Amendment of the Claims Before the International Bureau
Basis Article 19 (1)

In the International Bureau of WIPO

Applicant(s) : Lin Zhen-man)
Application No. PCT/SG03/00145) file a brief statement
Filed : 12 June 2003)
For : **Surface Treatment of SARS–Infected Lungs**

Patent Cooperation Treaty
International Bureau of Wipo
34 Chemin Des Colombettes
1211 GENEVA 20 SWITZERLAND

cc: Austrian Patent Office
Fax : 43 1 534 24 733

cc. **Per Designated Office**

Authorized officer:

Applicant brief statement for AU search report

1. The search authority of Austrian Patent Office was wrong in refusing to search the mailing date on Oct.20, 2003.

2. Therefore, inventor basis on the Article 19 & 34 of PCT law to change the claims, description and the drawings on Dec.12, 2003, the amendment claims are divided into two different editions: Claims A was used for medicine patent by patent-law of country only while Claim B was use for medicine and methods of medical treatment patent by patent-law of country, for instance US patent office and so on.

3. The AU search authority to rectify the wrong and gotten searches report on Apr.05, 2004.

4. But, the AU searches report does not searches report for applicant's amendment claim A only was wrong continually.

5. The AU searches report had crookedness three documents and which were a blind states at PCT/ISA/210 shown" **the certain claims were found unreachable".** The search authority obviously has to impact fair examine and violate the Rule 33 of PCT law, below:

   a. The first document US6242472 title " Methods for the pulmonary delivery of biological agents " was shown the medical methods of patent un-involve above claim A and different field for patent and only involve PFC of claim B;

   b. The second document was not disclosure on the public anywhere in the world, so the report must be obtained in the text that is approved as submitted by the applicant on PCT Form, because the website master had private copyright! In further, why the AU search authority whom could be to forgot the **Background of the invention** had state, the description of invent was also forwarded to "WHO-Padey", "WHO-Liden" by Mey-Verme, Mrs Cnia (WDC) and the leaders WHO were holding the Geneva meeting on 20 May 2003, the International Filing date could be to extend by the patent law naturally;

c. The Apply No.DE10000823A1 was the third document, the title " Bring in the yonder gas to eliminate malignant-flu " (translation) shown the subject matter was the gas ! The abstract " The invention involves an appliance to bringing of a gas into a malignant-flu's, into a Flus-Tissue of crowd diseases, or a Germany-flu… " (translation), it goes without saying, this case was not involve above applicant's claims in whichever point of view.

Conclusion

Under the PCT Article 15 the search authority shall be the subject of international search, to go a step further, under the PCT Article 17(2)(a)(1) that the international application relates to a subject matter which the International Searching Authority is not required to search for the unallied subject matter, the search authority of Austrian Patent Office was wrong for above three document.

Under the PCT Rule 33 " relevant Prior Art for the International Search " had stipulated, the relevant Prior Art for the International Search must to the public anywhere in the world by means of written disclosure… the search authority must to know the search report does not search into the unlawful recognition and controversial issue of personal website, as above the second document.

The search authority of Austrian Patent Office was once again wrong to made applicant difficult for this application, the "the certain claims were found unreachable" of state of PCT/ISA/210 was outstanding Misrepresentution Ordinance, but, just the opposite, the AU search authority was to play the role of a travesty role to irrefutable evidence for this invention was not any relevant to Prior Art for the International Search!

Respectfully submitted,

Apr.20, 2004
In the International Bureau of WIPO
Fax: 41 22 338 7140

PCT/SG03/00145 Applicant

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/SG 2003/000145	International filing date (*day/month/year*) 12 June 2003 (12.06.2003)	(Earliest) Priority Date (*day/month/year*)
Applicant LIN ZHEN-MAN		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. 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 the sequence listing:
      ☐ contained in the international application in written form.
      ☐ filed together with the international application in computer readable form.
      ☐ furnished subsequently to this Authority in written form.
      ☐ furnished subsequently to this Authority in computer readable form.
      ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☒ **Certain claims were found unsearchable** (See Box I).
3. ☐ **Unity of invention is lacking** (See Box II).
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is Figure No.: 4
   ☒ as suggested by the applicant. ☐ None of the figures.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG 03/00145-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 1-4
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-4 are directed to therapeutic methods of treatment of the human/animal body, the search has been carried out and is based on the alleged effects of the composition.

