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— *with international search report (Art. 21(3))*
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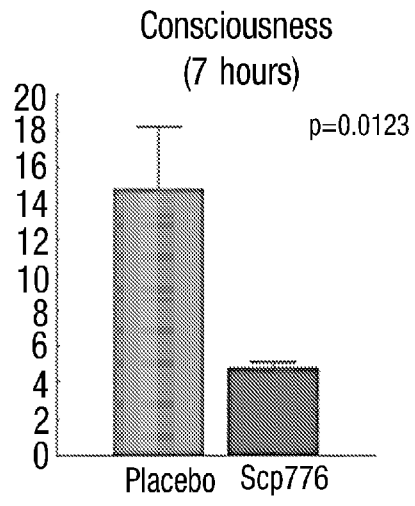
10 March 2022 (10.03.2022)

(54) Title: CHIMERIC PROTEINS AND METHODS OF USE FOR TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

(57) Abstract: Aspects of the present disclosure relate generally to kits and methods for treating acute central nervous systems disorders with chimeric proteins and pharmaceutical compositions comprising such chimeric proteins.

FIG. 11B



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/44019

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 38/00; C12N 15/62 (2021.01)

CPC - A61P 25/00; C07K 2319/00; A61K 38/00; C12N 15/115; A61K 47/66; A61K 9/0019; A61M 2205/00; A61M 5/00

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.
X --- Y	US 2020/0207826 A1 (SILVER CREEK PHARMA INC) 02 July 2020; paragraphs [0177], [0176], [0179], [0232], [0238], [0438], claim 1	1-5, 8-9, 15 --- 10 14, 16-20
Y	WO 2012/145183 A2 (PFIZER INC, et al.) October 26, 2012; page 22, lines 1-9; page 23, line 14; page 33, lines 20-32; page 35, lines 4-10; page 34, lines 27-28	10-14, 18-20
Y	WO 2008/079290 A2 (AMGEN INC, et al.) July 03, 2008; paragraphs [00165], [00187], [00193], table 3	16-20

☐ 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
16 December 2021 (16.12.2021)	JAN 18 2022
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 Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/44019

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:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/44019

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.:
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.:
Group I+, Claims 1-20; C316 mutation (human Annexin 5 mutation); E3 mutation (human insulin-like growth factor IGF-1 mutation); C58 mutation (human serum albumin mutation); mitigation of oxidative damage in primary cortical cultures (effect)

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.

-***-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.

Group I+, Claims 1-20, C316 mutation (human Annexin 5 mutation), E3 mutation (human insulin-like growth factor IGF-1 mutation), and C58 mutation (human serum albumin mutation) are directed toward methods and kits for treating acute central nervous systems disorders with chimeric proteins and pharmaceutical compositions comprising such chimeric proteins.

The methods and kits will be searched to the extent that they encompass a chimeric protein comprising a C316 mutation (first exemplary human Annexin 5 mutation), a E3 mutation (first exemplary human insulin-like growth factor IGF-1 mutation), a C58 mutation (first exemplary human serum albumin mutation), and mitigation of oxidative damage in primary cortical cultures (first exemplary effect). Applicant is invited to elect additional mutation(s) and/or effect(s), to be searched. Additional mutation(s) and/or effect(s) will be searched upon the payment of additional fees. It is believed that claims 1-5 (each in-part), 8-16 (each in-part), and 17-20 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a C316 mutation (human Annexin 5 mutation), E3 mutation (human insulin-like growth factor IGF-1 mutation), C58 mutation (human serum albumin mutation), and mitigation of oxidative damage in primary cortical cultures (effect). Applicants must specify the claims that encompass any additionally elected mutation(s) and/or effect(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 a Y24 mutation (human insulin-like growth factor IGF-1 mutation) and a N527 mutation (human serum albumin mutation).

No technical features are shared between the mutations and effects of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features including: a method of treating acute central nervous system injury, the method comprising administering by bolus injection to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier, wherein the chimeric protein comprises (a) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations; (b) an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations, and (c) a half-life modulator comprising a variant of human serum albumin (HSA) comprising one or more mutations; a kit for practicing the method, the kit comprising a plurality of individual containers, each individual container comprising about 20 mg to about 1,000 mg of the chimeric protein; a kit for treating acute central nervous system injury, the kit comprising: (a) a plurality of individual containers, each individual container comprising a volume of a pharmaceutical composition comprising a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is formulated for bolus injection, wherein the chimeric protein comprises (i) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations; (ii) an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations, wherein the one or more mutations, and (iii) a half-life modulator comprising a variant of human serum albumin (HSA) comprising one or more mutations, and combinations thereof, wherein each of the plurality of the individual containers comprises a volume ranging from about 1 ml to about 50 ml, wherein each of the plurality of the individual containers comprises an amount of chimeric protein ranging from about 20 mg to about 1,000 mg; and (b) instructions for use in treating acute central nervous system injury; these shared technical features are previously disclosed by US 2020/0207826 A1 (SILVER CREEK PHARMACEUTICALS, INC.) (hereinafter 'Silver') in view of WO 2008/079290 A2 (AMGEN INC.) (hereinafter 'Amgen').

