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(54) Title: COMPOSITIONS COMPRISING LARGE AND SMALL BINDING FRAGMENTS OF ANTIBODIES AGAINST THE SAME TOXIN

(57) Abstract: A pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin. The compositions are used in the treatment of toxin poisoning, for example following exposure to toxins such as Botulinum toxins.



WO 2004/106376 A1

COMPOSITIONS COMPRISING LARGE AND SMALL BINDING FRAGMENTS OF ANTIBODIES AGAINST THE SAME TOXIN

The present invention relates to pharmaceutical compositions containing combinations of antibody fragments, useful in the treatment of various conditions and in particular in the treatment of conditions caused by toxins. Methods of treatment utilising these compositions form a further aspect of the invention.

10 The concept of using animal or human-derived polyclonal antibodies and antidotes or antisera against toxins is well established. The British Pharmacopoeia lists antisera against a number of venoms and toxins produced by micro-organisms, as well as poisonous animals such as snakes and scorpions.

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The antisera are obtained by fractionation of the serum of horses or other mammals that have been immunised against the toxin of interest. In general, the active component of the antiserum consists of whole antibodies (e.g. IgG, IgT) although in recent years, there has been a move towards the use of despeciated antibody fragments such as $F(ab)_2$ and $F(ab')_2$.

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These fragments have the advantage of producing fewer side effects in the patients, and thus an improvement in safety.

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When dealing with the victims of some toxin intoxication however, there is a very short window of opportunity during which any medical countermeasures are effective.

30 The present invention provides a pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin.

35

Compositions of the invention have been found provide rapid and sustained antitoxin activity. This may be due to the fact that the compositions are able to produce an effect, which utilises the mutually complementary properties of the first and second specific binding agents to provide sustained antitoxin capability.

One factor that affects the window of opportunity in the treatment of toxin intoxication is the speed with which the antitoxin is distributed around the body to the sites of action of the toxin. Molecules of the first specific binding agent appear to be less extensively distributed into the extravascular space than molecules of the second specific binding agent. The second specific binding agent appears to provide an antitoxin capability that penetrates rapidly into the extravascular space to provide rapid protection.

The binding of antibodies such as IgG and fragments to toxins is reversible, and therefore there is a risk of a "rebound" effect due to toxin being released, unless at least some functional antibody or antibody fragment remains in the plasma to bind any released toxin. Rapid clearance of the smaller molecules of the second specific binding agent may mean that they are less available in the plasma to "mop up" released toxin. However, by virtue of their slower clearance and higher residual plasma level, the first specific binding agent may bind any toxin released and thereby minimise the rebound effect. In addition, they provide prolonged protection by virtue of their lower clearance rate.

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The first and second binding agents may bind the same or different antigens provided they are associated with the same toxin.

Suitably they have an inactivating effect on the toxin, and prevent the toxin from entering cells.

As used herein, the term "toxin" includes poisons and venoms produced by living organisms, such as bacteria, plants, snakes or insects such as scorpions. It may also include synthetic poisons.

5

The first specific binding agent may comprise an antibody such as an immunoglobulin, which may be IgG, IgM, IgE, IgA, IgD or any subclass thereof, but in particular is an IgG or IgT. The dosages of first specific binding agent required in a composition of the invention is lower than would be required conventionally and therefore adverse side effects or reactions, such as the possibility of anaphylactic shock, may be reduced or minimised. However, if desired the antibody may be "humanised" using conventional methods, or comprise a chimeric antibody.

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In particular however, the first specific binding agent comprises a large binding fragment of an antibody.

As used herein the expression "large binding fragment" refers to an antibody fragment that comprises a significant proportion of the antibody from which it is derived. For instance, it will comprise the entire variable domain, as well as some of a constant region (Fc). In particular, large antibody fragments include $F(ab')_2$ or $F(ab)_2$ fragments, but they may also comprise deletion mutants of an antibody sequence.

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In particular the first specific binding agent comprises a large binding fragment selected from $F(ab')_2$ or $F(ab)_2$ fragments. The acronyms used here are conventional in the art and are understood by a skilled person.