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG 03/00145-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 31/02, A61L 9/015

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]: A61K, A61L

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 practicable, search terms used)

WPI, EPODOC, PAJ, medline, internet, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6242472 B1 (SEKINS et al.) 5 June 2001 (05.06.2001) *claims.*	1-4
Y	SUNNEN G.V.,"SARS and OZONE Therapy: Theoretical Considerations", May 2003 [retrived on 11 February 2004 (11.02.2004)] Retrieved from the Internet:<URL: http://www.triroc.com/sunnen/topics/sars.html> *the whole document.*	1-4
Y	DE 10000823 A1 (HOBLER H.) 19 July 2001 (19.07.2001) *the whole document.*	1-4

☐ 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	Date of mailing of the international search report
9 March 2004 (09.03.2004)	5 April 2004 (05.04.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer KRENN M. Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SG 03/00145-0

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
	A			none	
DE	A	10000823	2001-07-19	none	

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
LIN ZHEN-MAN
10 AVA ROAD
AVA TOWER #19-07
SINGAPORE 329949

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference	Date of mailing (day/month/year) 5 April 2004 (05.04.2004)
	IMPORTANT NOTIFICATION
International application No. PCT/ SG 2003/000145	International filing date (day/month/year) 12 June 2003 (12.06.2003)
Applicant LIN ZHEN-MAN	

1. ☑ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statements under Article 19:

   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendements is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

2. ☐ The applicant is hereby notified that no international search will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ ***With regard to the protest*** against payment of (an) initial fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the text of both the protest decision thereon to the designated Offices
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminder:**

   Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, ***within 30 months*** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide* Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/AT	Authorized officer
Austrian Patent Office Dresdner Straße 87 A-1200 Vienna/Austria FAX No. +43 / 1 / 53424-200	Wolf Telephone No. +43 / 1 / 53424 - 450

See notes on accompanying sheet

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
LIN ZHEN-MAN
10 AVA ROAD
AVA TOWER #19-07
SINGAPORE 329949

PCT

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

	Date of mailing (day/month/year) 5 April 2004 (05.04.2004)
Applicant's or agent's file reference	**REPLY DUE** See paragraph 1 below
International application No. PCT/ SG 2003/000145	International filing date (day/month/year) 12 June 2003 (12.06.2003)
Applicant LIN ZHEN-MAN	

1. ☐ REPLY DUE within _____ months/days from the above date of mailing

   ☑ NO REPLY DUE

2. COMMUNICATION

Dear Sirs,

The Austrian Patent Office revises its declaration of nonestablishment of an international search report (PCT/ISA/203) mailed on 03 July 2003 (03.07.03). However we would like to inform the applicant that it is not possible to amend the claims before the International Searching Authority. Amendments under Article 19 PCT are only possible after the establishment of an international search report and have to be filed with the International Bureau. Therefore the amended claims have not been taken into consideration for the establishment of the international search report. A copy of this form will be sent to the International Bureau.

With kind regards,

Name and mailing address of the IPEA/AT Austrian Patent Office Dresdner Straße 87 A-1200 Vienna/Austria FAX No. +43 / 1 / 53424-200	Authorized officer Hofbauer Telephone No. +43 / 1 / 53424 - 225

Form PCT/ISA/224 (January 1994)

US **6,242,472** B1

http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=/netahtml/search-adv.htm&r=2&f=G&l=50&d=PTXT&p=1&p=1&S1=6242472&OS=6242472&RS=6242472

United States Patent ***6,242,472***

Sekins , et al. **June 5, 2001**

Methods for the pulmonary delivery of biological agents

Abstract

Methods of delivering a therapeutic or diagnostic agent in a perfluorochemical liquid carrier are provided. In preferred embodiments, the disclosed methods use compositions in the form of an emulsion or a dispersion for delivery of a biological agent to the pulmonary air passages.

What is claimed is:

1. A method for the delivery of a therapeutic or diagnostic biological agent to pulmonary air passages of a patient in need thereof comprising the steps of:
   combining said therapeutic or diagnostic biological agent in the form of a solid or immiscible liquid with a perfluorochemical liquid carrier to provide a pharmaceutical preparation; and administering said pharmaceutical preparation to the pulmonary air passages of said patient.
2. The method of claim 1 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.
3. The method of claim 1 wherein said perfluorochemical liquid carrier comprises a perfluorocarbon having a boiling point greater than about 55.degree. C.
4. The method of claim 1 wherein said perfluorochemical liquid carrier is selected from the group consisting of FC-84, FC-72, RM-82, FC-75, RM-101, FC-43, RM-175, FC-5311, FC-5312, trimethylbicyclononane, dimethyladamantine and perfluorodecalin, or a combination thereof.
5. The method of claim 1 wherein said pharmaceutical preparation is oxygenated.
6. The method of claim 1 in which the pharmaceutical preparation is administered at a temperature above the body temperature of the patient.
7. The method of claim 1 in which the pharmaceutical preparation is administered at a temperature below the body temperature of the patient.
8. The method of claim 1 wherein the biological agent is a solid.
9. The method of claim 8 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.
10. The method of claim 8 wherein the biological agent comprises a chemotherapeutic agent.
11. The method of claim 8 wherein the biological agent comprises an antibiotic.
12. The method of claim 8 wherein the biological agent comprises a bronchodilator.
13. The method of claim 1 wherein the biological agent is in the form of an immiscible liquid.
14. The method of claim 13 wherein the pharmaceutical preparation comprises an emulsion.
15. The method of claim 14 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

