(54) Title: RECOMBINANT INFECTIOUS LARYNGOTRACHEITIS VIRUS AND USES THEREOF

(57) Abstract

The present invention provides recombinant infectious laryngotracheitis virus (ILTV) which are useful as vaccines to protect chickens or other poultry from infectious laryngotracheitis virus. The present invention further provides methods for distinguishing an animal vaccinated with a vaccine of the present invention from an animal infected with a naturally-occurring infectious laryngotracheitis virus.
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RECOMBINANT INFECTIOUS LARYNGOTRACHEITIS VIRUS AND USES THEREOF

Within this application several publications are referenced by arabic numerals within parentheses. Full citations for these publications may be found at the end of the specification immediately preceding the claims. The disclosures of these publications are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Field of the Invention

The present invention involves recombinant infectious laryngotracheitis (ILT) viruses useful in vaccines to protect poultry from naturally-occurring infectious laryngotracheitis virus and other poultry diseases.

Background of the Invention

The ability to isolate viral DNA and clone this isolated DNA into bacterial plasmids has greatly expanded the approaches available to make viral vaccines. The methods used to make the present invention involve modifying cloned viral DNA sequences by insertions, deletions and single or multiple base changes. The modified DNA is then reinserted into the viral genome to render the virus non-pathogenic. The resulting live virus may then be used in a vaccine to elicit an immune response in a host animal and to protect the animal against a disease.

One group of animal viruses, the herpesviruses or Herpetoviridae, is an example of a class of viruses amenable to this approach. These viruses contain 100,000
to 200,000 base pairs of DNA as their genetic material. Importantly, several regions of the genome have been identified that are nonessential for the replication of virus in vitro in cell culture. Modifications in these regions of the DNA may lower the pathogenicity of the virus, i.e., attenuate the virus. For example, inactivation of the thymidine kinase gene renders human herpes simplex virus non-pathogenic (1), and pseudorabies virus of swine non-pathogenic (2).

Removal of part of the repeat region renders human herpes simplex virus non-pathogenic (3, 4). A repeat region has been identified in Marek's disease virus that is associated with viral oncogenicity (5). A region in herpesvirus saimiri has similarly been correlated with oncogenicity (6). Removal of part of the repeat region renders pseudorabies virus non-pathogenic (U.S. Patent No. 4,877,737, issued October 31, 1989). A region in pseudorabies virus has been shown to be deleted in naturally-occurring vaccine strains (7, 8) and it has been shown that these deletions are at least partly responsible for the lack of pathogenicity of these strains.

It is generally agreed that herpesviruses contain non-essential regions of DNA in various parts of the genome. Some of these regions are associated with virulence of the virus, and modification of them leads to a less-pathogenic virus, from which a vaccine may be derived.

Infectious laryngotracheitis virus (ILTV), an alpha herpesvirus (9), is an important pathogen of poultry in the USA, Europe, and Australia, responsible for egg production losses and death (10). It causes an acute disease of chickens which is characterized by respiratory depression, gasping and expectoration of bloody exudate. Viral replication is limited to cells of the respiratory
tract wherein infection of the trachea gives rise to tissue erosion and hemorrhage.

In chickens, no drug has been effective in reducing the degree of lesion formation or in decreasing clinical signs. Vaccination of birds with various modified forms of the ILT virus derived by cell passage and/or tedious regimes of administration have been used to confer acceptable protection in susceptible chickens. Due to the limited degree of attenuation of current ILTV vaccines care must be taken to assure that the correct level of virus is maintained; enough to provide protection, but not enough to cause disease in the flock (11-21). Furthermore, these viruses may revert back to virulence, causing disease rather than providing protection against it.

ILTV has been analyzed at the molecular level. Restriction maps of the ILTV genome have been reported (22-26). The DNA sequence of several genes have been identified, i.e., thymidine kinase (27, 28), glycoprotein gB (27, 29, 30), ribonucleotide reductase (27, 31), capsid p40 (31, 32).

Furthermore, Shepard, et al. (53) disclosed that several genes located in the unique long region of the infectious laryngotracheitis virus genomic DNA are non-essential for viral replication.

Applicants have unexpectedly found that the unique short region of the ILT virus genomic DNA contains genes that are associated with ILTV virulence and that a deletion in those genes leads to an attenuated ILTV. Particularly, it was found that a deletion in the glycoprotein gG gene of the ILT virus results in an attenuated virus, which is useful as a vaccine against subsequent attack by a virulent ILTV strains.
Applicants also found that a deletion in the glycoprotein g1 gene of the unique short region also attenuates the ILTV. Furthermore, it is contemplated that a deletion in the US2 gene, the UL-47 like gene, and the glycoprotein g60 gene of the unique short region will also attenuate the ILTV.

