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(54) Title: METHODS, COMPOSITIONS AND KITS FOR TREATING A SUBJECT USING A RECOMBINANT NEUTRALIZING BINDING PROTEIN

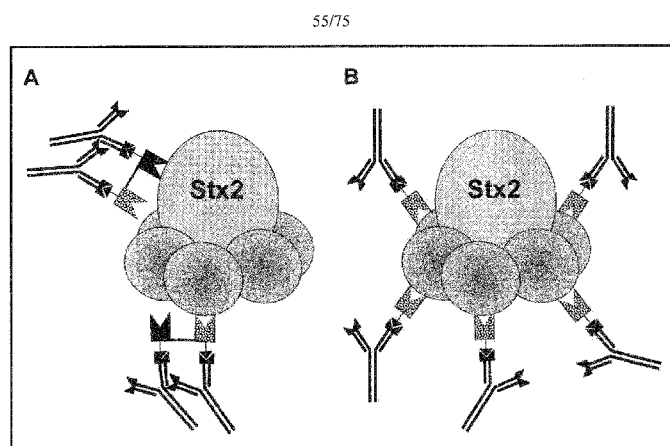


FIG. 32

(57) Abstract: Methods, compositions and kits are provided for treating a subject exposed to or at risk for exposure to a disease agent using a pharmaceutical composition including at least one recombinant binding protein or a source of expression of the binding protein, wherein the binding protein neutralizes a disease agent that is a toxin, for example a Clostridium difficile toxin, a Shiga toxin, a ricin toxin, or an anthrax toxin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/72340

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/40; A61K 39/00; C12P 21/08; C07K 16/00 (2015.01)

CPC - C07K 16/1282; C07K 16/12; A61K 2039/505; C07K 2317/60; A61K 39/00; G01N 33/54353

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)

IPC(8) - A61K 39/40; A61K 39/00; C12P 21/08; C07K 16/00 (2015.01); USPC - 424/167.1; 424/178.1, 163.1; 530/387.3, 389.5, 391.1

CPC - C07K 16/1282; C07K 16/12; A61K 2039/505; C07K 2317/60; A61K 39/00; G01N 33/54353 - see keyword below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - A61K 39/40; A61K 39/00; C12P 21/08; C07K 16/00 (2015.01); USPC - 424/167.1; 424/178.1, 163.1; 530/387.3, 389.5, 391.1

CPC - C07K 16/1282; C07K 16/12; A61K 2039/505; C07K 2317/60; A61K 39/00; G01N 33/54353 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google; Clostridium difficile, C. difficile, toxin A, TcdA, toxin B, TcdB, antibody, neutralize, disease agent, recombinant, camelid, Camelidae, single-domain, VH, heavy chain, heavy-chain-only, binding, protein, domain, region, VHHs, AH3, AA6, 5D, E3, two, more, three, plurality, 7A12, NB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 2013/0058962 A1 (SHOEMAKER et al.) 07 March 2013 (07.03.2013), Abstract, para [0006], [0007], [0010], [0013], [0023], [0034], [0035], [0045], [0054], [0087], [0089], [0097], [0150], [0175], [0264], [0266], [0319], and SEQ ID NO: 68	1-3, 10-12 ----- 13
A	US 2011/0318366 A1 (CROMIE et al.) 29 December 2011 (29.12.2011), Abstract, para [0035], and SEQ ID NO: 11 (760 a.a.), the region between amino acid residues of 159-760	13
A	US 2013/0230537 A1 (HUSSACK et al.) 05 September 2013 (05.09.2013), Abstract, para [0001], [0002], [0004], [0005], [0031], [0041], [0077], and [0102]	1-3, 10-13
A	US 2010/0233182 A1 (AMBROSINO et al.) 16 September 2010 (16.09.2010), para [0009]-[0012], and [0016], and [0018]	1-3, 10-13
A	WO 2013/087857 A2 (NOLTE et al.) 20 June 2013 (20.06.2013), Entire documentation, especially Abstract	1-3, 10-13

☐ 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

08 July 2015 (08.07.2015)

Date of mailing of the international search report

30 JUL 2015

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/72340

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 13ter.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 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.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:

Applicants submitted replacement pages and a Request for Rectification of obvious mistakes under Rule 91:

The clerical error "SEQ ID NO: 163" should be - SEQ ID NO: 174.

