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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: RESPIRATORY SYNCYTIAL VIRUS VACCINES EXPRESSING PROTECTIVE ANTIGENS FROM PROMOTOR-
PROXIMAL GENES

(57) Abstract: Recombinant respiratory syncytial virus (RSV) having the position of genes shifted within the genome or antigenome of the recombinant virus are infectious and attenuated in humans and other mammals. Gene shifted RSV are constructed by insertion, deletion or rearrangement of genes or genome segments within the recombinant genome or antigenome and are useful in vaccine formulations for eliciting an anti-RSV immune response. Also provided are isolated polynucleotide molecules and vectors incorporating a recombinant RSV genome or antigenome wherein a gene or gene segment is shifted to a more promoter-proximal or promoter-distal position within the genome or antigenome compared to a wild type position of the gene in the RSV gene map. Shifting the position of genes in this manner provides for a selected increase or decrease in expression of the gene, depending on the nature and degree of the positional shift. In one embodiment, RSV glycoproteins are upregulated by shifting one or more glycoprotein-encoding genes to a more promoter-proximal position. Genes of interest for manipulation to create gene position-shifted RSV include any of the NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G genes or a genome segment that may be part of a gene or extragenic. A variety of additional mutations and nucleotide modifications are provided within the gene position-shifted RSV of the invention to yield desired phenotypic and structural effects.



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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/20107

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N7/00 A61K39/155 A61P31/14

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 C12N A61K A61P

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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WHITEHEAD S.S. ET AL.: "Recombinant respiratory syncytial virus bearing a deletion of either the NS2 or SH gene is attenuated in chimpanzees" J. VIROL., vol. 73, no. 4, April 1999 (1999-04), pages 3438-3442, XP002192810 cited in the application figure 1 --- -/--	22,184

☒ 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

12 March 2002

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/20107

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 02530 A (WHITEHEAD STEPHEN S ;US HEALTH (US); COLLINS PETER L (US); JUHASZ) 22 January 1998 (1998-01-22) in particular, page 43, line 28-page 44, line 14, but see also page 11, line 21 - line 26 page 13, line 18 - line 37 page 31, line 19 - line 37 page 35, line 24 -page 38, line 7 page 40, line 22 -page 41, line 8 examples 13,17,18 claims 20-28,35,40-42,45,47	1-23,25, 28-52, 55,57, 58, 60-62, 64-66, 68-70, 72-74, 76,78, 80-185, 187
A	BUCHHOLZ U.J. ET AL.: "Chimeric bovine respiratory syncytial virus with glycoprotein gene substitutions from human respiratory syncytial virus /HRSV): effects on host range and evaluation as a live-attenuated vaccine." J. VIROL., vol. 74, no. 3, February 2000 (2000-02), pages 1187-1199, XP002192812 cited in the application the whole document	71,75, 77,79
X,P	BUKREYEV A. ET AL.: "Respiratory syncytial virus can tolerate an intergenic sequence of at least 160 nucleotides with little effect on transcription or replication in vitro and in vivo." J. VIROL., vol. 74, no. 23, December 2000 (2000-12), pages 11017-11026, XP002192811 the whole document	1-23,25, 28-52, 55,57, 58, 60-62, 64-66, 68-70, 72-74, 76,78, 80-185, 187

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/20107

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 100-108 and, as far as methods in vivo are envisaged, claim 198 are 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.:
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 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:

see additional 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 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.:

22, 184 and where applicable, partly 1-21, 23, 25, 28-52, 55, 57, 58, 60-62, 64-66, 68-70, 72-74, 76, 78, 80-183, 185, 187

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 I.2

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible.

Furthermore, most claims relate to a large number of possible recombinant constructs. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of such constructs. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be supported, disclosed, clear and concise, to wit:

- (1) the general concept of "shifting" to a promoter-proximal or promoter-distal position or
- (2) the general concept of bovine-human chimeric RSV (not involving "shifting") and
- (2) the specific constructs described in the application (examples),

which have been searched insofar as the corresponding search fees have been paid.