ILTV can become latent in healthy animals which makes them potential carriers of the virus. For this reason, it is clearly advantageous to be able to distinguish animals vaccinated with non-virulent virus from animals infected with disease-causing wild-type or naturally-occurring virus. The development of differential vaccines and companion diagnostic tests has proven valuable in the management of pseudorabies disease (55). A similar differential marker vaccine would be of great value in the management of ILTV caused disease. The construction of differential diagnostics has focused on the deletion of glycoproteins. Theoretically, the glycoprotein chosen to be the diagnostic marker should have the following characteristics: (1) the glycoprotein and its gene should be non-essential for the production of infectious virus in tissue culture; (2) the glycoprotein should elicit a major serological response in the animal; and (3) the glycoprotein should not be one that makes a significant contribution to the protective immunity.

The ILT virus has been shown to specify at least four major glycoproteins as identified by monoclonal antibodies (Mr= 205K, 115K, 90K and 60K). Three glycoproteins seem to be antigenically related (Mr= 205K, 115K, and 90K) (34-36).

Three major ILT virus glycoproteins, gB (29, 30), gC (27, 51), and g60 (34, 53) have been described in the literature. These three genes have been sequenced and
two of the ILTV genes have been shown to be homologous to the HSV glycoproteins gB, and gC.

Of these, it is known that the ILTV gB gene is an essential gene and would not be appropriate as deletion marker genes. Furthermore, the gC gene of herpesviruses has been shown to make a significant contribution to protective immunity as a target of neutralizing antibody (56) and as a target of cell-mediated immunity (57). Therefore, the gC gene is not desirable as a deletion marker gene.

As to other glycoprotein encoding genes cited above, it is not known whether or not they would be suitable candidates for deletion in order to construct a recombinant ILT virus which can be used as a diagnostic vaccine.

Applicants have unexpectedly found that there are two glycoprotein encoding genes located within the unique short region of the ILT viral genome which could be safely deleted in order to construct a recombinant ILT virus that can be used as a diagnostic vaccine. These are the glycoprotein gG gene and the glycoprotein GI gene. By genetically engineering an ILT virus with a deletion in the glycoprotein gG gene or the glycoprotein GI gene, a ILT virus is produced which does not express any glycoprotein gG or glycoprotein gI. None of the prior arts teach or suggest that these two genes in the unique short region of the virus are appropriate candidates for deletion in order to create a diagnostic ILT virus vaccine.

Although several of the herpesviruses have been genetically engineered, no examples of recombinant ILTV have been reported.
The ability to engineer DNA viruses with large genomes, such as vaccinia virus and the herpesviruses, has led to the finding that these recombinant viruses can be used as vectors to deliver vaccine antigens and therapeutic agents for animals. The herpesviruses are attractive candidates for development as vectors because their host range is primarily limited to a single target species (37) and they have the capacity for establishing latent infection (38) that could provide for stable in vivo expression of a foreign gene. Although several herpesvirus species have been engineered to express foreign gene products, recombinant infectious laryngotracheitis viruses expressing foreign gene products have not been constructed. The infectious laryngotracheitis viruses described above may be used as vectors for the delivery of vaccine antigens from microorganisms causing important poultry diseases. Other viral antigens which may be included in a multivalent vaccine with an ILTV vector include infectious bronchitis virus (IBV), Newcastle disease virus (NDV), infectious bursal disease virus (IBDV), and Marek's disease virus (MDV). Such multivalent recombinant viruses would protect against ILT disease as well as other diseases. Similarly the infectious laryngotracheitis viruses may be used as vectors for the delivery of therapeutic agents. The therapeutic agent that is delivered by a viral vector of the present invention must be a biological molecule that is a by-product of ILTV replication. This limits the therapeutic agent in the first analysis to either DNA, RNA or protein. There are examples of therapeutic agents from each of these classes of compounds in the form of anti-sense DNA, anti-sense RNA (39), ribozymes (40), suppressor tRNAs (41), interferon-inducing double stranded RNA and numerous examples of protein therapeutics, from hormones, e.g., insulin, to lymphokines, e.g., interferons and interleukins, to natural opiates. The discovery of these therapeutic
agents and the elucidation of their structure and function does not necessarily allow one to use them in a viral vector delivery system, however, because of the experimentation necessary to determine whether an appropriate insertion site exists.

Summary of the Invention

The present invention provides a recombinant, attenuated infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gg gene. This attenuated virus is useful as a vaccine against infectious laryngotracheitis virus.

The present invention also provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the glycoprotein gg gene so that upon replication, the recombinant virus produces no glycoprotein gg.