Accordingly, the reference to SEQ ID NO: 163 in the claim(s) is being interpreted instead as SEQ ID NO: 174.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/72340

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.: 4-9 and 14-18
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 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 and 10-13, directed to a pharmaceutical composition comprising: at least one recombinant binding protein that neutralizes a disease agent. The pharmaceutical composition will be searched to the extent that the pharmaceutical composition encompasses the amino acids sequences of SEQ ID NO: 167. It is believed that claims 1-3, 10-13 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the amino acids sequences of SEQ ID NO: 167. Additional amino acids sequence(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected amino acids 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. An exemplary election would be SEQ ID NO: 171 [claims 1-3 and 10-13].

*****Continued in the 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 10-13, limited to SEQ ID NO: 167

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 14/72340

Continuation of:
Box No III (unity of invention is lacking)

The inventions listed as Groups I+ 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 Feature

Among Groups I+, each SEQ ID NO represents a structurally different binding protein sequence.

Common Technical Features

The inventions of Groups I+ share the technical feature of a pharmaceutical composition comprising: at least one recombinant binding protein that neutralizes a disease agent, wherein the binding protein comprises at least one disease agent binding domain amino acid sequence selected from the group of:

QVQL VESGGGL VQTGGSLRLSCASSGSIAGFETVTWSRQAPGKSLQWV ASMTKTNNEI
YSDSVKGRFIIIRDNAKNTVYLQMNSLKPEDTGVYFCKGPELRGQGIQVTVSSEPKTPK
PQ (SEQ ID NO: 165).

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2013/0058962 A1 to SHOEMAKER et al. (hereinafter 'Shoemaker') as follows:

Shoemaker discloses a pharmaceutical composition comprising: at least one recombinant binding protein that neutralizes a disease agent (Abstract - 'pharmaceutical composition including at least one recombinant heteromultimeric neutralizing binding protein ... specifically binds a non-overlapping portion of the disease agent'; para [0013] - 'the pharmaceutical composition is a C. botulinum toxin, such that at least one of the binding regions includes a recombinant camelid heavy-chain-only antibody'; para [0007] - 'the pharmaceutical composition, at least one of the binding regions and/or the binding protein is selected from the group of: a single-chain antibody (scFv); a recombinant camelid heavy-chain-only antibody (VHH)'),

--wherein the binding protein comprises at least one disease agent binding domain amino acid sequence selected from the group of:

QVQL VESGGGL VQTGGSLRLSCASSGSIAGFETVTWSRQAPGKSLQWV ASMTKTNNEI
YSDSVKGRFIIIRDNAKNTVYLQMNSLKPEDTGVYFCKGPELRGQGIQVTVSSEPKTPK

PQ (SEQ ID NO: 165) (para [0035] - 'toxin in various embodiments is a C. difficile toxin B, such that at least one binding region of the binding protein includes a recombinant camelid heavy-chain-only antibody having an amino acid sequence selected from ... SEQ ID NO: 68', wherein SEQ ID NO: 68 is 100% identical to the claimed SEQ ID NO: 165).

Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

NOTE: Claims 4-9, 14-18 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note:

I) Claim 6 is objected to as it depends from a non-preceding claim 10, which is also lacking a proper antecedent basis for the "the flexible spacer amino acid sequences" limitation. For the purposes of this ISR, it is assumed that claim 6 depends from claim 5.

II) The clerical error "SEQ ID NO: 163" should be - SEQ ID NO: 162 - as follows:

Claims 1, 4, and 18: pg 139, lines 7 and 27, and pg 141 line 16; and,
Specification: page 2 line 20; page 4 line 20; page 6 lines 2 and 31; page 7 lines 5 and 12; page 22 lines 22 and 24; page 36 line 23; page 72 line 33; page 73 line 2; and page 128 lines 12 and 18.

Accordingly, Applicants submit replacement pages and a Request for Rectification of obvious mistakes under Rule 91.