30

The expression "small binding fragment" refers to an antibody fragment which lacks a significant element of the antibody from which it is derived, for instance, it may lack a significant proportion of the F_c chain, provided it retains its ability to bind the toxin. In particular, small antigen binding fragments

35

include Fab or Fab' fragments, as well as single chain (sc) antibodies, FV, VH or VK fragments.

In particular the second specific binding agent comprises a small
5 binding fragment selected from Fab or Fab' fragments.

Preferably at least one of the first or second specific binding agents will include a section corresponding to part of the Fc region of the antibody.

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Antibodies used in the compositions of the invention, or from which the large and small binding fragments are derived may be polyclonal or monoclonal, which may be produced using conventional methods.

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For instance, polyclonal antibodies may be generated by immunisation of an animal (such as a rabbit, rat, goat, horse, sheep etc) with the toxin or immunogenic subunits or fragments thereof, to raise antisera, from which antibodies may be
20 purified.

Monoclonal antibodies may be obtained by fusing spleen cells from an immunised animal such as with hybridoma cells, and selecting cells which secrete suitable antibodies.

25

Antibody binding fragments for use in the compositions, whether large or small, are suitably derived from polyclonal or monoclonal antibodies using conventional methods such as enzymatic digestion with enzymes such as papain or pepsin (to
30 produce Fab and F(ab')₂ fragments respectively). Alternatively, they may be generated using conventional recombinant DNA technology.

Small and large antigen binding fragments used in the composition
35 of the invention may be derived from the same or different sets or source of antibody. They may be specific for the same or

different antigens, provided that the antigens are associated with the same toxin.

In particular the antigen is associated with a toxin which is required to be inactivated in a patient. The toxin may be present as a result of exposure to the toxin. For example toxins such as botulinum toxin, anthrax toxin or plant derived toxins such as ricin toxin, may be inhaled in biological warfare situations or in laboratory accidents, or they may be ingested in food containing them. The latter also applies to *Staphylococcal* enterotoxins, which are typically associated with food poisoning. Alternatively, toxins may be produced as a result of infection with an organism. Particular organisms known to produce toxins include *C.botulinum*, such as is found in wound botulism or infant botulism, clostridial species in general, for example *C. perfringens*, *C. bifermentans*, *C. difficile* or *C. tetani*, *Staphylococcus* species and *Bacillus anthracis* which produces anthrax toxins.

In particular, the antigen is associated with a botulinum toxin, which may be any of type A, B, C, D, E, F or G.

Compositions of the invention may comprise first and second specific binding agents, which bind more than one toxin molecule, for example, a range of toxins produced by the same microorganism or animal. Thus the specific binding agents may be multivalent in nature, or they may be specific for antigens which are common to more than one toxin. Alternatively, the compositions may comprise more than one "set" of first and second specific binding agents, each set being specific for a different toxin molecule.

In a particular embodiment, the composition of the invention comprises two "sets" of first and second specific binding agents, each set binding a different botulinum toxin A, B, C, D, E or F. Preferably at least three sets of first and second specific binding agents are present, and most preferably, sets of specific

binding agents which are specific for all of toxins A-F are included.

Suitably, in each case, the ratio of the first specific binding agent to the second specific binding agent is in the w/w ratio of 90:10 to 10:90, more suitably from 70:30 to 30:70 or and preferably from 60:40 to 40:60.

Compositions of the invention may further comprise pharmaceutically acceptable carriers or excipients as are well known in the art. They may be solid or liquid carriers depending upon the intended mode of administration.

Any desired mode of administration may be used, and this will depend upon factors such as the nature of the toxin being treated, and the nature of the patient. In particular compositions of the invention will be intended for oral, parenteral (especially intravenous) or intranasal administration, or for administration by inhalation or insufflation.

Oral compositions may be in the form of tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs. Compositions for parenteral administration will suitably be in the form of a sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing.

Compositions for intranasal administration or for administration by inhalation or insufflation will suitably comprise a finely divided powder, and inhalable compositions may also be in the form of a liquid aerosol.

Compositions of the invention may comprise other components such as preservative agents, inert diluents, granulating and disintegrating agents, binding agents, lubricating agents,

anti-oxidants as well as colouring, sweetening or flavouring agents, depending upon the nature of the composition.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

The relative amounts of pharmaceutically acceptable carrier to the first and second binding agents in a formulation will vary depending upon factors such as the particular route of administration. Generally however, compositions will comprise from about 1 to about 98 percent by weight of pharmaceutically acceptable carrier, and preferably from 5 to 90 percent by weight of pharmaceutically acceptable carrier.