The present invention also provides a method for distinguishing chickens or other poultry vaccinated with a recombinant infectious laryngotracheitis virus which produces no glycoprotein gg from those infected with a naturally-occurring infectious laryngotracheitis virus.

The present invention also provides a recombinant, attenuated infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the US2 gene, UL47-like gene, ORF4 gene or glycoprotein g60 gene.

The present invention also discloses four non-essential regions of the infectious laryngotracheitis viral genome: human cytomegalovirus immediately early (HCMV IE)
promoter, pseudorabies virus glycoprotein gX (PRV gX) promoter, and infectious bovine herpesvirus virus 1.1 VP8 (BHV-1.1 VP8). These regions may be used as insertion sites for a foreign gene in constructing a recombinant infectious laryngotracheitis virus vector.
Brief Description Of The Figures

Figure 1. The nucleotide sequence of 13,473 base pairs of contiguous DNA from the unique short region of the ILT virus. This sequence contains the entire 13,098 base pair unique short region as well as 273 base pairs of repeat region at one end and 102 base pairs of repeat region at the other end. The nucleotide sequences of Figure 1 begin with the internal repeat sequence and end within the terminal repeat sequence. The unique short region begins at base pair 274 of this Figure.

Figure 2. Asp718 I restriction enzyme map of the infectious laryngotracheitis virus (ILTV) USDA 83-2 genome. The upper diagram identifies the unique long (U_L), internal repeat (IR), unique short (U_S), and terminal repeat (TR) sections found in the ILTV genome. A map of the Asp718 I restriction endonuclease sites in the ILTV genome is shown below. Letters A through O identify Asp718 I restriction endonuclease fragments with "A" representing the largest fragment. Fragment "L" is the 2.5 kb Asp718 I fragment, fragment "H" is the 5164 bp Asp718 I
fragment, and fragment "G" is the 8.0 kb Asp718 I fragment. The fragments marked with asterisks contain a hypervariable region of approximately 900 bp that is repeated from one to 12 times. Since no one size predominates, these fragments appear in submolar amounts that are not well resolved on an ethidium bromide stained gel. The position of these repeats is indicated in the figure by the crooked dashed lines.

Figure 3. Open reading frames within the unique short region of infectious laryngotracheitis virus (ILTV) USDA 83-2. The 13,473 base pairs of the short region of ILTV contains the entire 13,098 base pair unique short region as well as 273 base pairs of repeat region at one end and 102 base pairs of repeat region at the other end. The unique short region contains 13 methionine initiated open reading frames (ORF) of greater than or equal to 110 amino acids (excluding smaller nested ORFs). All 13 ORFs were aligned to the Entrez release 6.0 virus division of the Genbank DNA database utilizing the IBI MacVector Protein to DNA alignment option (default settings). Eight of the ORFs exhibited significant homology to one or more other virus genes:
unique short (US2), protein kinase (PK),
unique long 47-like (UL47-like), and
glycoproteins gG, g60, gD, gI, and gE.

Figure 4. Detailed description of the DNA insertion in
Homology Vector 472-73.27. Diagram showing
the orientation of DNA fragments assembled in
plasmid 472-73.27. The origin of each
fragment is indicated in the table. The
sequences located at each of the junctions
between fragments are also shown (SEQ ID
NO's: 20, 21, 22 and 23). The restriction
sites used to generate each fragment as well
as the synthetic linker sequences which were
used to join the fragments are described for
each junction. The location of several gene
coding regions and regulatory elements is
also given. Restriction sites in brackets []
indicate the remnants of sites which were
destroyed during construction. The following
abbreviations are used, infectious
laryngotracheitis virus (ILTV), human
cytomegalovirus immediate early (HCMV IE),
pseudorabies virus (PRV), lactose operon Z
gene (lacZ), Escherichia coli (E. coli),
polyadenylation signal (poly A), and base
pairs (BP).
Figure 5. Detailed description of the DNA insertion in Homology Vector 501–94. Diagram showing the orientation of DNA fragments assembled in plasmid 501–94. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 24, 25, 26, and 27). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [ ] indicate the remnants of sites which were destroyed during construction.

The following abbreviations are used, infectious laryngotracheitis virus (ILTV), human cytomegalovirus immediate early (HCMV IE), pseudorabies virus (PRV), lactose operon Z gene (lacZ), Escherichia coli (E. coli), polyadenylation signal (poly A), thymidine kinase (TK), and base pairs (BP).