16. The method of claim 14 wherein the biological agent comprises a chemotherapeutic agent.

17. The method of claim 14 wherein the biological agent comprises an antibiotic.

18. The method of claim 14 wherein the biological agent comprises a bronchodilator.

19. The method of claim 14 wherein the biological agent is dispersed in the perfluorochemical liquid carrier.

20. The method of claim 19 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

21. The method of claim 13 wherein the immiscible liquid biological agent comprises the therapeutic or diagnostic agent in an aqueous medium.

22. The method of claim 21 wherein said therapeutic or diagnostic agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

23. A method for the delivery of a therapeutic or diagnostic biological agent to pulmonary air passages of a patient in need thereof comprising the steps of:

    combining a liquid perfluorochemical with an immiscible liquid to form an emulsion wherein said emulsion further comprises at least one therapeutic or diagnostic biological agent;

    and administering the emulsion to the pulmonary air passages of said patient.

24. The method of claim 23 wherein said liquid perfluorochemical comprises a perfluorocarbon having a boiling point greater than about 55.degree. C.

25. The method of claim 23 wherein said perfluorochemical liquid carrier is selected from the group consisting of FC-84, FC-72, RM-82, FC-75, RM-101, FC-43, RM-175, RC-5311, FC-5312, trimethylbicyclononane, dimethyladamantine and perfluorodecalin, or a combination thereof.

26. The method of claim 23 wherein said emulsion is oxygenated.

27. The method of claim 23 in which the emulsion is administered at a temperature above the body temperature of the patient.

28. The method of claim 23 in which the emulsion is administered at a temperature below the body temperature of the patient.

29. The method of claim 23 wherein said immiscible liquid is aqueous.

30. The method of claim 23 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

31. The method of claim 23 wherein the biological agent comprises a chemotherapeutic agent.

32. The method of claim 23 wherein the biological agent comprises an antibiotic.

33. The method of claim 23 wherein the biological agent comprises a bronchodilator.

34. The method of claim 23 wherein the biological agent is dispersed in the liquid perfluorochemical.

35. The method of claim 34 wherein the biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

36. The method of claim 34 wherein the biological agent comprises a chemotherapeutic agent.

37. The method of claim 34 wherein the biological agent comprises an antibiotic.

38. The method of claim 34 wherein the biological agent comprises a bronchodilator.

39. The method of claim 23 wherein the liquid comprises the therapeutic or diagnostic agent in an aqueous medium.

40. The method of claim 39 wherein said therapeutic or diagnostic agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactic agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

41. A method for the delivery of a therapeutic or diagnostic biological agent to pulmonary air passages of a patient in need thereof comprising the steps of:

combining a liquid perfluorochemical with at least one therapeutic or diagnostic biological agent in solid form to provide a dispersion; and

administering the dispersion to the pulmonary air passages of said patient.

42. The method of claim 41 wherein said liquid perfluorochemical comprises a perfluorocarbon having a boiling point greater than about 55.degree. C.

43. The method of claim 41 wherein said liquid perfluorochemical is selected from the group consisting of FC-84, FC-72, RM-82, FC-75, RM-101, FC-43, RM-175, FC-5311, FC-5312, trimethylbicyclononane, dimethyladamantine and perfluorodecalin, or a combination thereof.

44. The method of claim 41 wherein said dispersion is oxygenated.

45. The method of claim 41 wherein the solid biological agent comprises a powder.

46. The method of claim 41 wherein the solid biological agent is selected from the group consisting of antibody-linked radionuclides, vasoconstrictors, vasodilators, bronchoconstrictors, bronchodilators, anti-cancer agents, surfactants, steroids, antibiotic agents, chemotactis agents, chemotherapeutic agents, contrast agents, antioxidants and antiproteases, or a combination thereof.

47. The method of claim 41 wherein the solid biological agent comprises a chemotherapeutic agent.

48. The method of claim 41 wherein the solid biological agent comprises an antibiotic.

49. The method of claim 41 wherein the solid biological agent comprises a bronchodilator.

50. The method of claim 41 wherein the solid biological agent comprises a surfactant.

SARS and Ozone Therapy: Theoretical Considerations

By Gérard V. S unnen, M.D.

