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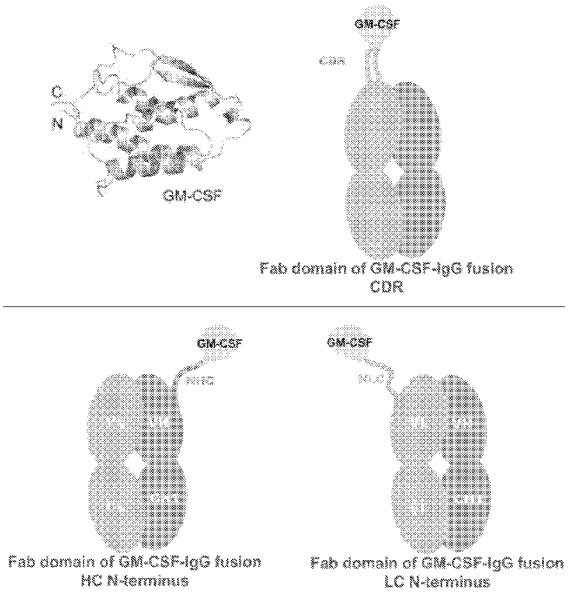
(54) Title: LONG-ACTING GM-CSF AND METHODS OF USE

FIG. 7



(57) Abstract: Disclosed herein are granulocyte-macrophage colony-stimulating factor (GM-CSF) peptides and compositions comprising GM-CSF peptides. These molecules may be useful for the treatment of neurological diseases or conditions.

[Continued on next page]

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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 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))*

(88) Date of publication of the international search report:
23 September 2021 (23.09.2021)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/17684

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 16/30, C07K 16/22, C07K 16/28 (2021.01)

CPC - C07K 14/535, C07K 2319/00, A61K 38/02, A61K 38/179, A61K 38/1808

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.
Y	US 2016/0159920 A1 (THE CALIFORNIA INSTITUTE FOR BIOMEDICAL RESEARCH) 9 June 2016 (09.06.2016) abstract, para [0325], SEQ ID NO: 235	1-3
Y	US 2019/0263882 A1 (THE CALIFORNIA INSTITUTE FOR BIOMEDICAL RESEARCH) 29 August 2019 (29.08.2019), para [0040] SEQ ID NO: 16	1-3

☐ 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
18 July 2021	AUG 03 2021
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 Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/17684

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.: 4-47, 54-62, 66-77, 82, 86-94, 98-103, 107-112, 116-159, 163-174 and 178-203
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 ----------

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, limited to polypeptides at least 98% identical to SEQ ID NO: 2 and at least 85% identical to SEQ ID NO: 16

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 21/17684

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:

Continuation of 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 1-3, 48-50, 63-65, 113-115 and 175-177 directed to a polypeptide composition comprising a first polypeptide comprising a granulocyte macrophage colony stimulating factor (GM-CSF) and a second and optional third polypeptide comprising variable heavy and optional light chain regions. The polypeptide composition will be searched to the extent that the polypeptide comprises a GM-CSF at least about 85% identical to SEQ ID NO: 16, and the second polypeptide comprising a sequence at least 98% identical to SEQ ID NO: 2. It is believed that claims 1-3 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass said GM-CSF antibody chain composition. Additional polypeptide compositions will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected polypeptide compositions. 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 a composition comprising an antibody variable domain comprising light and heavy chain sequences comprising polypeptides comprising sequences at least about 90% identical to SEQ ID NOs: 6 and 2, respectively, and a GM-CSF that comprises a sequence at least about 85% identical to SEQ ID NO: 77 (claims 48-50). Another exemplary election would be a composition comprising an antibody variable domain comprising light and heavy chain sequences comprising polypeptides comprising sequences at least about 90% identical to SEQ ID NOs: 26 and 2, respectively, and a GM-CSF that comprises a sequence at least about 85% identical to SEQ ID NO: 16 (claims 63-65). Another exemplary election would be a composition comprising an antibody variable domain comprising light and heavy chain sequences comprising polypeptides comprising sequences at least about 90% identical to SEQ ID NOs: 42 and 31 respectively, and a GM-CSF that comprises a sequence at least about 85% identical to SEQ ID NO: 77 (claims 175-177).

Group II: Claims 78-81, 83-85, directed to a composition comprising a sequence at least about 90-100% identical to SEQ ID NO: 18.