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 22,184 and, where applicable, partly 1-21,23,25,
28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

An isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, a RNA polymerase elongation factor, and a partial or complete recombinant RSV genome or antigenome having one or more shifted RSV gene(s) or genome segment(s) within said recombinant genome or antigenome that is/are positionally shifted to a more promoter-proximal or promoter-distal position relative to a position of said RSV gene(s) or genome segment(s) within a wild type RSV genome or antigenome.

Said RSV being RSV3120, bearing a deletion of nt 4499-4610.

2. Claims: partly 24, 186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 519-563.

3. Claims: partly 24,186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 1003-1086.

4. Claims: partly 24,186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 3073-3230.

5. Claims: partly 24,186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 4033-4197.

6. Claims: partly 24,186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 7387-7539.

7. Claims: partly 24,186 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 8433-8490.

8. Claims: partly 26,188 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 55-96.

9. Claims: partly 26,188 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 606-624.

10. Claims: partly 26,188 and, where applicable, partly 1-21,
23,25,28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a deletion of nt 4231-4300.

11. Claims: 27,189 and, where applicable, partly 1-21,23,25,
28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to an RSV bearing a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

deletion of nt 4683-4685.

12. Claims: 53,59,63,67,71,79 and, where applicable,
partly 1-21,23,25,28-52,55,57,58,60-62,64-66,
68-70,72-74,76,78,80-183,185,187

Idem as subject-matter 1, but relating to RSV G1/dSH,
G1F2/dSH, G1F2/dNS2dSH, G1F2/dNS1dNS2dSH as well as chimeric
viruses rBRSV/A2-G1F2, rBRSV/A2G1F2NS3NS4.

13. Claims: 56,159 and, where applicable, partly 1-21,23,25,
28-52,55,57,58,60-62,64-66,68-70,72-74,76,78,
80-183,185,187

Idem as subject-matter 1, but relating to RSV F1/deltaSH.

14. Claims: 75 and, where applicable, partly 1-21,23,25,28-52,
55,57,58,60-62,64-66,68-70,72-74,76,78,80-183,185,
187

Idem as subject-matter 1, but relating to chimeric
rBRSV/A2-MGF.

15. Claims: 77 and, where applicable, partly 1-21,23,25,28-52,
55,57,58,60-62,64-66,68-70,72-74,76,78,80-183,185,
187

Idem as subject-matter 1, but relating to chimeric
rBRSV/A2-G3F4

16. Claims: 202 and, where applicable, partly 200,201,203,205,
207

An isolated infectious recombinant respiratory syncytial
virus (RSV) comprising a major nucleocapsid (N) protein, a
nucleocapsid phosphoprotein (P), a large polymerase (L)
protein, a RNA polymerase elongation factor, and a partial
or complete bovine RSV genome or antigenome combined with a
plurality of heterologous gene(s) and/or genome segment(s)
of a human RSV selected from heterologous gene(s) and/or
genome segment(s) of RSV NS1, NS2,M, SH, G, and/or F to form
a human-bovine chimeric RSV genome or antigenome.

Said chimeric RSV being rBRSV/A2-NS1+2.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

17. Claims: 204 and, where applicable, partly 200,201,203,205,
207

Idem as subject-matter 16, but relating to rBRSV/A2-NS1+2GF.

18. Claims: 206 and, where applicable, partly 200,201,203,205,
207

Idem as subject-matter 16, but relating to rBRSV/A2-MSHGF.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/20107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9802530 A	22-01-1998	AU 3799797 A	09-02-1998
		BR 9710363 A	11-01-2000
		CA 2257823 A1	22-01-1998
		EP 0912724 A1	06-05-1999
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		WO 9802530 A1	22-01-1998
		US 5993824 A	30-11-1999
