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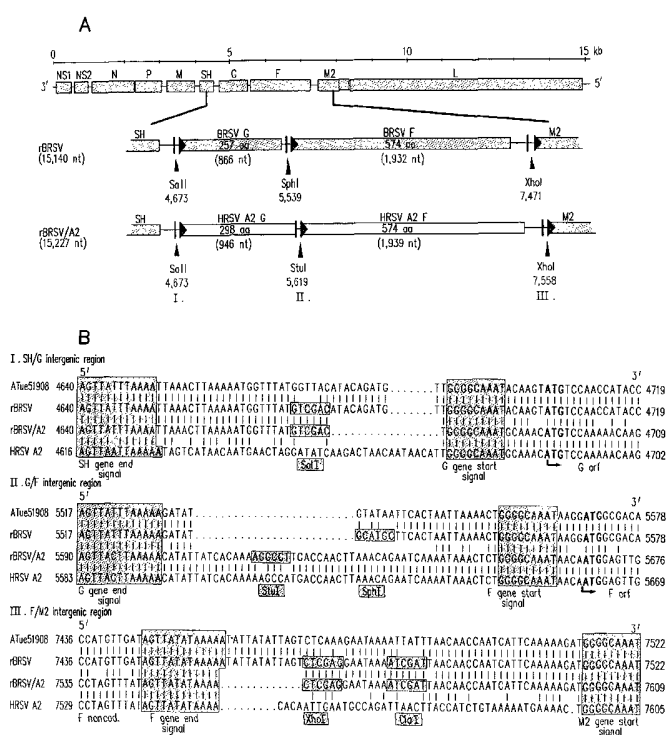
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[Continued on next page]

(54) Title: HUMAN-BOVINE CHIMERIC RESPIRATORY SYNCYTIAL VIRUS VACCINES



(57) Abstract: Chimeric human-bovine respiratory syncytial virus (RSV) are infectious and attenuated in humans and other mammals and useful in vaccine formulations for eliciting an anti-RSV immune response. Also provided are isolated polynucleotide molecules and vectors incorporating a chimeric RSV genome or antigenome which includes a partial or complete human or bovine RSV "background" genome or antigenome combined or integrated with one or more heterologous gene(s) or genome segment(s) of a different RSV strain or subgroup virus to form the human-bovine chimeric RSV genome or antigenome. In preferred aspects of the invention, chimeric RSV incorporate a partial or complete bovine RSV background genome or antigenome combined with one or more heterologous gene(s) or genome segment(s) from a human RSV. Genes of interest include any of the NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G genes or a genome segment including a protein or portion thereof. A variety of additional

mutations and nucleotide modifications are provided within the human-bovine chimeric RSV of the invention to yield desired phenotypic and structural effects.



patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

Inte I Application No
PCT/US 00/17755

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/86 C12N7/04 C07K14/14 C12N15/62 A61K38/17

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 C07K A61K

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	BUCHHOLZ, U.J. ET AL.: "Generation of Bovine Respiratory Syncytial Virus (BRSV) from cDNA: BRSV is not essential for virus replication in tissue culture, and the human RSV Leader region acts as a functional BRSV genome promoter" JOURNAL OF VIROLOGY., vol. 73, no. 1, January 1999 (1999-01), pages 251-259, XP002154541 ICAN SOCIETY FOR MICROBIOLOGY US cited in the application page 252, column 1, last paragraph -column 2, paragraph 2; figure 1	1,2,6-8, 16, 35-37, 46, 63-66, 83-86,88
Y	page 258, column 1, line 3 -column 2, last paragraph	1-14, 16-20, 25-28, 30-70, 82-101