Figure 6. Detailed description of the DNA insertion in Homology Vector 544–55.12. Diagram showing the orientation of DNA fragments assembled in
plasmid 544-55.12. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 28, 29, 30, and 31). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [] indicate the remnants of sites which were destroyed during construction. The following abbreviations are used, infectious laryngotracheitis virus (ILTV), herpes simplex virus type 1 (HSV-1), pseudorabies virus (PRV), β-glucuronidase gene (uidA), Escherichia coli (E. coli), polyadenylation signal (poly A), and base pairs (BP).

Figure 7. Detailed description of the DNA insertion in Homology Vector 562-61.1F. Diagram showing the orientation of DNA fragments assembled in plasmid 562-61.1F. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 32, 33, 34 35, 36 and 37). The
restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [] indicate the remnants of sites which were destroyed during construction. The following abbreviations are used, infectious laryngotracheitis virus (ILTV), herpes simplex virus type 1 (HSV-1), pseudorabies virus (PRV), β-glucuronidase gene (uidA), Escherichia coli (E. coli), polyadenylation signal (poly A), and base pairs (BP).

Figure 8. Detailed description of the DNA insertion in Homology Vector 560-52.F1. Diagram showing the orientation of DNA fragments assembled in plasmid 560-52.F1. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 38, 39, 40, 41, and 42). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction.
The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [ ] indicate the remnants of sites which were destroyed during construction. The following abbreviations are used, infectious laryngotracheitis virus (ILTv), herpes simplex virus type 1 (HSV-1), pseudorabies virus (PRV), $\beta$-glucuronidase gene (uidA), Escherichia coli (E. coli), polyadenylation signal (poly A), unique long 47 (UL47-like), open reading frame 4 (ORF4), glycoprotein G (gG), and base pairs (BP).

Figure 9. Detailed description of the DNA insertion in Homology Vector 579-14.G2. Diagram showing the orientation of DNA fragments assembled in plasmid 579-14.G2. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 43, 44, 45, and 46). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [ ] indicate the remnants of sites which were
destroyed during construction. The following abbreviations are used, infectious laryngotracheitis virus (ILTV), herpes simplex virus type 1 (HSV-1), pseudorabies virus (PRV), β-glucuronidase gene (uidA), Escherichia coli (E. coli), polyadenylation signal (poly A), and base pairs (BP).

Figure 10. Detailed description of the DNA insertion in Plasmid Vector 544-39.13. Diagram showing the orientation of DNA fragments assembled in plasmid 544-39.13. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 47, 48, 49, and 50). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The synthetic linker sequences are underlined by a heavy bar. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [] indicate the remnants of sites which were destroyed during construction. The following abbreviations are used, pseudorabies virus (PRV), β-glucuronidase gene (uidA), Escherichia coli
(E. coli), herpes simplex virus type 1 (HSV-1), polyadenylation signal (poly A), and base pairs (BP).

Figure 11. Detailed description of the DNA insertion in Plasmid Vector 388-65.2. Diagram showing the orientation of DNA fragments assembled in plasmid 388-65.2. The origin of each fragment is indicated in the table. The sequences located at each of the junctions between fragments are also shown (SEQ ID NO's: 51, 52, 53, and 54). The restriction sites used to generate each fragment as well as the synthetic linker sequences which were used to join the fragments are described for each junction. The synthetic linker sequences are underlined by a heavy bar. The location of several gene coding regions and regulatory elements is also given. Restriction sites in brackets [ ] indicate the remnants of sites which were destroyed during construction. The following abbreviations are used, human cytomegalovirus immediate early (HCMV IE), lactose operon Z gene (lacZ), Escherichia coli (E. coli), pseudorabies virus (PRV), polyadenylation signal (poly A), and base pairs (BP).
Detailed Description Of The Invention

The present invention provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the glycoprotein gG gene. Said deletion attenuates the virus, rendering it suitable for use as a vaccine against infectious laryngotracheitis virus. A preferred embodiment of this invention is a recombinant infectious laryngotracheitis designated S-ILT-014 (ATCC Accession No. XXXX). The S-ILT-014 virus has been deposited pursuant to the Budapest Treaty on the International Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 U.S.A. on September 22, 1993 under ATCC Accession No. ). Another preferred embodiment of this invention is a recombinant infectious laryngotracheitis virus designated S-ILT-002.

For purposes of this invention, "a recombinant infectious laryngotracheitis virus" is a live infectious laryngotracheitis virus which has been generated by the recombinant methods well known to those of skill in the art, e.g., the methods set forth in HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT ILTV in Materials and Methods, and the virus has not had genetic material essential for the replication of the infectious laryngotracheitis virus deleted.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene and a deletion in the US2 gene. One preferred embodiment of this invention
is a recombinant infectious laryngotracheitis virus designated S-ILT-009.

The present invention further provides a recombinant laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene and a deletion in the ORF4 gene.

