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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))*

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

(88) Date of publication of the international search report:
31 December 2014

(54) Title: PRODUCT AND PROCESS FOR MUCUS VISCOSITY NORMALIZATION

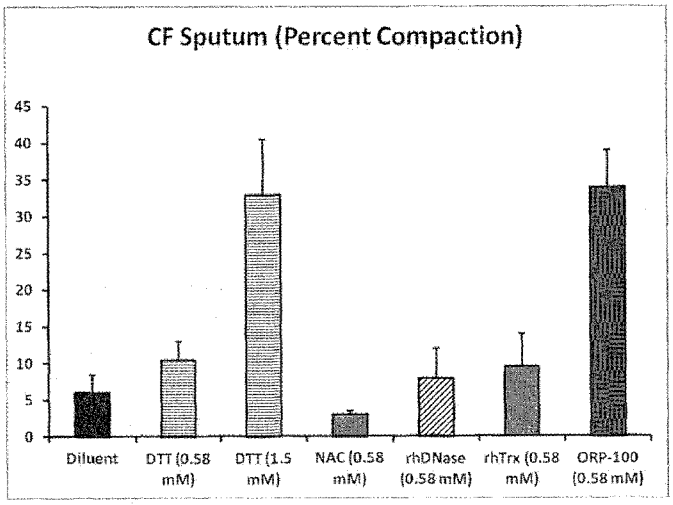

Fig. 2

(57) Abstract: Disclosed are compositions and methods for decreasing the viscosity and/or cohesiveness of and/or increasing the liquefaction of excessively or abnormally viscous or cohesive mucus or sputum. The composition contains a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state and optionally further contains a reducing system.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/46, 38/00, 39/00 (2014.01)
CPC - A61K 38/47, 38/00
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)
CPC: A61K 38/47, 38/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: A61K 38/47, 38/00 (text search)
USPC: 424/94.62, 185.1; 514/1.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase, Google Scholar, Google Patents, GenCore sequence search (AA)
Search terms: thioredoxin, monocysteinic active site, mutant, variant, C32S, C35S, mucus,sputum, viscosity, lung, gastrointestinal cystic fibrosis, coccidiosis, treat*, administer*, forced expiratory volume (FEV)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0311231 A1 (WHITE) 17 December 2009 (17.12.2009). Especially claims 1-6, para [0005], [0010],[0029], [0032], [0042], [0043], [0044]	1-17, 19, 20, 43, 44, 53, 54.
Y	US 2006/0148057 A1 (MIN et al.) 06 July 2006 (06.07.2006). Especially SEQ ID NO: 3, para [0043], abstract.	1-17, 19, 20, 43, 44, 53, 54.
Y	US 3,683,069 A (HOOREMAN) 08 August 1972 (08.08.1972). Especially col 11 ln 65-col 12 ln 10.	6, (10-17,19,20)/6

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

* 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	Date of mailing of the international search report
02 September 2014 (02.09.2014)	05 NOV 2014
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

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/30545

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.: 18, 25-27, 50-52
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:
------go to Extra Sheet for continuation--------

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.:
1-17, 19, 20, 43, 44, 53, 54

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.
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Continuaton of Box III (Lack of Unity of Invention)

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 1-17, 19, 20, 43, 44, 53, 54 drawn to a method to decrease viscosity of mucus or sputum in a patient that has excessively viscous or cohesive mucus or sputum, comprising contacting the mucus or sputum of the patient with a composition comprising a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state effective to decrease the viscosity of the mucus or sputum as compared to prior to the step of contacting.

Group II: Claims 21-24, 28-36, 47-48, drawn to a pharmaceutical composition for use in decreasing viscosity of mucus or sputum, wherein the composition is formulated for oral administration or aerosol administration to the lung.

Group III: Claims 37-42, drawn to a method to decrease viscosity of mucus or sputum in a patient that has excessively viscous or cohesive mucus or sputum, comprising contacting the mucus or sputum of the patient with a composition comprising a disulfide bond reducing agent and a cysteine blocking agent.

Group IV: Claims 45-46, drawn to a method of preventing systemic exposure to a drug substance in a patient following delivery by a route selected from the group consisting of pulmonary, oral and topical delivery, by administering a drug that forms a covalent bond to its target site.

Group V: Claim 49, drawn to an animal feed composition comprising a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state.

The inventions listed as Groups I-V 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:

Special Technical Features:
Group I has the special technical feature of a method to decrease viscosity of mucus or sputum in a patient comprising contacting the mucus or sputum of the patient with a composition comprising a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state, not required by Groups II-V.

Group II has the special technical feature of a composition for use in decreasing viscosity of mucus or sputum, not required by Groups I and III-V.

Group III has the special technical feature of a method to decrease viscosity of mucus or sputum in a patient that has excessively viscous or cohesive mucus or sputum, comprising contacting the mucus or sputum of the patient with a composition comprising a disulfide bond reducing agent and a cysteine blocking agent., not required by Groups I-II or IV-V.

Group IV has the special technical feature of a method of preventing systemic exposure to a drug substance in a patient following delivery, not required by Groups I-III and V.

Group V requires the technical feature of an animal feed composition, not required by Groups I-IV.

Common Technical Features:
Groups I and II are related to as a composition (Group II) and use of said composition (Group I) for decreasing viscosity of mucus or sputum, and share the common technical feature of a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state.

Groups I and III share the common technical feature of a method to decrease viscosity of mucus or sputum in a patient that has excessively viscous or cohesive mucus or sputum, comprising contacting the mucus or sputum of the patient with a composition comprising an agent(s).

Groups II and IV share the common technical feature of pulmonary or oral delivery of a drug that forms a covalent bond to its target site.

Groups I, II, and V share the common technical feature of a thioredoxin monocysteinic active site in a reduced state.

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continued from previous sheet

However, said common technical features to not represent a contribution over the prior art of US 2009/0311231 A1 (WHITE). White discloses a protein or peptide containing a thioredoxin monocysteinic active site in a reduced state and a composition for or method of treatment of excessively viscous or cohesive mucus or sputum in order to decrease the viscosity of the mucus or sputum (claim 1; 1. A method to increase the liquefaction of mucus or sputum in a patient that has excessively viscous or cohesive mucus or sputum, comprising contacting the mucus or sputum of the patient with a composition comprising a protein or peptide containing a thioredoxin active-site in reduced state effective to increase the liquefaction of the mucus or sputum as compared to prior to the step of contacting") wherein said composition can be delivered via either oral or pulmonary delivery (para [0097]). White further discloses that the protein or peptide that forms a covalent bond to its target site (para [0029]; "Biochemical analyses have revealed that mucins MUC5AC and MUC5B, secreted by cells lining the respiratory tract, are the major gel forming polymers components of airway mucus. Cysteine domains present on these mucins contribute to polymer formation, and possibly interaction with neighboring mucin chains, by disulfide bond formation. Since disulfide bonds on proteins are the preferred substrates for Trx enzymatic activity, it was hypothesized by the inventor that mucin polymers were targets for reduction during the liquefaction of sputum by Trx"). As the common technical features were known in the art at the time of the invention, this cannot be considered a common special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I-V lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note concerning item 4: Claims 18, 25-27, 50-52 are multiple dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

International application No.
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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 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:

GenCore ver 6.4.1 SEQ ID NOs: 25, 27