Silver discloses a method of treating acute central nervous system injury (method of treating ischemic stroke (acute central nervous system injury); paragraphs [0431], [0438]), the method comprising administering by bolus injection to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier (the method comprising administering by bolus injection to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier; paragraphs [0232], [0238], [0438], [0467]), wherein the chimeric protein comprises (a) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations (wherein the chimeric protein comprises (a) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations; paragraphs [0017], [0025]; claim 1); (b) an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations (an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations; claim 1), and (c) a half-life modulator comprising a variant of human serum albumin (HSA) comprising one or more mutations (a half-life modulator comprising a variant of human serum albumin comprising one or more mutations; figure 10; paragraphs [0014], [0020]); a kit for practicing the method (a kit for practicing the method; paragraph [0429]), the kit comprising a container (paragraph [0428]); a kit for treating acute central nervous system injury (a kit for treating ischemic stroke (acute central nervous system injury); paragraphs [0428]-[0429], [0431], [0438]), a pharmaceutical composition comprising a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier (kit comprising one or more of the bi-specific proteins for use to treat tissue damage wherein pharmaceutical compositions comprise a therapeutically effective amount of a chimeric protein and a pharmaceutically acceptable carrier; paragraphs [0231], [0428]-[0429], [0467]), wherein the pharmaceutical composition is formulated for bolus injection (wherein the pharmaceutical composition is formulated for bolus injection; paragraph [0438]), wherein the chimeric protein comprises (i) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations (wherein the chimeric protein comprises (a) a targeting domain comprising a variant of human Annexin 5 (AnxV) comprising one or more mutations; paragraphs [0017], [0025]; claim 1); (ii) an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations (an activator domain comprising a variant of human insulin-like growth factor IGF-1 comprising one or more mutations; claim 1), and (iii) a half-life modulator comprising a variant of human serum albumin (HSA) comprising one or more mutations (a half-life modulator comprising a variant of human serum albumin comprising one or more mutations; figure 10; paragraphs [0014], [0020]), and combinations thereof; and (b) instructions for use in treating acute central nervous system injury (instructions for use in treating acute central nervous system injury; paragraph [0428]-[0429], [0431], [0438]). Silver further discloses 20 mg to 1,000 mg of the chimeric protein (paragraph [0443]).

Silver does not disclose the kit comprising a plurality of individual containers, each individual container comprising about 20 mg to about 1,000 mg of the chimeric protein; the kit comprising: (a) a plurality of individual containers, each individual container comprising a volume

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

of a pharmaceutical composition, wherein each of the plurality of the individual containers comprises a volume ranging from about 1 ml to about 50 ml, wherein each of the plurality of the individual containers comprises an amount of chimeric protein ranging from about 20 mg to about 1,000 mg.

Amgen discloses the kit comprising a plurality of individual containers (kit comprising a plurality of vials (individual containers); paragraphs [00165], [00187]); the kit comprising: (a) a plurality of individual containers, each individual container comprising a volume of a pharmaceutical composition (each individual container comprising a volume of a pharmaceutical composition; paragraph [00193]), wherein each of the plurality of the individual containers comprises a volume ranging from about 1 ml to about 50 ml (wherein each of the plurality of the individual containers comprises a volume ranging from about 1 ml to about 50 ml; paragraph [00193]); wherein each of the plurality of the individual containers comprises an amount of chimeric protein ranging from about 20 mg to about 1,000 mg (wherein each of the plurality of the individual containers comprises an amount of protein ranging from about 20 mg to about 1,000 mg; Table 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the disclosure Silver to include a kit comprising a plurality of individual containers, each individual container comprising about 20 mg to about 1,000 mg of the chimeric protein; the kit comprising: (a) a plurality of individual containers, each individual container comprising a volume of a pharmaceutical composition, wherein each of the plurality of the individual containers comprises a volume ranging from about 1 ml to about 50 ml, wherein each of the plurality of the individual containers comprises an amount of chimeric protein ranging from about 20 mg to about 1,000 mg, as disclosed by Amgen, in order to provide new formulations that retain increased stability of a biopharmaceutical under a variety of different manufacturing and storage conditions, for faster administration by bolus injection to subject in need thereof.

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 a combination of the Silver and Amgen references, unity of invention is lacking.