☒ 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

26 March 2001

Date of mailing of the international search report

03 04 2001 03 04 2001

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INTERNATIONAL SEARCH REPORT

 Inte I Application No
 PCT/US 00/17755

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) cited in the application page 11, line 9 - line 20	1-3, 6-12, 30-70, 82-99
Y	page 36, line 10 -page 40, line 21; claims	1-14, 16-20, 25-28, 30-70, 82-101
Y	--- WO 99 24564 A (UNIV MARYLAND ;SAMAL SIBA K (US)) 20 May 1999 (1999-05-20) the whole document	16,35
X	--- WO 97 12032 A (US HEALTH ;COLLINS PETER L (US)) 3 April 1997 (1997-04-03)	1-10, 16-18, 30-70, 88,89
Y	the whole document	1-14, 30-70, 82-101
X	--- WO 99 15631 A (AVIRON INC) 1 April 1999 (1999-04-01)	1-3, 7-11,14, 35-37, 42, 46-48, 52-54, 57,60, 61,63, 82-86, 88-92, 96-99
Y	the whole document	1-11,14, 46-66, 82, 88-101
P,X	--- BUCHHOLZ UJ, GRANZOW H, SCHULDT K, WHITEHEAD SS, MURPHY BR, COLLINS PL.: "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 HRSV vaccine." J VIROL. 2000 FEB;74(3):1187-99., XP000972255 the whole document -----	1-3,6, 10, 16-18, 20,21, 25,26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/17755

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 48 to 56 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 composition.
2. ☒ Claims Nos.: 87 35
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.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

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

1. Claims: 10-15, 68-72, 92, 94-97 and partially 1-9, 30-67, 82-91, 93, 98-101

An isolated infectious chimeric human-bovine respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), a RNA polymerase elongation factor, characterised by combining a partial or complete human RSV (HRSV) background genome or antigenome with one or more heterologous gene(s) and/or genome segment(s) of a bovine RSV (BRSV) to form a human-bovine chimeric RSV genome or antigenome; a method for stimulating the immune system of an individual to induce protection against RSV which comprises administering to the individual an immunologically sufficient amount of said chimeric RSV combined with a physiologically acceptable carrier; an immunogenic composition to elicit an immune response against RSV comprising an immunologically sufficient amount of said chimeric RSV combined with a physiologically acceptable carrier; an isolated polynucleotide molecule comprising said chimeric RSV genome or antigenome;

2. Claims: 16-29, 73-81 and partially 1-9, 30-67, 82-91, 93, 98-101

An isolated infectious chimeric bovine-human respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), a RNA polymerase elongation factor, characterised by combining a partial or complete bovine RSV (BRSV) background genome or antigenome with one or more heterologous gene(s) and/or genome segment(s) of a human RSV (HRSV) to form a human-bovine chimeric RSV genome or antigenome a method for stimulating the immune system of an individual to induce protection against RSV which comprises administering to the individual an immunologically sufficient amount of said chimeric RSV combined with a physiologically acceptable carrier; an immunogenic composition to elicit an immune response against RSV comprising an immunologically sufficient amount of said chimeric RSV combined with a physiologically acceptable carrier; an isolated polynucleotide molecule comprising said chimeric RSV genome or antigenome;

Continuation of Box I.2

Claims Nos.: 87 35

Present claim 87 is related to a the "polynucleotide of claim 59". However, present claim 59 is not concerning a polynucleotide. The reference could be to claim 63, but it is not obvious and for a clarification from the applicant would be necessary.

Present claim 35 relates to a product defined by reference to a desirable characteristic namely comprising a nucleotide modification specifying a phenotypic change selected from a change in growth characteristics, attenuation, temperature-sensitivity, cold-adaptation, plaque size, host range restriction or a change in immunogenicity.

The claim covers all products having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. 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. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products exemplified in claims 30-34, 36-41, 43-45.

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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17755

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9802530 A	22-01-1998	AU 3799797 A BR 9710363 A CA 2257823 A EP 0912724 A US 5993824 A	09-02-1998 11-01-2000 22-01-1998 06-05-1999 30-11-1999
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WO 9915631 A	01-04-1999	AU 9585298 A EP 1017791 A	12-04-1999 12-07-2000