The size of the dose for therapeutic purposes of a composition of the invention will naturally vary according to the nature and severity of the condition, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. Generally however, patients are given from 0.5 mg to 75 mg per kg body weight of the first and second binding agents.

Compositions of the invention are suitably administered to a patient in need thereof, as soon as possible after exposure to the toxin. In the case of a poisoning incident, such as a snake or scorpion bite, this may be carried out as soon as possible after the incident has occurred. In the case of toxins produced by microorganisms, which have infected a patient and where exposure is not known of, the compositions are suitably administered as soon as symptoms are noted.

Early administration of the composition of the invention is particularly effective, as the inclusion of the second binding agent results in fast inactivation of toxin molecules, which may prevent the toxin entering cells, to cause irreparable damage.

- 5 The window of opportunity will vary depending upon the particular patient or animal exposed, and the dosage of the toxin.

In a further aspect, the invention provides a combination of (i) a first specific binding agent selected from an antibody or a
10 large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin, for use in the treatment of the effects of the toxin.

- 15 Thus in yet a further aspect, the invention provides the use of a combination of (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an
20 antibody which binds said toxin, in the preparation of a medicament for the treatment of the effects of the toxin.

The invention further comprises a method of preventing the effects of a toxin on a mammal such as a human, said method
25 comprising administering to a mammal in need thereof, a composition as described above.

- The composition is suitably administered as soon as possible after the toxin has entered the mammal's body, either as a result
30 of a poisoning incident or as a result of infection with a microorganism, which produces a toxin. Repeat administrations using the administration methods and dosages in accordance with standard clinical practice, may be necessary.

The invention will now be particularly described by way of example with reference to the accompanying diagrammatic drawings in which:

- 5 Figure 1 shows a summary of the results of a range of therapies including those of the invention on the symptoms observed in mice to which the therapies were administered 30 minutes after exposure to Type A botulinum toxin (100MLD₅₀);
- 10 Figure 2 illustrates the mean symptoms score produced following administration of compositions comprising varying amounts of the components of the compositions of the invention to mice 20 minutes after exposure to Type A botulinum toxin (100MLD₅₀);
- 15 Figure 3 shows a comparison of symptoms of botulinum intoxication in surviving mice following post-exposure therapy with individual antitoxin fragments or combinations.

Example 1

- 20 Studies were carried out to investigate the effectiveness of goat derived polyclonal antisera raised against toxoids of botulinum toxin (types A to E). The antisera was purified to whole IgG and its fragments F(ab')₂, Fab' and Fab using conventional methods.
- 25 Balb/c mice (6 per group) were given type A botulinum toxin (100MLD₅₀) intraperitoneally. Thirty minutes later, antitoxin treatment consisting of antibodies, or fragments or combinations were administered intravenously. Treatment groups consisted of:
1. IgG (2mg)
 - 30 2. F(ab')₂ (1.6mg)
 - 3 IgG (1mg) + Fab(0.8mg)
 4. IgG (1mg) + F(ab')₂(0.8mg)
 5. F(ab')₂(0.8mg) + F(ab)(0.8mg)
 6. F(ab')₂ (0.8mg) + F(ab')(0.8mg)
 - 35 7. F(ab') (1.6mg)
 8. Fab (1.6mg)

Thus, when given as combinations, the doses of each were reduced to maintain equimolar doses of antigen recognition sites. The ability of the individual fragments and combinations to protect mice from death and also to reduce symptoms of intoxication was monitored. Symptom scores were calculated as follows:

- 1= increased rate of breathing
- 2= 1 + slight pinching of abdomen
- 3= 1 + medium pinching of abdomen
- 4= 1 + medium pinching of abdomen + pilo erection.

The symptom scores (mean per group) at various times measured at 6, 24, 48 and 72 hours after administration are shown in Figure 1. The Fab fragment alone was unable to prevent death.

It was found that, when administered as individual fragments, IgG, $F(ab')_2$ and Fab' were equally effective at preventing death. However, the combinations of fragments gave better protection against the development of symptoms.