The present invention further provides a recombinant infectious laryngotracheitis virus which comprises the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene and a deletion in the UL47-like gene.

The present invention further provides a recombinant infectious laryngotracheitis virus which comprises the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene, a deletion in the ORF4 gene, and a deletion in the UL47-like gene. A preferred embodiment of this invention is a recombinant infectious laryngotracheitis virus designated S-ILT-015.

The present invention further provides a recombinant infectious laryngotracheitis virus which comprises the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene and a deletion in the glycoprotein g60 gene. A preferred embodiment of this invention is a recombinant infectious laryngotracheitis virus designated S-ILT-017.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the glycoprotein gG gene and a deletion in the glycoprotein gI gene.
The present invention further provides a recombinant infectious laryngotracheitis virus which comprises the infectious laryngotracheitis viral genome containing a deletion in the glycoprotein gG gene and a deletion in the thymidine kinase (TK) gene.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis virus genome which contains a deletion in the unique short region of the viral genome, wherein the deletion in the glycoprotein gG gene, and which also contains an insertion of a foreign gene. The foreign gene is inserted into a non-essential site of the infectious laryngotracheitis viral genome in such a way that it is capable of being expressed in a recombinant infectious laryngotracheitis infected host cell.

For purposes of this invention, "a non-essential site" of the infectious laryngotracheitis viral genome is a region of the viral genome which is not necessary for viral infection and replication.

The following non-essential sites of the infectious laryngotracheitis viral genome are preferred sites for inserting a foreign gene into the virus: the thymidine kinase (TK) gene, the US2 gene, the UL47-like gene, the ORF4 gene, the glycoprotein gG gene, the glycoprotein g60 gene, and the glycoprotein gI gene.

The foreign gene, which is inserted into a non-essential site in the infectious laryngotracheitis viral genome, may encode a screenable marker, such as E. coli β-galactosidase or E. coli β-glucuronidase.

The foreign gene which is inserted into a non-essential site in the infectious laryngotracheitis viral genome,
may encode an antigenic polypeptide which, when introduced into the host cell, induces production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable. Such antigenic polypeptide may be derived or derivable from infectious bronchitis virus, Newcastle disease virus, infectious bursal disease virus, and Marek's disease virus. Such antigenic polypeptide may also be derived or derivable from avian encephalomyelitis virus, avian reovirus, avian paramyxovirus, avian influenza virus, avian adenovirus, fowl pox virus, avian coronavirus, avian rotavirus, chick anemia agent, Salmonella spp., E. coli., Pasteurella spp., Bordetella spp. Eimeria spp. Histomonas spp., Trichomonas spp., poultry nematodes, cestodes, trematodes, poultry mites/lice, poultry protozoa.

The foreign gene may be put under control of an endogenous upstream infectious laryngotracheitis virus promoter, or it may be put under control of a heterologous upstream promoter. The heterologous upstream promoter may be derived from the HCMV IE promoter, the PRV gX promoter, and BHV-1.1 VP8 promoter.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gG gene, so that upon replication, the recombinant virus produces no glycoprotein gG. The following recombinant viruses are preferred embodiments of this invention: A recombinant infectious laryngotracheitis virus designated S-ILT-002, S-ILT-014, S-ILT-009, S-ILT-015, and S-ILT-017.

The present invention further provides a recombinant
infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gI gene, so that upon replication, the recombinant virus produces no glycoprotein gI.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gG gene and in the glycoprotein gI gene, so that upon replication, the recombinant virus produces no glycoprotein gG and no glycoprotein gI.

The present invention further provides a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the US2 gene, UL47-like gene, or glycoprotein g60 gene. It is contemplated that a deletion in any one of these genes will attenuate the virus, rendering it suitable to be used as a vaccine against infectious laryngotracheitis virus.

The present invention further provides a recombinant infectious laryngotracheitis virus which comprises a foreign gene inserted within the unique short region of the infectious laryngotracheitis viral genome, provided, however, that the insertion is not in the protein kinase gene, the glycoprotein gD gene, the glycoprotein gE gene and the ORF10 gene. Preferred insertion sites are the US2 gene, the UL47-like gene, the ORF4 gene and the glycoprotein g60 gene.
A foreign gene may be inserted within any one of these sites in such a way that it may be expressed in a host cell which is infected which the recombinant infectious laryngotracheitis virus of the present invention.

The foreign gene thus inserted may encode a screenable marker, such as E. coli β-galactosidase or E. coli β-glucuronidase.

