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[Continued on next page]

(54) Title: COMPOSITIONS, METHODS AND USES FOR ALPHA-1 ANTITRYPSIN FUSION MOLECULES

pCAG.neo/hulgG1aFc-AAT

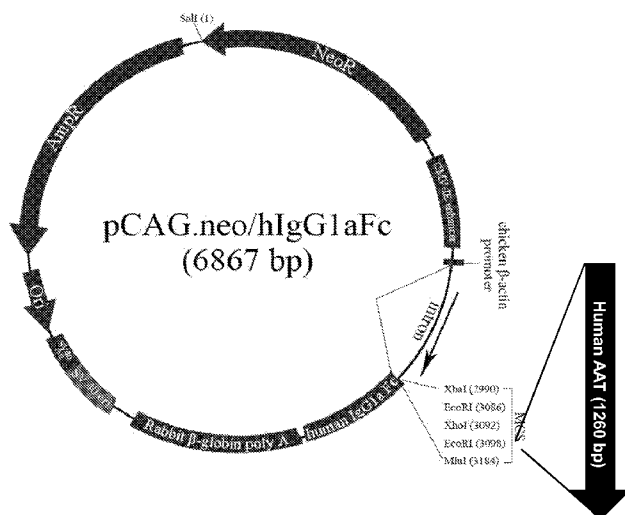


Fig. 1

(57) Abstract: Embodiments herein report compositions of alpha-1 antitrypsin fusion polypeptides or peptide derivatives thereof. In certain embodiments, compositions and methods relate to generating a construct of use in pharmaceutically acceptable compositions to treat a subject in need of alpha-1 antitrypsin therapy or treatment. In other embodiments, compositions and methods disclosed herein concern linking alpha-1 antitrypsin or derivative thereof to an immune fragment.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

— *with sequence listing part of description (Rule 5.2(a))*

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28 March 2013

— *with international search report (Art. 21(3))*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/43869

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12P 21/04 (2012.01)

USPC - 435/69.7; 530/387.3

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)
USPC - 435/69.7; 530/387.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/69.1, 326, 328 (text search, see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; PubWEST (PGPB,USPT,EPAB,JPAB; Google Scholar (text search, see terms below)
Search Terms: Serpina 1, A1A, A1AT, AAT, alpha1AT, alpha 1-antitrypsin, alpha 1-proteinase inhibitor, A1P1, Fc, spacer, linker, antitrypsin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0020269 A1 (STROM et al.) 27 January 2011 (27.01.2011); Figure 11, paras [0042], [0054], [0064]	1-3, 13
Y	US 2010/0061979 A1 (BLANCHE et al.) 11 March 2010 (11.03.2010); paras [0061], [0082]	1-3, 13

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 26 November 2012 (26.11.2012)	Date of mailing of the international search report 04 DEC 2012
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/43869

Box No. 1 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 filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☐

in the international application as filed

☐

together with the international application in electronic form

☒

subsequently to this Authority for the purposes of search

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 in 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/US 12/43869

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:
This application contains the following inventions or groups of inventions which are not so linked 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 1-3 and 13 directed to a fusion polypeptide.

Group II claims 4-13 directed to a nucleic acid construct.

Group III claims 14-17 directed to a process for purifying a fusion polypeptide.

-----Please 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 and 13

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.

Continuation of Box III: Observations where unity of invention is lacking

Group IV claims 18 and 19 directed to a pharmaceutical composition.

Group V claims 20, and 21 directed to a vector.

Group VI claim 22 directed to an isolated preparation of expressed inclusion bodies.

Group VII claims 23-36 directed to a method for treating a condition in a subject.

Group VIII claim 37 directed to a method for preserving an organ, tissue or cells for transplantation in a subject.

Group IX claim 38 directed to a nucleic acid construct.

Group X claim 39-41 directed to a method for treating a subject having been exposed to radiation.