The graph of Figure 1 shows that the combination of $F(ab')_2$ with either Fab or $F(ab')$ gave a reduction in the severity of symptoms observed at various time points during the next few days compared to other combinations or fragments alone. All animals went on to fully recover.

Example 2

Variation in composition of the combination

In order to determine the effect of altering the ratio of $F(ab')_2$ and Fab' on prevention of development of symptoms of intoxication in mice following toxin administration, $F(ab')_2$ and Fab' were administered intravenously in varying proportions, with a total dose always of 1.6mg, 20 minutes after intraperitoneal administration of 100MLD₅₀ of type A botulinum toxin. Again symptoms were recorded at various times using the symptom scoring route

- 1 = increased rate of breathing
- 2 = 1 + slight pinching of abdomen

The group means are shown in Figure 2.

5

It is clear that the combinations were all better than the individual fragments alone. Furthermore, complete prevention of symptoms was possible using a combination of $F(ab')_2$ and Fab' administered within the early window of opportunity (i.e. within 10 20 minutes of exposure), and prevent any symptoms developing compared to mild symptoms developing with the fragments when used alone. This was achieved using relative proportions of the fragments in the range of from a 6:4 mixture to a 4:6 mixture.

15 Example 3

Investigation of the therapeutic window

Although it was found that the combination of the invention did not generally lengthen the therapeutic window (results not shown), if administered early, the combination of the invention 20 did lead to a reduction in symptoms.

Groups of six balb/c mice were dosed intravenously with one of the following treatment regimes:

- 25 1. $F(ab')_2$ (1.6mg)
- 2. $F(ab')_2$ (0.8mg) + Fab' (0.8mg)
- 3. Fab' (1.6mg)

at various time points (60, 75, 90 or 240 minutes) following ip 30 administration of 10 MLD₅₀ type A botulinum toxin. Symptoms of individual mice were scored 24 hours later using the scoring scale described in Example 1 above. The mean score per group per time point are shown in Figure 3A.

35 The experiment was repeated, but on this occasion, the mice were given 100MLD₅₀ type A botulinum toxin and the antitoxins were

given at either 20, 30 or 60 minutes later. Symptoms of individual mice were scored 24 hours later using the scoring scale described in Example 1 above. The mean score per group per time point are shown in Figure 3B.

5

These results suggest that beyond a certain time point following exposure enough toxin has entered the cells to cause irreparable damage and no therapy can be successfully reverse these effects. If given early enough, the fragments can prevent the emergence of any symptoms of intoxication, but the effect of the combination is better.

10

However at interim time points, symptoms of intoxication are apparent although the animals usually recover fully. At early and interim time points, the use of a combination of antitoxin fragments produced clear superiority in the reduction of the severity of symptoms that develop in comparison to the fragments or IgG administered alone. This is an important finding as the milder the symptoms the less incapacitating the illness is.

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Claims

1. A pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin.
2. A composition according to claim 1 wherein the first specific binding agent comprises a large binding fragment of an antibody.
3. A composition according to claim 2 wherein the large binding fragment of an antibody is a $F(ab')_2$ or $F(ab)_2$ fragment.
4. A composition according to claim 1 wherein the first specific binding agent is an antibody which is an IgG or IgT.
5. A composition according to claim 4 wherein the antibody is humanised.
6. A composition according to any one of the preceding claims wherein the second specific binding agent comprises an Fab, Fab', a single chain (sc) antibody or an FV, VH or VK fragment.
7. A composition according to claim 6 wherein the second specific binding agent comprises Fab or Fab' fragment.
8. A composition according to any one of the preceding claims wherein the first and/or second binding agents are derived from polyclonal antibodies.
9. A composition according to any one of claims 1 to 7 wherein the first and/or second binding agents are derived from monoclonal antibodies.

10. A composition according to any one of the preceding claims wherein at least one of the first or second specific binding agents includes a section corresponding to part of the Fc region of an antibody.

5

11. A composition according to any one of the preceding claims wherein the toxin is a *Botulinum toxin*.

12. A composition according to claim 11 wherein the first and second specific binding agents bind at least one of type A, B, C, D, E, F or G botulinum toxin.

