



(51) International Patent Classification:

C07K 16/46 (2006.01) *A61P 35/00* (2006.01)
A61K 39/395 (2006.01) *C12N 15/09* (2006.01)

(21) International Application Number:

PCT/US2016/065779

(22) International Filing Date:

9 December 2016 (09.12.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/265,344 9 December 2015 (09.12.2015) US

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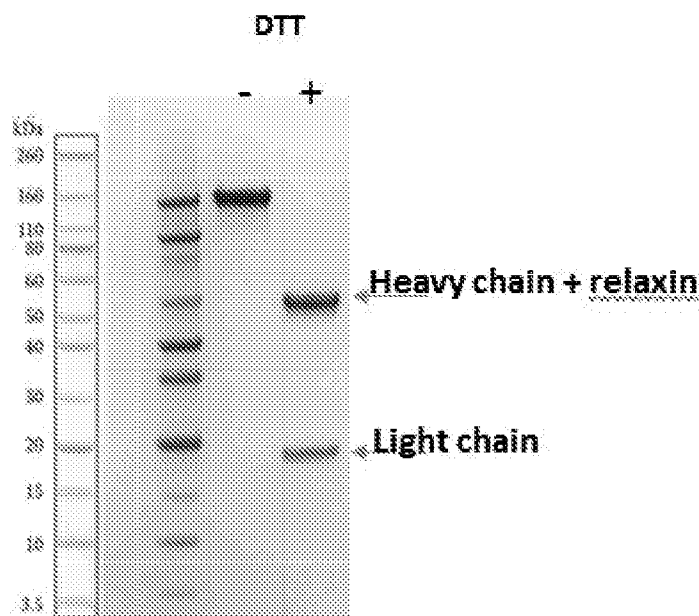
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,

[Continued on next page]

(54) Title: RELAXIN IMMUNOGLOBULIN FUSION PROTEINS AND METHODS OF USE

FIG. 5A



(57) Abstract: Disclosed herein are relaxin immunoglobulin fusion proteins useful for the treatment or prevention of a disease or condition in a subject.



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, 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).

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))*

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))*

(88) Date of publication of the international search report:

20 July 2017

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/65779

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 16/46; A61K 39/395; A61P 35/00; C12N 15/09 (2017.01)

CPC - A61K 39/395, 47/48715, 47/48338; C07K 14/47, 14/61, 14/64, 14/505, 14/535, 14/811, 14/605, 14/5759, 14/43522, 14/57563, 14/70503, 16/32, 16/1027, 16/2863, 16/2866

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	WO 2015/006744 A1 (THE CALIFORNIA INSTITUTE FOR BIOMEDICAL RESEARCH, et al.) January 15, 2015; abstract; paragraphs [0011], [00256], [00346]-[00348], [00353], [00382], [00518]	18-19, 20/18-19, 21/20/18-19, 24/18-19, 25/24/18-19, 27-28
Y	US 2007/0293485 A1 (LIM, J et al.) December 20, 2007; paragraph [0006]; claim 1	18-19, 20/18-19, 21/20/18-19, 24/18-19, 25/24/18-19
Y	US 2006/0257918 A1 (RAMANATHAN, CS et al.) November 16, 2006; paragraph [0633]	27-28
A	US 2014/0187491 A1 (WILMEN, A et al.) July 3, 2014; abstract	1-2, 3/1-2
A	US 2002/0164326 A1 (YOUNG, JF et al.) November 7, 2002; paragraph [0122]; Table 1	1-2, 3/1-2

☐ 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

"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

19 April 2017 (19.04.2017)

Date of mailing of the international search report

31 MAY 2017

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

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PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/65779

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.: 4-17, 22, 23, 26, 29-47
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.:
1-2, 3/1-2, 18-19, 20/18-19, 24/18-19, 25/24/18-19, 27-28; SEQ ID NO: 75

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.

Groups I+, Claims 1-3, 18-21, 24, 25, 27, 28 and SMITFGGFDV (SEQ ID NO: 75, wherein X1 is F, X2 is G and X3 is G) are directed toward a composition comprising: (a) relaxin therapeutic peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain; and (b) an antibody variable domain; and methods of treating a disease associated therewith.