BACK TO HOME

May 2003

Abstract

SARS (Severe Acute Respiratory Syndrome) is a global disease of significant lethality with an expanding incidence and prevalence base. Of massive public health importance, SARS presents supremely challenging problems in light of its pathogenic capacity and mutational potential. Ozone, because of its special biological properties, has theoretical and practical attributes to make it a viable candidate as a SARS virus inactivator through a variety of physicochemical and immunological mechanisms.

The Family of Coronaviruses

The SARS virus belongs to the viral family *Coronaviridae*. which includes two genera, coronavirus and togovirus, each showing similar replication mechanisms and genomic organization but distinct genome lengths and viral architecture. First identified in the 60's, this family identifies itself by large, enveloped, positive-stranded RNA virions. Their appearance is characteristically distinct, with envelopes endowed with host cell membrane-tropic petal shaped spikes (peplomers). The large, amply spaced peplomers on the virion surface suggests a coronal (crown-like) appearance.

Prior to SARS, *Coronaviridae* were responsible for relatively mild cold-like syndromes in humans corresponding to their predilection for the ciliary epithelium of the trachea, nasal mucosa, and alveolar cells of the lungs. At times they were only rarely implicated in serious respiratory illnesses in frail older adults (Falsey 2002). SARS represents a quantum leap in *Coronaviridae* infectivity by way of its significant lethality. Widely seen in nature, coronaviruses infect a spectrum of animal hosts and are responsible for avian infectious bronchitis, murine hepatitis, and porcine gastroenteritis, among others. Of possible significance to humans is that animal coronaviruses are able to penetrate into the central nervous system.

SARS: Virion architecture and molecular biology

The SARS virion differs from other members of the *Coronaviridae* family in its genomic composition. The other viral structures, however, are similar, including virion architecture, and the fundamental composition of structural and non-structural proteins.

The software for viral replication is the nucleic acid core, a single strand long chain RNA nucleotide. The core is surrounded by the nucleic acid coat or capsid. The capsid is rigid and determines the shape of the virus; it is made of repeating units called capsomeres. The SARS viral nucleocapsid is tubular with a helical symmetry.

The nucleocapsid is surrounded by an envelope which forms the outer layer of the virion and maintains intimate contact with host bodily fluids. As such, it is sensitive to the composition and alterations in its milieu, such as temperature, pH, and ionic balance. The viral envelope is formed at the time of budding, an intricate process in which the nucleocapsid exits the host cell. In order to do this, it fuses with the host cell membrane, appropriating its components to form its own envelope. It is known that the lipid composition of viral membranes reflects the lipid composition through which the particles exit. Viral envelopes are composed of lipid bilayers associated with a union of carbohydrates and proteins, glycoproteins, and lipids and phosphates, phospholipids. Up to 60% of the lipid component of the envelope is composed of phospholipid and the remainder is mostly cholesterol. This lipid-carbohydrate envelope is closely articulated with the peplomers which determine attachment and penetration into host cells.

The genome composition and sequence of the SARS virus has recently been identified (Marra 2003; Rota 2003). Marra et al. described a viral genome configuration of 29,727 nucleotides in length, within which exists

a gene order similar to other coronaviruses. However, because the genetic composition of SARS does not closely resemble any of the three known classes of coronaviruses, they propose a new and fourth class of coronaviruses, the SARS-CoV. Postulated, is a hypothesis that an animal virus recently mutated to successfully infect humans, or that the SARS virus mutated from a common human coronavirus.

Rota et al. reported a nucleotide sequence of 29,727 in SARS-CoV, with 11 open reading frames. Phylogenetic analyses and sequence comparisons showed that the SARS virus is not closely related to any of the previously characterized coronaviruses.

Virion structural proteins are essential elements in determining the morphological and functional dimensions of the SARS virus. Coronavirus structural proteins include the N nucleocapsid phosphoprotein which binds to viral RNA; the membrane glycoprotein M which forms the shell of the internal viral core and is responsible for triggering virus assembly ; the protein E associated with the virion envelope; the spike glycoprotein S which binds to specific cellular receptors and elicits cell-mediated immunity; and the Hemagglutinin-esterase glycoprotein HE forming small spikes on the coronavirus envelope (Knipe 2001).

SARS: Viral replication

The viral replication cycle follows the pattern seen in mammalian viruses and may be divided into several stages (Cann 1997; Evans 1997; Knipe 2001). The coronavirus attaches to the membrane of the host cells by binding the S and HE proteins of its peplomers to receptor glycoproteins or glycans.