13. A composition according to claim 12 wherein the composition comprises sets of first and second specific binding agents each set of specific binding agents binding a different one of botulinum toxins A, B, C, D, E, F or G.

14. A composition according to any one of the preceding claims wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 90:10 to 10:90.

15. A composition according claim 14 wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 70:30 to 30:70.

16. A composition according to claim 15 wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 60:40 to 40:60.

30

17. A composition according to any one of the preceding claims which further comprises a pharmaceutically acceptable carrier or excipient.

18. A composition according to any one of the preceding claims which is suitable for oral, parenteral, or intranasal

administration, or for administration by inhalation or insufflation.

19. A combination of (i) a first specific binding agent
5 selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding fragment of an antibody which binds said toxin, for use in the treatment of the effects of the toxin.

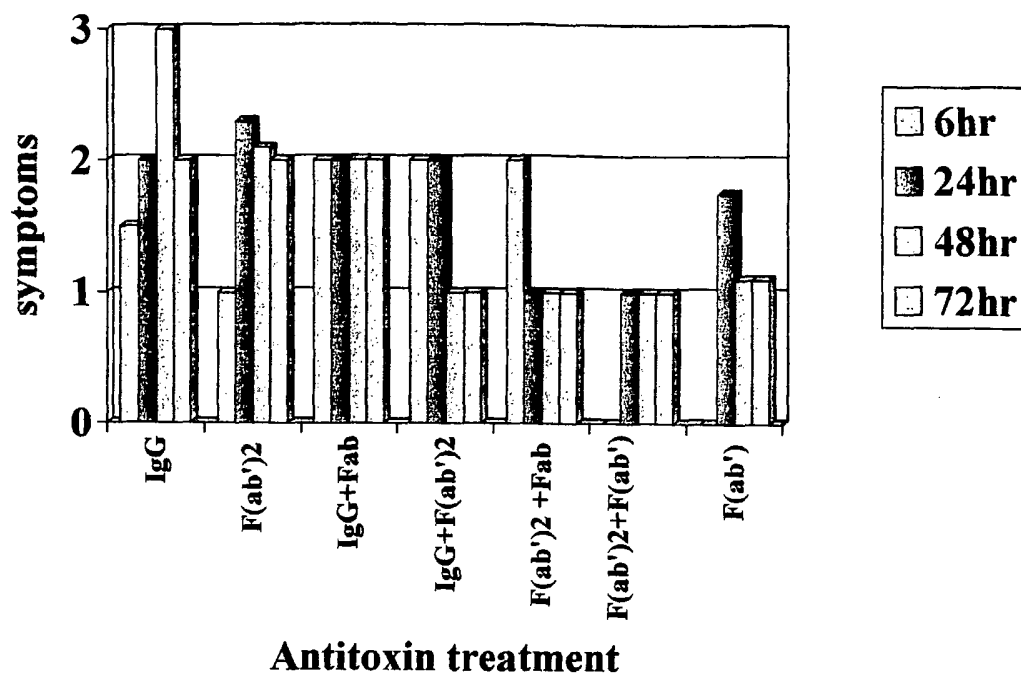
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20. The use of a combination of (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific binding agent which comprises a small binding
15 fragment of an antibody which binds said toxin, in the preparation of a medicament for the treatment of the effects of the toxin.

21. A method of preventing the effects of a toxin on a mammal
20 such as a human, said method comprising administering to a mammal in need thereof, a composition according to any one of claims 1 to 18.