The relaxin therapeutic will be searched to the extent that it encompasses an antibody variable domain encompassing SMITFGGFDV (SEQ ID NO: 75, wherein X1 is F, X2 is G and X3 is G) (first exemplary antibody variable domain sequence). Applicant is invited to elect additional fully specified (i.e. no variable or optional residues) antibody variable domain sequence(s), with specified SEQ ID NO: for each, to be searched. Additional antibody variable domain sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 18-21, 24, 25, 27 and 28 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SMITFGGFDV (SEQ ID NO: 75, wherein X1 is F, X2 is G and X3 is G) (antibody variable domain sequence). Applicants must specify the claims that encompass any additionally elected antibody variable domain 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 an antibody variable domain encompassing SMITAAFDV (SEQ ID NO: 75, wherein X1 is A, X2 is A and X3 is A) (first exemplary elected antibody variable domain sequence).

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

Groups I+ share the technical features including: a composition comprising: (a) relaxin therapeutic peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain; and (b) an antibody variable domain comprising: SMITX(1)X(2)X(3)FDV; and wherein the relaxin therapeutic peptide is connected to the amino-terminus of the antibody variable domain with a connecting peptide; a method of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide; wherein the composition is intravenously or subcutaneously administered in less than or equal to 6 hours; and a method of treating a disease or condition in an individual in need thereof, the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide; wherein the composition is administered to the eye.

However, these shared technical features are previously disclosed by WO 2015/006744 A1 to The California Institute for Biomedical Research et al. (hereinafter 'California') in view of US 2014/0187491 A1 to Wilmen et al. (hereinafter 'Wilmen').

California discloses a composition (a composition; abstract) comprising: (a) relaxin therapeutic peptide (comprising: (a) relaxin therapeutic peptide; paragraphs [00256], [00382]); and (b) an antibody variable domain comprising: SMITX(1)X(2)X(3)FDV (palivizumab, comprising SEQ ID NO: 31 (an antibody variable domain comprising: SMITX(1)X(2)X(3)FDV; paragraphs [00172], [00175], [00304]; SEQ ID NO: 31, residues 99-107); and wherein the relaxin therapeutic peptide (wherein the relaxin therapeutic peptide; paragraphs [00256], [00382]) is connected to the amino-terminus of the antibody variable domain (is connected to the amino-terminus of the antibody variable domain; paragraph [00229]) with a connecting peptide (with an extender (connecting) peptide; paragraphs [00229], [00230]); a method of treating a disease or condition in an individual in need thereof (a method of treating a disease or condition in an individual in need thereof; paragraph [0011]), the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide (the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide; paragraphs [0011], [00256], [00382]); wherein the composition is intravenously or subcutaneously administered (wherein the composition is intravenously or subcutaneously administered; paragraph [00347]); and a method of treating a disease or condition in an individual in need thereof (a method of treating a disease or condition in an individual in need thereof; paragraph [0011]), the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide (the method comprising administering to the individual a composition comprising a relaxin therapeutic peptide; paragraphs [0011], [00256], [00382]); wherein the composition is administered to the eye (wherein the composition is administered intraocularly (to the eye); paragraph [00347]).

California does not disclose a relaxin peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain; and wherein the composition is intravenously or subcutaneously administered in less than or equal to 6 hours.

Wilmen discloses a relaxin peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain (a relaxin peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain; abstract); wherein the peptides have an extended half-life (wherein the peptides have an extended half-life; abstract).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of California to have indicated wherein a reasonable period of time for intravenous or subcutaneous administration of a composition, such as a period of time of 6 hours or less, or 1 hour or less, or 1 minute or less, or 30 seconds or less, or 10 seconds or less in order to reduce pain and stress in the recipient of an injection. It further would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of California to have used a relaxin peptide comprising a relaxin B chain connected via a peptide linker to a relaxin A chain, as disclosed by Wilmen, in order to provide a therapeutically useful relaxin agent for the composition of California, having an extended half-life, as disclosed by Wilmen, in order to provide more effective treatment.

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 California and Wilmen references, unity of invention is lacking.