Once cell entry is achieved, the virion sheds its envelope to commence its replication in the host cell cytoplasm. It binds to cellular ribosomes and released viral polymerase begins the RNA replication cycle. Newly formed nucleocapsids continue their assembly with the acquisition of new envelopes by means of budding through membranes of the cell's endoplamic reticulum.

Virions are then released into the general blood and lymphatic circulation, ready to infect new cells, other organ systems, and new hosts.

SARS: Clinical findings

Recently, the clinical manifestations of SARS have been comprehensively described (Peiris 2003). In this study of 50 hospitalized patients, fever, chills, myalgia, and dry cough were the most frequent presenting complaints. Also reported, were rhinorrhea, sore throat, and gastrointestinal symptoms.

Radiological examination showed evidence of pulmonary consolidation approximately 5 days after the onset of symptoms. Laboratory examination showed leucopenia and lymphopenia, despite the presence of fever; also anemia, thrombocytopenia, liver enzyme elevations (alanine aminotransferase), and skeletal and heart muscle enzyme elevation (creatinine phosphokinase). All these features point to severe systemic inflammatory insults.

The incubation of SARS is 2 to 10 days, and in some patients perhaps longer. Viral transmission is achieved by the respiratory route where it may infect the new host through aerosol and droplet contact with mucosal surfaces of the mouth, nose, throat, and probably the conjunctiva. SARS virions have been found in feces and the importance of this route of tranmission is being evaluated, as it is known that several animal coronaviruses use this propagation venue. Moreover, since it is appreciated that SARS particles remain viable on fomites for 48 hours or longer, any eradication effort must address the infectivity of objects in the environment.

The syndrome progresses to severe disease with respiratory distress and oxygen desaturation requiring ventilatory support in over a third of patients, approximately 8 days after symptom onset. Mortality has been noted to vary according to transmission clusters, ranging from 3 to 20%. This suggests that the etiology of SARS depends upon a heterogenous population of viral quasispecies with variable degrees of virulence.

SARS: Genetic creativity

As is the case in the majority of RNA viruses, coronaviruses mutate at a high rate (Steinhauer 1986). Within any one afflicted individual, coronaviruses particles do not show a homogeneous population. Instead, they

function as a pool of genetically variant strains known as quasispecies. This is due to the high error frequency of RNA polymerases, the presence of deletion mutants, the high frequency of RNA recombination and point mutations, and the occurrence of defective-interfering RNA (DI RNA). The net result of these diverse and complex mechanisms is the continuous spawning of novel virions and divergent quasispecies. Some of the genetic creations will find themselves at an advantage in negotiating new host antibody responses and pharmacological antiviral countermeasures; and they will propagate accordingly, thus expanding their ecological terrain. Other genetic creations will be too lethal to their hosts, work against their own survival, and will prove to be non-adaptive. If we can speak of a viral psychology, an efficient survival balance aims somewhere between defeat by host defenses on one hand, and viral suicide through aggressive lethality on the other.

Ozone: Physical and physiological properties

The oxygen atom exists in nature in several forms: (1) as a free atomic particle (O), it is highly reactive and unstable; (2) Oxygen (O2), its most common and stable form, is colorless as a gas and pale blue as a liquid; (3) Ozone (O3), has a molecular weight of 48, a density one and a half times that of oxygen and contains a large excess of energy in its molecule (O3 (3/2 O2 + 143 KJ/mole). It has a bond angle of 127 (3(, which resonates among several forms, is distinctly blue as a gas and dark blue as a solid; (4) O4 is a very unstable, rare, nonmagnetic pale blue gas which readily breaks down into two molecules of oxygen.

Ozone (O3), a naturally occurring configuration of three oxygen atoms, has a half life of about one hour at room temperature, reverting to oxygen. A powerful oxidant, ozone has unique biological properties. Since medicinal ozone is administered by interfacing it with blood, basic research on ozone's biological dynamics have centered upon its effects on blood cellular elements (erythrocytes, leucocytes, and platelets), and to its serum components (proteins, lipids, lipoproteins, glycolipids, carbohydrates, electrolytes).

The effects of ozonation on whole blood are extraordinarily complex and are far from adequately elucidated. If the biochemical configuration of serum - with its proteins, including enzymes, immunoglobulins, clotting factors; its hormones, vitamins, lipoproteins and cholesterol; its carbohydrates including glucose, and electrolytes, among others (Dailey 1998) - can be compared to an orchestra, ozone administration can be likened to the introduction of a novel and powerful musical instrument, affecting the interactions of all the other instruments.

