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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER

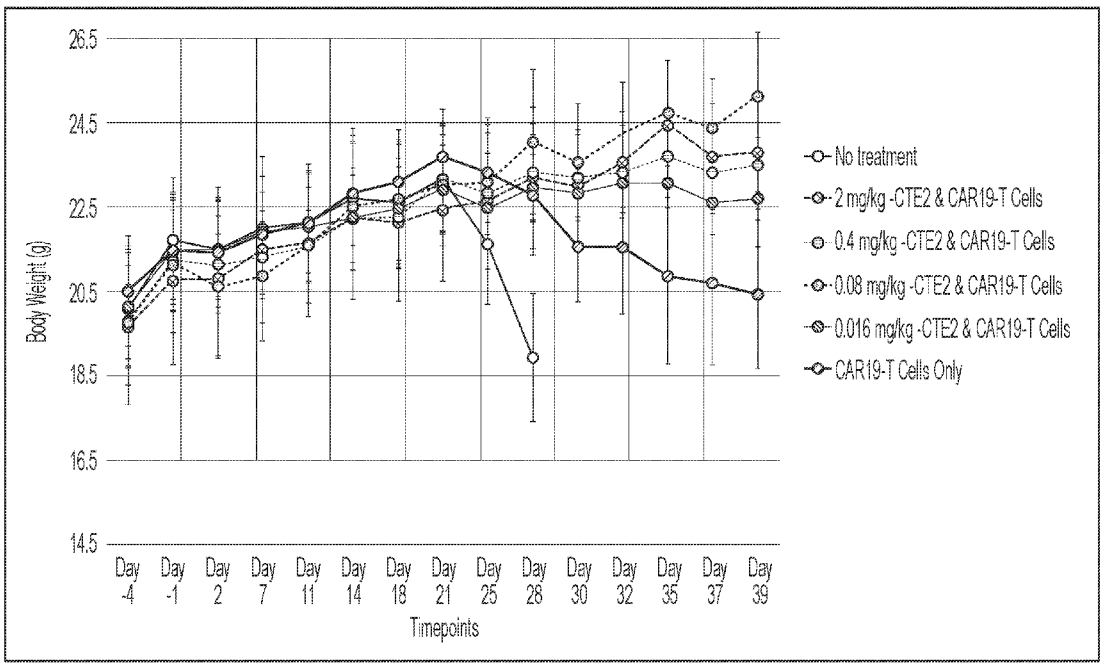

FIG. 12

(57) Abstract: The present disclosure provides a fusion protein comprising an antibody, or antigen binding fragment thereof: that hinds a tumor antigen; and a target polypeptide. In one aspect the present disclosure provides a fusion protein comprising an antibody, or antigen binding fragment thereof that binds a tumor antigen; a target polypeptide; and a half-life extension polypeptide. In some embodiments, a fusion protein comprises at least a first linker. In some embodiments, a fusion protein compares at least a first linker and a second linker, Fusion proteins and their use in treating subjects having cancer are described.

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[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))*

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.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 39/395; A61K 38/17; A61K 38/38; A61K 47/64; A61K 47/68; C07K 14/47; C07K 14/765; C07K 16/28 (2023.01)
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ADD. A61K 2039/507; A61P 35/00; C07K 2317/565; C07K 2317/73; C07K 2319/31; C07K 2319/33

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 database consulted during the international search (name of database 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 --- Y	US 2021/0179735 A1 (HARPOON THERAPEUTICS INC.) 17 June 2021; Paragraphs [0004], [0008], [0029], [0092], [0094]	1-5, 7/1-5 --- 6, 7/6, 8-10
X --- Y	US 2021/0024631 A1 (ORIONIS BIOSCIENCES INC.) 28 January 2021; Paragraphs [0330], [0331], [0747], [0918], [1140], [1141]	46-49 --- 8-10
Y	WO 2021/199046 A1 (BIOND BIOLOGICS LTD.) 07 October 2021; Paragraph [083]	6, 7/6, 8-10
A	US 2019/0040378 A1 (CUREVAC AG) 07 February 2019; Table 1	35
A	US 2019/0241633 A1 (CUREVAC AG) 08 August 2019; Paragraph [0112]	35
A	US 2014/0010861 A1 (MODERNA THERAPEUTICS) 09 January 2014; Claim 2	35