The foreign gene thus inserted may encode an antigenic polypeptide which, when introduced into the host cell, induces production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable. Such antigenic polypeptide may be derived or derivable from infectious bronchitis virus, Newcastle disease virus, infectious bursal disease virus, and Marek's disease virus. Such antigenic polypeptide may also be derived or derivable from avian encephalomyelitis virus, avian reovirus, avian paramyxovirus, avian influenza virus, avian adenovirus, fowl pox virus, avian coronavirus, avian rotavirus, chick anemia agent, Salmonella spp. E. coli, Pasteurella spp., Bordetella spp. Eimeria spp. Histomonas spp., Trichomonas spp, Poultry nematodes, cestodes, trematodes, poultry mites/lice, poultry protozoa.

The foreign gene thus inserted may be put under control of an endogenous upstream infectious laryngotracheitis virus promoter, or it may be put under control of a heterologous upstream promoter. The heterologous upstream promoter may be the HCMV IE promoter, the PRV gX promoter or BHV-1.1 VP8 promoter.

The present invention further provides a vaccine for infectious laryngotracheitis virus which comprises a
suitable carrier and an effective immunizing amount of any of the recombinant infectious laryngotracheitis virus of the present invention. This vaccine may contain either inactivated or live recombinant virus.

Suitable carriers for the recombinant virus are well known in the art and include proteins, sugars, etc. One example of such a suitable carrier is a physiologically balanced culture medium containing one or more stabilizing agents such as hydrolyzed proteins, lactose, etc. Preferably, the live vaccine is created by taking tissue culture fluids and adding stabilizing agents such as stabilizing, hydrolyzed proteins. Preferably, the inactivated vaccine uses tissue culture fluids directly after inactivation of the virus.

The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the glycoprotein gG gene. A preferred embodiment of this invention is a vaccine which comprises a suitable carrier and an effective immunizing amount of any one of the following viruses: recombinant infectious laryngotracheitis viruses designated S-ILT-014, S-ILT-002, S-ILT-009, S-ILT-015 and S-ILT-017.

The present invention further provides a multivalent vaccine for infectious laryngotracheitis virus and for one or more of other avian diseases which comprises an effective immunizing amount of a recombinant virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region, wherein the deletion is in the glycoprotein gG gene, and an insertion of a foreign gene into a non-essential site
of the viral genome.

The foreign gene encodes an antigenic polypeptide which induces host cell production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable.


The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome containing a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gG gene, so that upon replication, the recombinant virus produces no glycoprotein gG. A preferred embodiment of this invention is a vaccine which comprises a suitable carrier and an effective immunizing amount of any one of the following viruses: recombinant infectious laryngotracheitis viruses designated S-ILT-014, S-ILT-002, S-ILT-009, S-ILT-015 and S-ILT-017.

The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis
virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gI gene so that upon replication, the recombinant virus produces no glycoprotein gI.

The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion or other alteration in the unique short region of the viral genome, wherein the deletion or alteration is in the glycoprotein gG gene and the glycoprotein gI gene so that upon replication, the recombinant virus produces no glycoprotein gG and glycoprotein gI.

The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the US2 gene, UL47-like gene, or glycoprotein g60 gene.

The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the US2 gene, ORF4 gene, UL47-like gene, or glycoprotein g60 gene, and insertion of a foreign gene into a non-essential site in the viral genome.

The foreign gene encodes an antigenic polypeptide which
induces host cell production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable.


The present invention further provides a vaccine which comprises a suitable carrier and an effective immunizing amount of a recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains an insertion of a foreign gene into a non-essential site in the viral genome. The foreign gene encodes an antigenic polypeptide which induces host cell production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable.

protozoa.

The present invention further provides a method of immunizing an animal against infectious laryngotracheitis virus which comprises administering to chickens or other poultry an effective immunizing dose of any of the vaccines of the present invention.

The present invention further provides a method for distinguishing chickens or other poultry which are vaccinated with an effective immunizing amount of a recombinant virus which produces no glycoprotein gG from those which are infected with a naturally-occurring infectious laryngotracheitis virus. This method comprises analyzing a sample of body fluid from the chickens or other poultry for the presence of glycoprotein gG of the infectious laryngotracheitis virus and at least one other antigen normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus. The presence of antigen which is normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus and the absence of glycoprotein gG in the body fluid is indicative of being vaccinated with the recombinant vaccine and not infected with a naturally-occurring infectious laryngotracheitis virus. The presence of glycoprotein gG and the antigen in the body fluid may be determined by detecting in the body fluid antibodies specific for the antigen and glycoprotein gG.