Even though an in-depth analysis of ozone's multifaceted effects upon the panoply of blood constituents is beyond the intent and scope of this article (The reader is referred to Bocci, 2002; Sunnen, 1988), the following points of research interest are advanced:

Erythrocytes have been extensively studied in relation to ozone administration. Many studies which have used erythrocyte suspension in physiologic saline (Kourie 1998; Fukunaga 1999) have found hemolysis at relatively low ozone dosages (10 to 30 ug/ml). When ozone is administered in whole blood, however, the dynamics of ozone interaction are such that hemolysis begins to be observed at significantly higher doses, implying a buffering action of blood constituents. Moreover, the functionality of erythrocyte enzymes are maintained, suggesting a protective role of antioxidant systems (Cross 1992). There is some evidence that ozone administration may stimulate erythrocyte formation and release (Hernandez 1999).

Leucocytes, intimately connected to immune function, show good resistance to ozone because they possess enzymes which protect them from oxidative confrontation. These enzymes include superoxide dismutase, glutathione, and catalase. A promising area of research centers on cytokine and interferon stimulation in ozone administration and its implication for enhancing immune function (Paulesu 1991; Bocci 1994; Larini 2001). A classical adage of ozone therapy is that lower ozone dosages are stimulating to immune action while higher dosages become inhibitory (Viebahn 1999). Further research will need to clarify the parameters of this phenomenon, as well as the effects of ozone infusion upon different types of leucocytes in relation to the disease process being treated.

Ozone: Antipathogenic properties

Recently, there has been renewed interest in the potential of ozone for viral inactivation in vivo. It has long been established that ozone neutralizes bacteria, viruses, fungi, and parasites in aqueous media. This has

prompted the creation of water purification processing plants in numerous major municipalities worldwide. Ozone's unique physicochemical and biological properties, and environmentally-friendly aspects, have since been applied to a panoply of industrial uses such as the packaging of pharmaceuticals, the fumigation of homes and buildings (sick building syndrome), the treatment of indoor air in operating rooms and nursing homes, and the disinfection of large scale air conditioning systems in hospitals (Rice 2002).

Ozone's remarkable capacities for pan-antipathogenic action has been applied to the treatment of poorly healing wounds and burns (Sunnen 1999). A partial list of organisms susceptible to ozone inactivation in these clinical situations includes aerobic and anaerobic bacteria, Bacteroids, Campylobacter, Clostridium, Corynebacteria, Escherichia, Klebsiella, Legionella, Mycobacteria, Propriobacteria, Pseudomonas, Salmonella, Shigella, Staphylococcus, Streptococcus, and Yersinia. Susceptible viruses include Adenoviridae, *Filiviridae*, Hepnaviridae, Herpesviridae, Orthomyxoviridae, Picornaviridae, Reoviridae, and Retroviridae. Ozone-sensitive fungi include Actinomycoses, Aspergillus, Candida, Cryptococcus, Epidermophyton, Histoplasma, Microsporum, and Trichophyton.

Some viruses are more susceptible to ozone's action than others. It has been found that lipid-enveloped viruses are the most sensitive. This makes intuitive sense, since enveloped viruses are designed to blend into the dynamically constant milieu of their mammalian hosts. This group includes, hepatitis B and C, herpes 1 and 2, Cytomegalus (Epstein-Barr), HIV 1 and 2, Influenza A and B, West Nile virus, Togaviridae, Eastern and Western equine encephalitis, rabies, and *Filiviridae* (Ebola, Marburg), among others.

The envelopes of viruses provide for intricate cell attachment, penetration, and cell exit strategies. Peplomers, finely tuned to adjust to changing receptors on a variety of host cells, constantly elaborate slightly new glycoprotein configuration under the direction of portions of the viral genome, thus adapting to host cell defenses. Envelopes are fragile. They can be disrupted by ozone and its by-products.

Lipid enveloped viruses in aqueous media are readily inactivated by ozone via the oxidation of their envelope lipoproteins and glycoproteins (Akey 1985; Shinriki 1988; Vaughn 1990; Wells 1991; Carpendale 1991). In whole blood, however, ozone's virucidal actions are buffered by the spectrum of its components and ozone becomes less effective. This situation is further complicated in the case of retroviruses which ensconce themselves within host DNA (Chun 1999), and in Herpesviridae, where virions have the capacity to persist indefinitely in their host through the formation of an episome in the nuclei of the cells that harbor them (White 1994).

Several studies have reported the safety and the benefits of ozone administration in vivo. Wells et al. (1991) showed that ozone-treated HIV-spiked Factor VIII maintained its biological capacity; and that, concomitantly, there was an 11 log reduction in detectable virions. The improvement of liver enzymes in hepatitis C patients after several months of ozone therapy was described (Viebahn 1999; Amato 2000). An 80% hepatitis C viral load reduction in 82 patients using AHT was reported by Luongo et al., 2000.

