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(54) Title: ANTI-TNFR2 ANTIBODIES AND METHODS OF USE

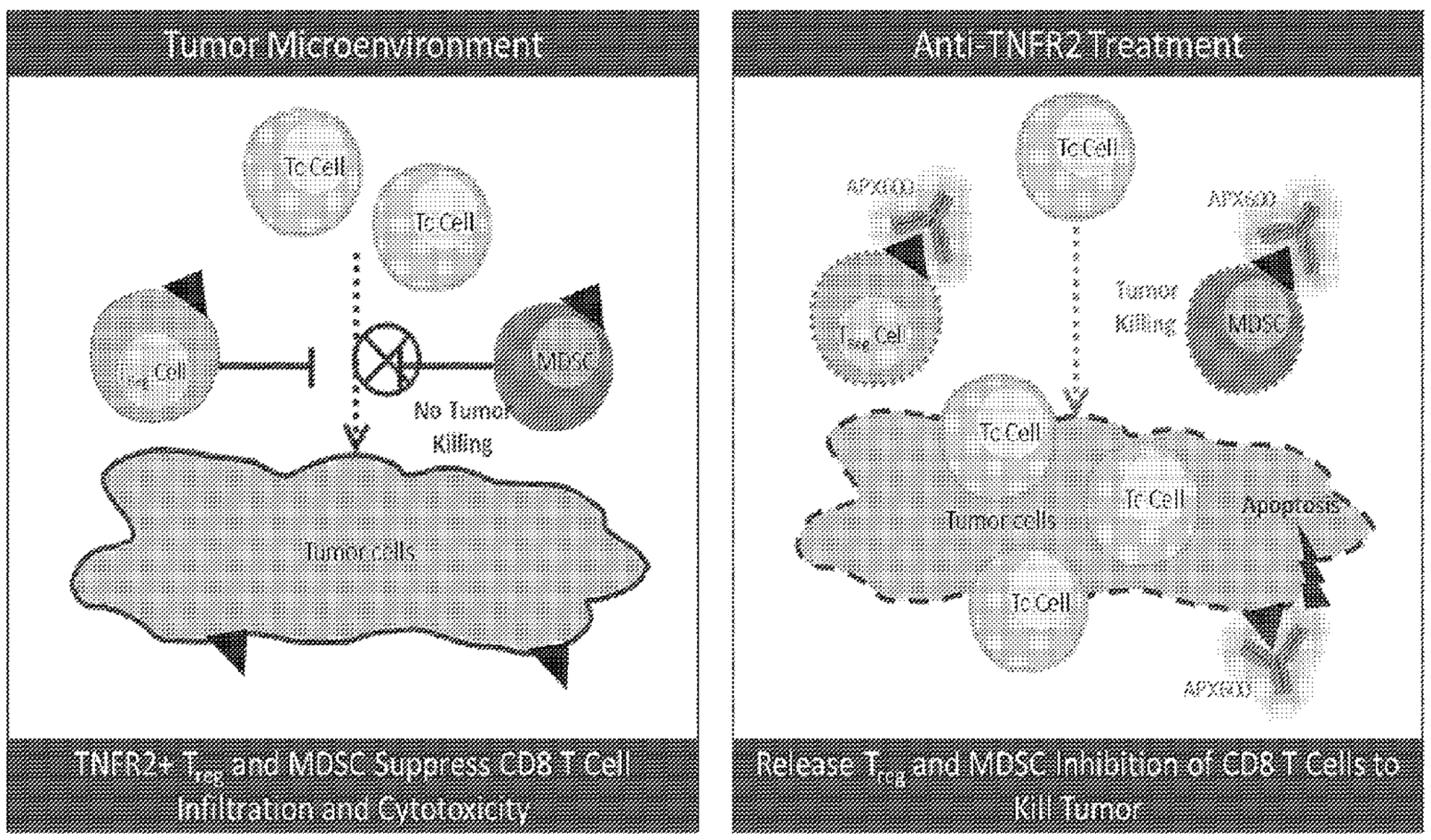

FIG. 1

(57) Abstract: Provided are anti-tumor necrosis factor receptor 2 (TNFR2) antibodies and related compositions, which may be used in any of a variety of therapeutic or diagnostic methods, including the treatment or diagnosis of oncological diseases, inflammatory and/or autoimmune diseases, and others. In some embodiments, the isolated antibody, or antigen-binding fragment thereof, does not substantially bind to TNFR1, herpesvirus entry mediator (HVEM), CD40, death receptor 6 (DR6), and/or osteoprotegerin (OPG).