The present invention further provides a method for distinguishing chickens or other poultry which are vaccinated with an effective immunizing amount of a recombinant infectious laryngotracheitis virus which produces no glycoprotein gI from those which are infected with a naturally-occurring infectious laryngotracheitis
virus. This method comprises analyzing a sample of body fluid from the chickens or other poultry for the presence of glycoprotein gI of the infectious laryngotracheitis virus and at least one other antigen normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus. The presence of the antigen which is normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus and the absence of glycoprotein gI in the body fluid is indicative of being vaccinated with the recombinant vaccine and not infected with a naturally-occurring infectious laryngotracheitis virus. The presence of the antigen and glycoprotein gI in the body fluid may be determined by detecting in the body fluid antibodies specific for the antigen and glycoprotein gI.

The present invention further provides a method for distinguishing chickens or other poultry which are vaccinated with an effective immunizing amount of a recombinant virus which produces no glycoprotein gG and no glycoprotein gI from those which are infected with a naturally-occurring infectious laryngotracheitis virus. This method comprises analyzing a sample of body fluid from the chickens or other poultry for the presence of glycoprotein gG and gI of the infectious laryngotracheitis virus and at least one other antigen normally expressed in an animal infected by a naturally-occurring infectious laryngotracheitis virus. The presence of the antigen which is normally expressed in chickens or other poultry by a naturally-occurring infectious laryngotracheitis virus and the absence of glycoprotein gG and gI in the body fluid is indicative of being vaccinated with the vaccine and not infected with a naturally-occurring infectious laryngotracheitis virus. The presence of the antigen and glycoprotein gG and gI in the body fluid may be determined by detecting in the body
fluid antibodies specific for the antigen and glycoprotein gG and gI.

The present invention further provides a homology vector for producing a recombinant infectious laryngotracheitis virus by inserting a foreign DNA into the unique short region of the infectious laryngotracheitis genomic DNA, which comprises a double-stranded DNA molecule consisting essentially of a double-stranded foreign gene, which is flanked on either side by the double-stranded DNA homologous to the DNA located in the unique short region of the genomic DNA, provided, however, that the flanking sequences are not homologous to the glycoprotein gD gene, the glycoprotein gE gene, the protein kinase gene, and the ORF10 gene. The foreign gene may encode a screenable marker, such as *E. coli* B-galactosidase or *E. coli* B-glucuronidase.

The present invention further provides a homology vector for producing a recombinant infectious laryngotracheitis virus by deleting DNA which encodes a screenable marker, which has been inserted into the infectious laryngotracheitis virus genomic DNA, which comprises a double-stranded DNA molecule consisting essentially of a double-stranded DNA to be deleted, which is flanked on each side by a double-stranded DNA homologous to the infectious laryngotracheitis virus glycoprotein gG gene, glycoprotein gI gene, US2 gene, or UL-47 like gene. Preferred embodiments of this invention are the homology vectors designated Homology Vector 544-55.12, Homology Vector 562-61.1F, Homology Vector 472-73.27, Homology Vector 560-52.F1 and Homology Vector 579-14.G2.
MATERIALS AND METHODS

PREPARATION OF INFECTIOUS LARYNGOTRACHEITIS VIRUS STOCK SAMPLES. Infectious laryngotracheitis virus stock samples were prepared by infecting primary chicken embryo kidney cells (CEK; obtained from Spafas, Inc.) or primary chicken kidney cells (CK; obtained from chicks hatched from fertile eggs supplied by Hyvac) (50) in 225 cm² flasks with 0.5 ml of viral stock containing $10^5$-$10^6$ pfu in 1X Eagle's Basal Medium (modified) with Hank's salts (BME), 10% bromoethylamine(BEI)-treated fetal bovine serum (FBS), 1% glutamine stock, 2% penicillin/streptomycin (P/S) stock, and 1% sodium bicarbonate stock (these components are obtained from Irvine Scientific or an equivalent supplier, and hereafter the growth medium is referred to as complete BME medium). Viral stocks were then harvested 4-5 days later. Infected media and cells were resuspended in complete medium containing 20% sterile whole milk and stored frozen at -70°C.

PREPARATION OF INFECTIOUS LARYNGOTRACHEITIS VIRUS DNA. Four to five days after viral infection, cells and media were scraped from each flask into 15 ml conical centrifuge tubes and pelleted at 1700 x g for 5 minutes at 4°C. Because as much as 50% of the virus may be in the media, the supernatants were saved and treated as will be described below. The cell pellets were resuspended in 1
ml PBS per tube, combined and centrifuged again at 1700 x g for 5 minutes. The pellets were resuspended in 1 ml/flask of a buffer containing 10 mM Tris-HCl pH 7.5, 1 mM EDTA, and 1.5 mM MgCl₂ and were incubated for 15 minutes at 4°C. Twenty five μls of 20% NP40 per flask was added, and the mixture was then homogenized in a dounce homogenizer using an A pestle. The preparation was centrifuged at 1700 x g for 10 minutes at 4°C and the supernatant was retained. Ten μl of 0.5 M EDTA, 50 μl of 20% SDS, and 25 μl of 10 mg/ml proteinase K was added to the supernatant (per original flask). In some cases, this was then combined with virus obtained from the cell media supernatants (see above). The mixture was then treated at 65°C for 1-16 hours, followed by two extractions with phenol saturated with 100 mM Tris-HCl, pH 8. DNA in the aqueous phase was then precipitated with added 3 M sodium acetate (1/10th volume) and 2.5 vols of 100% ethanol.