☐ 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
14 July 2023 (14.07.2023)	SEP 29 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/17795

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 13*ter*.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/US23/17795

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.: 11-34, 36-45, 50-51
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:
-***-Please See Supplemental Page-***-

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.:
Groups I+, claims 1-10, 35, and 46-49, SEQ ID NO: 37 (anti-CD20 VHH), SEQ ID NO: 1 (nucleic acid).

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/US23/17795

-***-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 must be paid.

Groups I+, claims 1-10, 35, and 46-49, SEQ ID NO: 37 (anti-CD20 VHH) and SEQ ID NO: 1 (nucleic acid), are directed to methods of generating a fusion protein comprising an antibody that binds a tumor antigen, target polypeptide and a half-life extension polypeptide; nucleic acid; antibody comprising a VHH; antibody wherein the VHH comprises at least on CDR.

The methods of Claims 1-8, 9-10 (each-in-part), 35 (in-part), 46-47 (in-part), and 48-49 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they include SEQ ID NO: 37 (first exemplary anti-CD20 VHH) and SEQ ID NO: 1 (first exemplary nucleic acid). This first named invention of Group I+ has been selected to encompass the first species of the genus found in claim 9-10, 35, and 46-47 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional anti-CD20 VHH sequences and the nucleic acid sequence encoding that sequence to be searched. Additional sequence(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected sequence(s). 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/examined. An exemplary election would be SEQ ID NO: 39 (second exemplary anti-CD20 VHH sequence) and SEQ ID NO: 13 (second exemplary nucleic acid encoding anti-CD20 VHH sequence).

The inventions listed as 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:

Groups I+ share the following technical features: a fusion protein comprising an antibody, or antigen binding fragment thereof that binds a tumor antigen, a target polypeptide, and a half-life extension polypeptide; a nucleic acid comprising the nucleotide sequence; an antibody, or antigen-binding fragment thereof, comprising a VHH having the amino acid sequence; and an antibody, or antigen-binding fragment thereof wherein the VHH comprises at least one CDR "e.g., CDR1, CDR2, and/or CDR3".

However, these shared technical features are previously disclosed by US 2021/0179735 A1 to Harpoon Therapeutics Inc. (hereinafter "Harpoon") in view of US 2019/0092871 A1 to VIB VZW et al. (hereinafter "VIB").

Harpoon discloses a fusion protein comprising an antibody, or antigen binding fragment thereof that binds a tumor antigen, a target polypeptide, and a half-life extension polypeptide (trispecific protein (fusion protein) designed with domain binding to CD20 (antibody fragment that binds a tumor antigen), CD3 (target polypeptide) and domain for half-life extension; abstract; paragraphs [0004] [0094]); a nucleic acid comprising the nucleotide sequence (nucleic acid sequence encoding any trispecific protein described in method; paragraph [0017]).

Harpoon does not disclose an antibody, or antigen-binding fragment thereof, comprising a VHH having the amino acid sequence; an antibody, or antigen-binding fragment thereof wherein the VHH comprises at least one CDR "e.g., CDR1, CDR2, and/or CDR3".

VIB discloses an antibody, or antigen-binding fragment thereof (antibody designated in method comprising VHH; paragraph [0005]), comprising a VHH having the amino acid sequence (targeting moiety binding specifically comprises VHH in amino acid sequence; paragraphs [0005], [0010]); an antibody, or antigen-binding fragment thereof wherein the VHH comprises at least one CDR "e.g., CDR1, CDR2, and/or CDR3" (VHH regions comprises amino acid with CDR1-3; paragraph [0010]).

It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the heavy chain of Harpoon to include antibody comprising a VHH, as taught by VIB, because targeting moieties can be effective with single domain antibodies which comprise VHH and CDR1-3 (VIB; paragraph [0003], [0005], [0010]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the a combination of the Harpoon and VIB references, unity of invention is lacking.