22. A composition substantially as hereinbefore described.
25

1/3

Figure 1

2/3

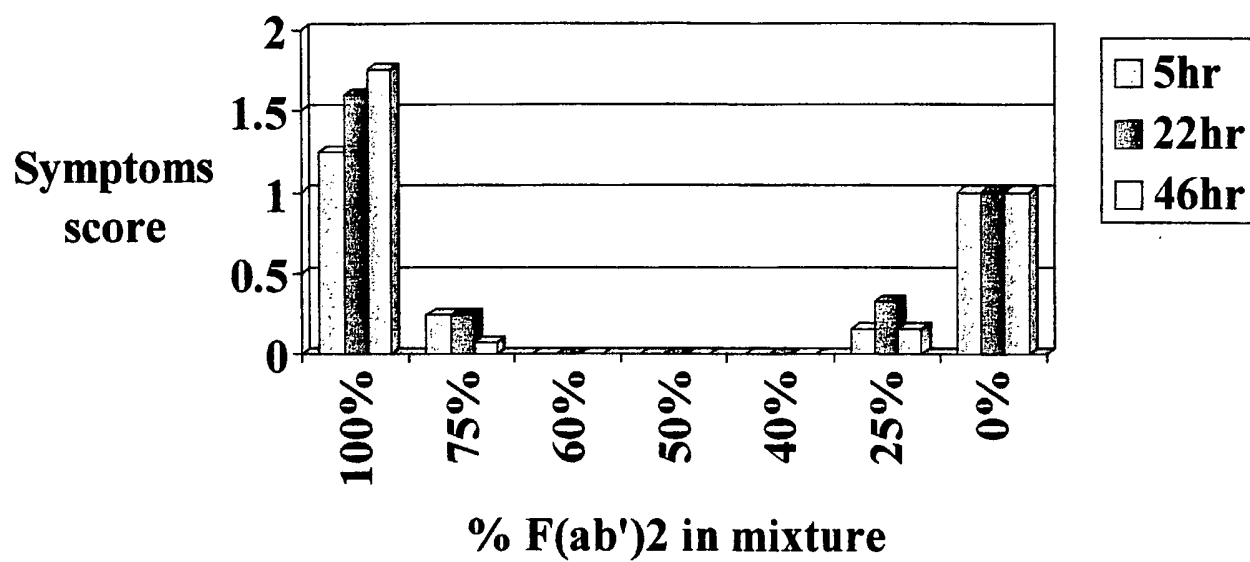
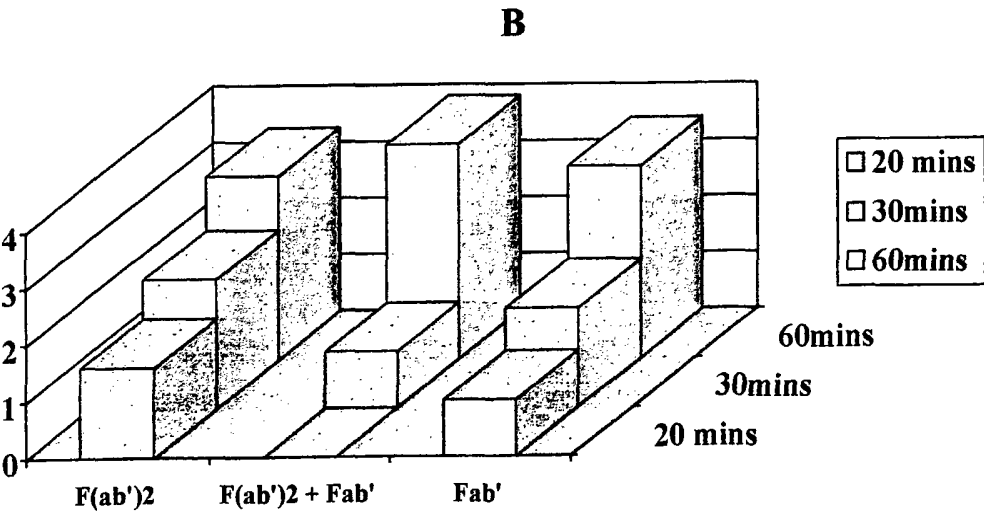
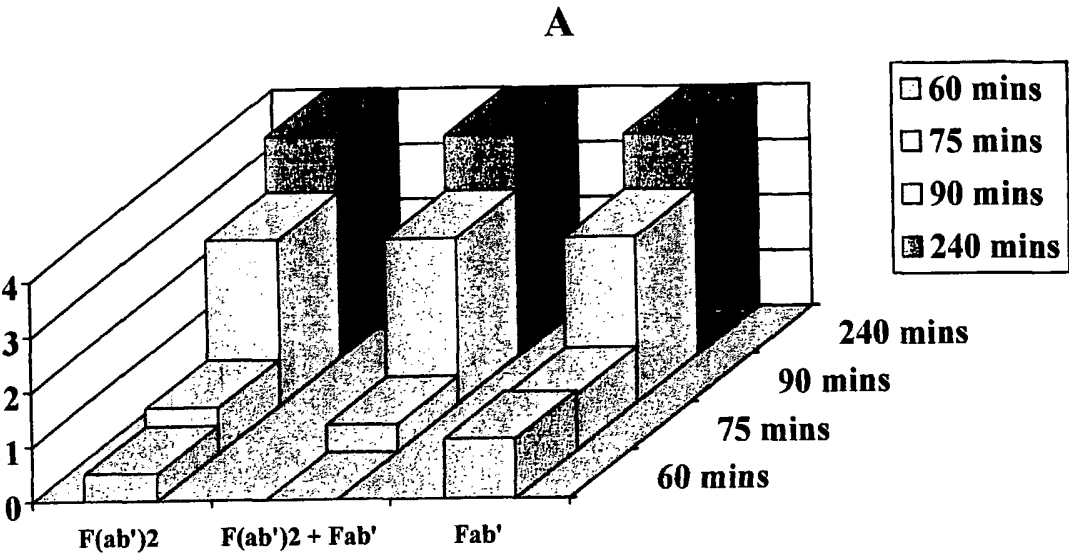
Figure 2