Group III+: Claims 95-97, 104-106 and 160-162, directed to a polypeptide composition comprising first and second antibody variable domain light and heavy polypeptides, optionally comprising six sub-sequences. Group III+ will be searched upon payment of additional fees. The two-peptide composition may be searched, for example, to the extent that the first polypeptide comprises (subsequences) SEQ ID NOS: 22, 23, and 16, and the second polypeptide comprises SEQ ID NOS: 19-21. It is believed that claims 95-97 limited to said sequences, read on this exemplary invention. Additional two polypeptide compositions will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected two polypeptide compositions. 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 a two-peptide composition wherein the first polypeptide comprises (subsequences) SEQ ID NOS: 37-39, and the second polypeptide comprises SEQ ID NOS: SEQ ID NOS: 34, 35 and 16 (Claims 104-106). Another exemplary election would be a composition comprising first and second antibody variable domain light and heavy polypeptides, the polypeptides comprising sequences at least about 90% identical to SEQ ID NOs: 31 and 29, respectively (claims 160-162).

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:

Additionally, even if the inventions listed as Group I+ and Group II+ were considered to share technical features, these shared technical features are previously disclosed by the prior art, as further discussed below.

Group I+ requires a composition comprising a first polypeptide comprising a granulocyte macrophage colony stimulating factor (GM-CSF) and second and/or third polypeptide(s), not required by Groups II and III+.

Group II requires a composition comprising a sequence at least about 90% identical to SEQ ID NO: 18, required by Groups I+ and III+.

Group III+ requires a two-antibody-derived polypeptide composition, wherein each polypeptide may comprise three subsequences having specified amino acid sequences, not required by Groups I+ and II.

Common Technical Features

The inventions of Group I+ share the technical feature of compositions comprising a first polypeptide comprising a granulocyte macrophage colony stimulating factor (GM-CSF) and second and/or third polypeptides comprising polypeptide comprising antibody variable heavy (VH) and light (VL) domain(s) optionally fused to said GM-CSF.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is made obvious by the article entitled "A human cytokine/single-chain antibody fusion protein for simultaneous delivery of GM-CSF and IL-2 to Ep-CAM overexpressing tumor cells" by Schanzer et al. (hereinafter 'Schanzer'). Schanzer teaches GM-CSF fused to antibodies (pg 2, col 1 para 3 "A recombinant cytokine fusion protein was constructed that allows simultaneous targeting of GM-CSF and IL-2 to the tumor -associated antigen Ep-CAM by way of single-chain antibodies ... The cDNA structures of constructs used in this study are shown in Figure 1A, and the domain structures of DCH and variants are shown in Figure 1, panels B-D.", see Fig. 1 for various fusion configurations). Although Schanzer does not expressly teach that the GM-CSF moiety is attached directly to a VH or VL (e.g. fused in frame), would have been obvious to an artisan of ordinary skill in the art to vary the location of the GM-CSF moiety, such as to a kappa chain in a single chain antibody fusion as taught by Schanzer, or at other locations such as a VH or VL in binding constructs lacking the kappa chain site.

********** See Next Extra Sheet to continue **********

continuation of previous extra sheet:

The inventions of Groups I+ and III+ share the technical feature of polypeptide compositions having heavy and light chain variable domains (VH and VL).

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 2017/0218061 A1 to Morphosys AG (hereinafter 'Morphosys'). Morphosys teaches said compositions (para [0058] "the invention provides antibodies having an antigen-binding region", para [0068] "An antibody is composed of two peptide chains, each containing one (light chain) or three (heavy chain) constant domains and a variable region (VL, VH)").

The inventions of Groups I+ and II share the technical feature of a polypeptide composition comprising a first polypeptide comprising a granulocyte macrophage colony stimulating factor (GM-CSF) [note SEQ ID NO: 18 of Gr II is a GM-CSF polypeptide].

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 6,689,351 B1 to Pierce, et al. (hereinafter 'Pierce').
Pierce teaches composition comprising GM-CSF and other proteins (abstract "A method utilizing GM-CSF to promote accelerated wound healing ... comprising admixtures containing GM-CSF and at least one other protein"), claim 11 " a pharmaceutically acceptable formulation comprising 40-67 .mu.g/kg of GM-CSF").

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 under PCT Rule 13 because they do not share the same or corresponding special technical feature.