thereof comprising the primary cancer is colorectal cancer, the second location is liver, the target antigen is CEA, and the trafficking signal comprises CXCR6, and the inhibitory signal comprises knockout of beta7 integrin (claims 1-2, 4, 6-7, 14-17, 168-173, 176, 178, 183, 189, 192, 195).

Group II+: Claims 18-96, directed to a cell genetically modified to express i) a chimeric antigen receptor comprising a CEA binding domain; ii) a CXC motif chemokine receptor 6 (CXCR6); and iii) CD69. Group II+ will be searched upon payment of additional fees. The cell may be searched for an additional fee and election as such, for example, to the extent that the cell encompasses the target antigen is CEA, and the trafficking signal comprises CXCR6, and the retention signal comprises CD69; and SEQ ID NOs: 59, 63-65, 107, 204-205 (claims 18-23, 39-62, 71-86). Additional cells will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected cells. 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. Another exemplary election would be a cell genetically modified to express i) a chimeric antigen receptor comprising a CEA binding domain; ii) a CXC motif chemokine receptor 6 (CXCR6); and iii) CD69 comprising SEQ ID NOs: 59, 63-65, 108, 204-205 (claims 18-23, 39-62, 71-86).

Group III+: Claims 97-161 and 200-267, directed to a genetic construct. Group II+ will be searched upon payment of additional fees. The genetic construct may be searched for an additional fee and election as such, for example, to the extent that the genetic construct encompasses the target antigen is CEA, and the trafficking signal comprises CXCR6, and the retention signal comprises CD69; and SEQ ID NOs: 77, 107, 204-205 (claims 97-99, 101, 108-127, 136-161, 200-203, 205-234, 251-267). Additional genetic constructs will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected genetic constructs. 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. Another exemplary election would be a genetic construct comprising the target antigen is CEA, and the trafficking signal comprises CXCR6, and the retention signal comprises CD69; and SEQ ID NOs: 78, 107, 204-205 (claims 97-99, 101, 108-127, 136-161, 200-203, 205-234, 251-267).

The inventions listed as Groups I+, II+, and III+ 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:

Special Technical Features

The technical feature of each of the inventions listed as Group I+ is a method of treating a subject in need thereof with the specific target antigens, trafficking signals, and retention signals recited therein, not required by Groups II+ and III+.

The technical feature of each of the inventions listed as Group II+ is a cell genetically modified to express i) a chimeric antigen receptor comprising a CEA binding domain; ii) a CXC motif chemokine receptor 6 (CXCR6); and iii) CD69 the specific sequences recited therein, not required by Groups I+ and III+.

The technical feature of each of the inventions listed as Group III+ is a genetic construct comprising the specific sequences recited therein, not required by Groups I+ and II+.

Common Technical Features

Groups I+, II+, and III+ share the technical features of a sequence encoding a recombinant receptor; a sequence encoding a trafficking signal or a sequence encoding a retention signal.

The inventions of Group I+ share the technical feature of a method of treating a subject in need thereof comprising identifying a subject with a cancer; and administering to the subject a therapeutically effective amount of a cell genetically modified to express i) a chimeric antigen receptor comprising a binding domain that binds a target antigen of the cancer; and ii) a (a) trafficking signal that directs the cell to a treatment location, (b) a retention signal that maintains the cell within the treatment location, and/or (c) an inhibitory signal that reduces migration of the cell to an off-target location; thereby treating the subject in need thereof.

---See next Supplemental Box ---

Box No. III Observations where unity of invention is lacking

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2021/0213063 A1 to Novartis AG et al. (hereinafter "Novartis").

Novartis discloses a method of treating a subject in need thereof (para [0005] - "methods of treating a disorder such as cancer...in a subject in need thereof") comprising identifying a subject with a cancer (para [0119] - "analyzing a sample from the subject, wherein: (i) determination of MRD status comprises identifying the subject as being MRD positive"); and administering to the subject a therapeutically effective amount of a cell genetically modified to express
i) a chimeric antigen receptor comprising a binding domain that binds a target antigen of the cancer (para [0015] - "comprising administering to the subject an effective amount of a cell (e.g., a population of cells) that expresses a CAR molecule"; para [0485] - "wherein the CAR comprises an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) that binds specifically to a cancer associated antigen described herein"); and
ii) a (a) trafficking signal that directs the cell to a treatment location (para [0802] - "chemokine receptors expressed in CAR-expressing cells that recognize chemokines secreted by tumors, e.g., solid tumors, can improve homing of the CAR-expressing cell to the tumor...A chemokine receptor molecule suitable for expression in a CAR-expressing cell described herein include a CXC chemokine receptor (e.g., CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6"; Note: a trafficking signal is defined as expression of CXCR6 by the instant application (para [0013] - "a trafficking signal includes expression of CXCR6"),
(b) a retention signal that maintains the cell within the treatment location (para [0754] - "the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of...CD69"; Note: a retention signal is defined as expression of CD69 by the instant application (para [0014] - "a retention signal includes expression of CD69")).

The inventions of Group II+ share the technical feature of a cell genetically modified to express i) a chimeric antigen receptor comprising a CEA binding domain; ii) a CXC motif chemokine receptor 6 (CXCR6); and iii) CD69.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by Novartis.

Novartis discloses a cell genetically modified to express (para [0015] - "comprising administering to the subject an effective amount of a cell (e.g., a population of cells) that expresses a CAR molecule"; para [0485] - "wherein the CAR comprises an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) that binds specifically to a cancer associated antigen described herein") i) a chimeric antigen receptor comprising a CEA binding domain (para [0015] - "comprising administering to the subject an effective amount of a cell (e.g., a population of cells) that expresses a CAR molecule"; para [0485] - "wherein the CAR comprises an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) that binds specifically to a cancer associated antigen described herein"; para [0168] - "the CAR molecule comprises an antigen binding domain that binds to a tumor antigen selected from a group consisting of:...CEA"); ii) a CXC motif chemokine receptor 6 (CXCR6) (para [0802] - "chemokine receptors expressed in CAR-expressing cells that recognize chemokines secreted by tumors, e.g., solid tumors, can improve homing of the CAR-expressing cell to the tumor...A chemokine receptor molecule suitable for expression in a CAR-expressing cell described herein include a CXC chemokine receptor (e.g., CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6"); and iii) CD69 (para [0754] - "the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of...CD69").

The inventions of Group III+ share the technical feature of a genetic construct comprising at least two of: a sequence encoding a recombinant receptor; a sequence encoding a trafficking signal or a sequence down-regulating a trafficking signal; or a sequence encoding a retention signal or a sequence down-regulating a retention signal.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by Novartis.

Novartis discloses a genetic construct (para [0473] - "a recombinant DNA construct comprising sequences encoding a CAR") comprising at least two of:
a sequence encoding a recombinant receptor (para [0473] - "a recombinant DNA construct comprising sequences encoding a CAR");
a sequence encoding a trafficking signal or a sequence down-regulating a trafficking signal (para [0802] - "chemokine receptors expressed in CAR-expressing cells that recognize chemokines secreted by tumors, e.g., solid tumors, can improve homing of the CAR-expressing cell to the tumor...A chemokine receptor molecule suitable for expression in a CAR-expressing cell described herein include a CXC chemokine receptor (e.g., CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6"; Note: a trafficking signal is defined as expression of CXCR6 by the instant application (para [0013] - "a trafficking signal includes expression of CXCR6").

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Groups I+, II+, and III+ therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/33096

Continuation of: A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07K 14/705 (2024.01)