It is remarkable, however, that to date, no adequate double blinded study has addressed ozone therapy in viral conditions such as hepatitis B and C, HIV, or herpes.

Ozone: Clinical methodology

Ozone may be utilized for the therapy of a spectrum of clinical conditions (Viebahn 1999). Routes of administration are varied and include external, and internal (blood interfacing) methods. In the technique of ozone major autohemotherapy (AHT), an aliquot of blood (50 to 300 ml) is withdrawn from a virally-afflicted patient, anticoagulated, interfaced with an ozone/oxygen mixture, then re-infused. This process is repeated serially, in a manner consonant with the treatment protocol until viral load reduction and symptom abatement are observed.

Recently there has been interest in new methods of interfacing oxygen-ozone mixtures with whole blood, serum, and serum components (Sunnen and Robinson, 2001).

Another, more experimental and more intensive technique of ozone administration, is called the Extracorporeal Blood Circulation Versus O2-O3 (EBOO), which treats the entire blood volume using a hollow-fibre oxygenator-ozonizer (Di Paolo 2000).

Ozone: Possible mechanisms of anti-viral action

The average adult has 4 to 6 liters of blood, accounting for about 7% of body weight. How can any viral load reduction reported via AHT ozone therapy be explained in the face of a technique that treats relatively small percentages of blood volume, albeit serially?

The viral culling effects of ozone in infected blood may recruit a variety of mechanisms. Research is needed to ascribe relative importance to these, and possibly other mechanisms of ozone's anti-viral action:

1. The denaturation of virions through direct contact with ozone. Ozone, via this mechanism, disrupts viral proteins, lipoproteins, lipids, glycolipids, or glycoproteins. The presence of numerous double bonds in these molecules makes them vulnerable to the oxidizing effects of ozone which readily donates its oxygen atom and accepts electrons in redox reactions. Unsaturated bonds are thus reconfigured, molecular architecture is disrupted, and breakage of the envelope ensues. Deprived of an envelope, virions cannot sustain nor replicate themselves.
2. Ozone proper, and the peroxide compounds it creates, may alter structures on the viral envelope which are necessary for attachment to host cells. Peplomers, the viral glycoproteins protuberances which connect to host cell receptors are likely sites of ozone action. Even minimal alteration in peplomer integrity through glycoprotein peroxidation could impair attachment to host cellular membranes foiling viral attachment and penetration.
3. Introduction of ozone into the serum portion of whole blood induces the formation of lipid and protein peroxides. While these peroxides are not toxic to the host in quantities produced by ozone therapy, they nevertheless possess oxidizing properties of their own which persist in the bloodstream for several hours. Peroxides created by ozone administration show long-term antiviral effects which may serve to further reduce viral load.
4. The immunological effects of ozone have been documented (Bocci 1992; Paulesu 1991). Cytokines are proteins manufactured by several different types of cells which, in turn, regulate the functions of other cells. Mostly released by leucocytes, they are important in mobilizing immune reactivity. Ozone-induced release of cytokines may constitute an avenue for the reduction of circulating virions.
5. Ozone action on viral particles in infected blood yield several possible outcomes. One outcome is the modification of virions so that they remain structurally grossly intact yet sufficiently dysfunctional as to be nonpathogenic. This attenuation of viral particle functionality through slight modifications of the viral envelope, and possibly the viral genome itself, not only modifies pathogenicity, but allows the host to diversify its immune response. The creation of dysfunctional viruses by ozone offers unique therapeutic possibilities. In view of the fact that so many mutational variants exist in any one afflicted individual, the creation of an antigenic spectrum of crippled virions could provide for a unique host-specific stimulation of the immune system, thus designing what may be called a host-specific autovaccine.
6. A very exiting avenue of research suggests that the virucidal properties of antibodies is predicated upon their ability to catalyse highly active forms of oxygen including ozone (Marx 2002; Wentworth 2002). A key element in the viral-inactivating capacity of antibodies may thus reside in the formation of ozone integral to antigen-antibody reactions. Exogenously administered ozone may, in this model, amplify the efficacy of antigen-antibody dynamics.

SARS and Ozone: Special considerations

SARS is produced by a novel coronavirus which has succeeded in finding breaches in the immunological defenses in our contemporary human population. It appears to have developed an aggressive balance between viral propagation and lethality.

The universal strategy in mastering infections, whether bacterial or viral, is the culling of pathogenic organisms to the point where they no longer represent an invasive and replicative threat; and, concomitantly,

the elaboration of systems of immune defense capable of neutralizing subsequent viral attacks. This goal is achieved mainly through direct pathogen inactivation on one hand, and by the actuation of host immune competence on the other.