Figure 3



INTERNATIONAL SEARCH REPORT

International Application No
/GB2004/002351

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/08 C07K16/12 C07K16/14 C07K16/16 C07K16/18
A61P31/00

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)

IPC 7 C07K

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

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

EPO-Internal, BIOSIS, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MAYER-CN ET AL.: "Antitoxin therapy for botulinum intoxication" REVIEWS IN MEDICAL MICROBIOLOGY, vol. 12, no. 1, January 2001 (2001-01), pages 29-37, XP002299273 the whole document	1-21
A	MULLER B H ET AL: "Phage-displayed and soluble mouse scFv fragments neutralize rabies virus." JOURNAL OF VIROLOGICAL METHODS. SEP 1997, vol. 67, no. 2, September 1997 (1997-09), pages 221-233, XP002299274 ISSN: 0166-0934 abstract	1-21



Further documents are listed in the continuation of box C.



Patent family members are listed in 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 document 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

7 October 2004

Date of mailing of the international search report

21/10/2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

itional Application No
/GB2004/002351

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STEELE E J ET AL: "Further evidence for cross-linking as a protective factor in experimental cholera: properties of antibody fragments." THE JOURNAL OF INFECTIOUS DISEASES. AUG 1975, vol. 132, no. 2, August 1975 (1975-08), pages 175-180, XP009037451 ISSN: 0022-1899 abstract -----	1-21
A	ISMAIL M ET AL: "Pharmacokinetics of 125I-labelled IgG, F(ab')₂ and Fab fractions of scorpion and snake antivenins: merits and potential for therapeutic use." TOXICON : OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY ON TOXINOLOGY. NOV 1998, vol. 36, no. 11, November 1998 (1998-11), pages 1523-1528, XP002299275 ISSN: 0041-0101 the whole document -----	1-21
A	BEHR T M ET AL: "Anti-carcinoembryonic antigen antibodies versus somatostatin analogs in the detection of metastatic medullary thyroid carcinoma: are carcinoembryonic antigen and somatostatin receptor expression prognostic factors?" CANCER. 15 DEC 1997, vol. 80, no. 12 Suppl, 15 December 1997 (1997-12-15), pages 2436-2457, XP002299276 ISSN: 0008-543X the whole document -----	1-21
P,A	MAYERS CARL N ET AL: "Anti-immunoglobulin responses to IgG, F(ab')₂, and Fab botulinum antitoxins in mice." IMMUNOPHARMACOLOGY AND IMMUNOTOXICOLOGY, vol. 25, no. 3, August 2003 (2003-08), pages 397-408, XP009037543 ISSN: 0892-3973 the whole document -----	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/002351

Box 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.: 22
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 22
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: - 22

The application contains two claims numbered as claim 21. For the sake of clarity second claim 21 is referred to as claim 22.

Claim 22 does not state any (essential) technical feature of an invention, thus, it is considered to lack clarity in the sense of Art. 6, PCT to such an extent, that it was not searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.