The inventions listed as Groups I-X do not relate to a single inventive concept under Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical features of the Groups are delineated above. Groups I, III, IV, VI-VIII, and X share the common technical feature of a fusion polypeptide comprising consecutive amino acids which, beginning at the amino terminus of the protein, correspond to consecutive amino acids present in (i) alpha-I antitrypsin or carboxyterminal fragment thereof, (ii) a peptide linker, and (iii) an immune fragment, wherein the consecutive amino acids (i) remain bound to (iii) when purified. Groups I and III further share the special technical feature wherein the immune fragment comprises an Fc fragment. However, this is not an improvement over the prior art of US 2011/0020269 A1 to Strom et al. (hereinafter 'Strom') and US 2010/0061979 A1 to Blanche et al. (hereinafter Blanche). Strom discloses a fusion polypeptide comprising consecutive amino acids which, beginning at the amino terminus of the protein, correspond to consecutive amino acids present in (i) alpha-I antitrypsin or carboxyterminal fragment thereof (para [0042]; para [0064]; Figure 11), and (iii) an immune fragment, wherein the immune fragment comprises an Fc fragment (para [0042]; para [0064]; Figure 11) wherein the consecutive amino acids (i) remain bound to (iii) when purified (para [0064]). Strom does not expressly disclose (ii) a peptide linker between the alpha 1-antitrypsin and Fc portions of the fusion protein. Blanche discloses an FGF receptor-Fc fusion protein comprising a peptide linker between the FGF receptor and Fc domain (para [0061]). It would have been obvious to one of ordinary skill in the art that the peptide linker of Blanche could have been added to the AAT fusion polypeptide of Strom between the AAT protein and Fc domain, because Blanche discloses that doing so in an analogous molecule produces functional fusion proteins (para [0082]).

Groups II and V share the special technical feature of a nucleic acid construct comprising: a nucleic acid encoding alpha-I antitrypsin (AAT) or fragment or peptide cleavage molecule thereof; a linker; and a nucleic acid encoding an immune fragment wherein the immune fragment is an immunoglobulin molecule. Likewise, this is not an improvement over the prior art of Strom that teaches a nucleic acid construct comprising: a nucleic acid encoding alpha-I antitrypsin (AAT) or fragment or peptide cleavage molecule thereof (para [0064]); and a nucleic acid encoding an immune fragment wherein the immune fragment is an immunoglobulin molecule (i.e., Fc region) (para [0064]), but does not disclose a linker between the alpha 1-antitrypsin and Fc portions. Blanche discloses an FGF receptor-Fc fusion protein comprising a peptide linker between the FGF receptor and Fc domain (para [0061]) and nucleic acids encoding it (para [0062]). It would have been appreciated by a person of skill in the art that the linker of Blanche could be added to the AAT fusion of Strom between the AAT and Fc domain, because Blanche discloses that doing so produces functional fusion poly nucleotides/proteins (para [0082]).

Groups I and II share the common technical feature of recombinant cell clone. Likewise, this is not an improvement over the prior art of Blanche that teaches a recombinant cell clone comprising the nucleic acid construct or fusion polypeptide (para [0064]).

Groups II and IX share the common technical feature of a nucleic acid construct comprising a nucleic acid encoding alpha-I antitrypsin (AAT) or fragment or peptide cleavage molecule thereof and a nucleic acid encoding an immune fragment wherein the immune fragment is an immunoglobulin molecule. As above, this is not an improvement over the prior art of Strom that teaches a nucleic acid construct comprising: a nucleic acid encoding alpha-I antitrypsin (AAT) or fragment or peptide cleavage molecule thereof (para [0064]); and a nucleic acid encoding an immune fragment wherein the immune fragment is an immunoglobulin molecule (i.e., Fc region) (para [0064]). Group II differs from Group IX in that Group II further requires a linker which is not required by Group IX. Further, Group IX requires the nucleic acid that encodes a mutant AAT having a mutation at the reactive center loop (RCL), wherein the serine protease inhibition activity is significantly reduced which is not required by Group II nor any of the other Groups.

Group III further requires a process for purifying a fusion polypeptide which is not required by any of the other Groups. Group IV further requires a pharmaceutical composition which is not required by any of the other Groups. Group V further requires a vector which is not required by any of the other Groups. Group VI further requires an isolated preparation of expressed inclusion bodies which is not required by any of the other Groups. Group VII further requires a method for treating a condition in a subject which is not required by any of the other Groups. Group VIII further requires a method for preserving an organ, tissue or cells for transplantation in a subject which is not required by any of the other Groups. Group IX further requires the nucleic acid that encodes a mutant AAT having a mutation at the reactive center loop (RCL), wherein the serine protease inhibition activity is significantly reduced, as above, and which is not required by any of the other Groups. Group X further requires a method for treating a subject having been exposed to radiation which is not required by any of the other Groups.

Therefore the inventions listed as Groups I-X do not relate to a single general inventive concept under PCT Rule 13.1 because they do not share a same or corresponding special technical feature.