SARS, as an acute, rapidly progressing, pan-inflammatory infection which, predicated upon the quasispecies involved, may present distressful mortality outcomes. A salient clinical configuration of this disease rests upon its acute involvement of the respiratory system in its disruption of the harmonious homeostasis of blood gases. When pO2 and Pco2 are sufficiently compromised, central nervous system cortical changes in the level of consciousness occur which impair volition to breathe, along with depression of the respiratory chemoreceptors in the medulla.

Antiviral agents and inhibitors to inflammation (steroids) have, thus far, not been effective in significantly softening the virulence of SARS.

Because of its acuteness, SARS is likely to require proactive viral culling. With an estimated 10 billion SARS viral particles generated daily - a reproductive magnitude commonly observed in viremic episodes in enveloped viruses - it is suggested that ozone administration may likely need to be more intensive than in chronic infections, such as hepatitis B and C. Whereas the latter conditions have been addressed with AHT frequencies ranging from once daily to once weekly, SARS may require more accelerated attention, either with AHT or with EBOO.

SARS and sterilization of the environment

The recent findings that the SARS virus has the capacity to remain infectious on fomites for up to several days indicates that it is a hardier organism than most of its other lipid enveloped colleagues.

Predictably, disinfectants such as bleach, phenol, and formaldehyde have been found to be effective in deactivating the SARS virus; detergents, however, were less capable.

Caustic liquid agents have the disadvantage of faring poorly in decontaminating complex medical equipment and the complex hospital room milieu of SARS patients.

Ozone, in light of its pan-virucidal profile, offers the advantage of existing as a gas, with its attendant ability to disinfect poorly accessible spaces. Moreover, ozone has the distinct benefit of reverting to oxygen, while liquid-based disinfectants are likely to injure the surfaces to which they are applied, and to leave toxic residues. Ozone-mediated environmental decontamination, however, needs to respect stringent protocols to insure that the ambient ozone in the process of sterilizing the target environment has time to revert to its stable parent, oxygen, without inflicting toxicity to the personnel.

Summary and conclusions

SARS is an acute pan-inflammatory multi-system syndrome caused by a hitherto unknown coronavirus. This virion incorporates a novel RNA genome and a lipid bilayered glycoprotein envelope. The SARS virus, based upon what is known about *Coronaviridae* is likely to have a high rate of mutation allowing any one individual to harbor numerous quasispecies.

Ozone is a naturally occurring energy-rich molecule embodying unique physico-chemical and biological properties suggesting a possible role in the therapy of SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens.

This paper outlines six possible mechanisms by which ozone may exert its antiviral actions. Due to the excess energy contained within the ozone molecule, it is theoretically likely that ozone, unlike organism-specific antiviral options available today, will show effectiveness across the entire genotype and subtype spectrum of SARS.

Ozone has unique disinfectant properties. As a gas, it has a penetration capacity that liquids do not possess. In view of the fact that SARS persists on fomites for up to several days, it is suggested that ozone technology be applied to the decontamination of SARS-contaminated medical environments.

In conclusion, it is suggested that this treatment modality, which has been demonstrated to be innocuous to humans and animals in contemporary treatment protocols, be granted research consideration for SARS. It may then be found therapeutically useful not only in SARS, but also in future epidemics caused by novel organisms which, unfortunately, are certain to emerge.

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DE 100 00823 A1 **Translate**

German

74 Offenlegungstag

54 Einbringen yon Gasen in sine Korperflussigkeit

57 Die Erfindung betrifft eine Vorrichtung zum Einbringen eines Gases in eine Korperflussigkeit, in eine Gewebeflus, sigksit oder in eine Kulturflussigkeit. Die Vorrichtung waist mindestens einen Kanal auf, durch den das Gas unter Druck stromt. Der kanal besitzt mindestens eine Gasaustrittsoffnug, dutch die des Gas in die Flussigkeit austritt. Die Offnung ist dutch eine gasdurchlasslge Barriers verschlossen.

Translate

74 Offenlegungstag. (Disclosure day.)

(21) Appl. No. : **DE 100 00 823 A 1**
(54) Title: Bring in the yonder gas to eliminate malignant-flu
(57)ABSTRACT:

The invention involves an appliance to bringing of a gas into a malignant-flu’s, into a Flus-Tissue of crowd diseases, or a Germany-flu.

The appliance shows at least one duct and through which the gas under pressure valve.

The duct possesses at least one “ Gasaustrittsoffnung " and it was pass through the ga into the infect position to eliminate. This must be avoid to pass through to breathe freely by th railings floodgate.