[Continued on next page]

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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))*

— *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:
29 April 2021 (29.04.2021)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/050515

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; A61P 35/00; C07K 16/28; C07K 16/30 (2021.01)
CPC - A61K 2039/505; A61P 35/00; C07K 16/2878; C07K 2317/76 (2021.02)

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 2019/0144556 A1 (THE GENERAL HOSPITAL CORPORATION) 16 May 2019 (16.05.2019) entire document	1-3, 5
A	WO 2019/094559 A2 (THE GENERAL HOSPITAL CORPORATION) 16 May 2019 (16.05.2019) entire document	1-3, 5
A	US 2019/0135929 A1 (THE GENERAL HOSPITAL CORPORATION) 09 May 2019 (09.05.2019) entire document	1-3, 5
A	WO 2018/213064 A1 (THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 22 November 2018 (22.11.2018) entire document	1-3, 5
A	US 2019/0202925 A1 (OPI VI - IP HOLDCO LLC et al) 04 July 2019 (04.07.2019) entire document	1-3, 5
A	WO 2017/220711 A1 (UNIVERSITE PARIS EST CRETEIL VAL DE MARNE et al) 28 December 2017 (28.12.2017) entire document	1-3, 5

☐ 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
22 February 2021	MAR 12 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/050515

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:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 1-60 and 103-122 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/050515

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.: 4, 11-37
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 extra sheet(s).

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.:

1-3 and 5 to the extent that they read on an anti-TNFR2 antibody comprising SEQ ID NOs: 1-6, 103, and 104.

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/US2020/050515

Continued from 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 examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3 and 5-10 are drawn to anti-TNFR2 antibodies.

The first invention of Group I+ is restricted to an anti-TNFR2 antibody comprising a heavy chain variable region, wherein in the heavy chain variable region is selected to be SEQ ID NO:103, the heavy chain further comprising heavy chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:1, CDR2 is selected to be SEQ ID NO:2, and CDR3 is selected to be SEQ ID NO:3; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:104, the light chain further comprising light chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:4, CDR2 is selected to be SEQ ID NO:5, and CDR3 is selected to be SEQ ID NO:6. It is believed that claims 1-3 and 5 read on this first named invention and thus these claims will be searched without fee to the extent that they read on an anti-TNFR2 antibody comprising SEQ ID NOs 1-6, 103, and 104.

Applicant is invited to elect additional heavy and light chain variable regions, each with specified SEQ ID NO, to be searched in a specific combination for each anti-TNFR2 antibody by paying an additional fee for each set of election. An exemplary election would be an anti-TNFR2 antibody comprising a heavy chain variable region, wherein in the heavy chain variable region is selected to be SEQ ID NO:105, the heavy chain further comprising heavy chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:7, CDR2 is selected to be SEQ ID NO:8, and CDR3 is selected to be SEQ ID NO:9; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:106, the light chain further comprising light chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:10, CDR2 is selected to be SEQ ID NO:11, and CDR3 is selected to be SEQ ID NO:12. Additional anti-TNFR2 antibodies 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 binding TNFR2, requiring the selection of alternatives for the amino acid sequences of the heavy and light chain variable regions, where "the VH region comprises an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOs: 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, and 135" and "the VL region comprises an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NOs: 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 134, and 136".

Additionally, even if Groups I+ were considered to share the technical features of an isolated antibody, or an antigen-binding fragment thereof, that binds to tumor necrosis factor receptor 2 (TNFR2), comprising: a heavy chain variable (VH) region comprising VHCDR1, VHCDR2, and VHCDR3 regions, and a VL region comprising VLCDR1, VLCDR2, and VLCDR3 regions; these shared technical features do not represent a contribution over the prior art.

Specifically, US 2019/0202925 A1 to OPI VI - IP HoldCo LLC et al. discloses an isolated antibody, or an antigen-binding fragment thereof, that binds to tumor necrosis factor receptor 2 (TNFR2) (an antibody that binds to TNFR2 and blocks TNFa binding to TNFR2, Para. [0005]; anti-TNFR2 antibody can be isolated, Para. [0111]), comprising: a heavy chain variable (VH) region comprising VHCDR1, VHCDR2, and VHCDR3 regions (Some exemplary murine variable region heavy chain (VH) sequences, as shown in TABLE 1, Para. [0109]; HCDR1 ...HCDR2 ...HCDR3, Para. [0112]), and a VL region comprising VLCDR1, VLCDR2, and VLCDR3 regions (paired with exemplary murine variable region light chain (VL) sequences, as shown in Table 2, Para. [0109]; LCDR1 ...LCDR2 ...LCDR3, Para. [0112]).

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