To obtain virus from the media, the cell media supernatants were centrifuged at 23,500 x g for 30 minutes, and drained well. The pellet was resuspended in the above proteinase K-containing mixture as described. The DNA pellets were resuspended in 20 μl TE/flask and could be used at this point for further experiments or treated further to remove RNA with pancreatic RNase A, followed by phenol extraction and ethanol precipitation to obtain the DNA.
To prepare viral DNA minipreps, infected 10 cm dishes were scraped into conical centrifuge tubes and centrifuged 5 minutes at 1000 x g. Cell media supernatants were kept and treated as above. The cell pellets were each resuspended in 0.5 ml of 10 mM Tris-HCl pH 7.5, 1 mM EDTA, 0.5% NP40, and incubated 10 minutes at room temperature. Ten μl of 10 mg/ml RNase A was added, and the preparation was centrifuged 5 minutes at 1000 x g. Twenty-five μl of 20% SDS and 25 μl of 10 mg/ml proteinase K was added to the supernatant, and the entire preparation was added to the viral pellet from the cell media if it was used. The mixture was incubated at 55-65°C for one hour, extracted with buffer-saturated phenol and precipitated by the addition of 1 ml of ethanol. The DNA pellet was resuspended in 20 μl of TE and stored at 4°C.

POLYMERASE FILL-IN REACTION. DNA was resuspended in buffer containing 50 mM Tris pH 7.4, 50 mM KCl, 5 mM MgCl₂, and 400 micromolar each of the four deoxyribonucleotides. Ten units of Klenow DNA polymerase (Gibco BRL) were added and the reaction was allowed to proceed for 15 minutes at room temperature. The DNA was phenol extracted and ethanol precipitated as above.

DNA SEQUENCING. Sequencing was performed using the Sequenase Kit (US Biochemicals) and α³⁵S-dATP (New England
Nuclear). Reactions using both the dGTP mixes and the dITP mixes were performed to clarify areas of compression. Alternatively, compressed areas were resolved on formamide gels. Templates were double-stranded plasmid subclones or single stranded M13 subclones, and primers were either made to the vector just outside the insert to be sequenced, or to previously obtained sequence. Sequence obtained was assembled and compared using Dnastar software. Manipulation and comparison of sequences obtained was performed with IBI MacVector, Superclone and Supersee Align programs from Coral Software.

MOLECULAR BIOLOGICAL TECHNIQUES. Techniques for the manipulation of bacteria and DNA, including such procedures as digestion with restriction endonucleases, gel electrophoresis, extraction of DNA from gels, ligation, phosphorylation with kinase, treatment with phosphatase, growth of bacterial cultures, transformation of bacteria with DNA, and other molecular biological methods are described (42, 43). The polymerase chain reaction (PCR) was used to introduce restriction sites convenient for the manipulation of various DNAs (44). In general amplified fragments were less than 500 base pairs in size and critical regions of amplified fragments were confirmed by DNA sequencing. Except as noted, these techniques were used with minor variation.
SOUTHERN BLOTTING OF DNA. The general procedure for Southern blotting was taken from Maniatis et al. (1982) and Sambrook, et al. (1989) (42, 43). DNA was blotted to nylon membrane (Biorad Zetaprobe) in 0.4M NaOH and prehybridized for 5 minutes in a solution containing 0.25 M Na₂HPO₄, pH 7.2, 1 mM EDTA, 7% SDS at 65°C. Labeled probe was added that had been labeled by random priming using a Genius™ non-radioactive labeling kit from Boehringer-Mannheim. Hybridization was overnight at 65°C. Filters were washed twice with 40 mM Na₂HPO₄, pH 7.2, 1 mM EDTA, 5% SDS and then twice with 40 mM Na₂HPO₄, pH 7.2, 1 mM EDTA, 1% SDS for 30 minutes each at 65°C. Detection of bound probe was performed using the Boehringer Mannheim Genius™ non-radioactive detection kit.

DNA TRANSFECTION FOR GENERATING RECOMBINANT ILT VIRUS. The method is based upon the CaCl₂ procedure of Chen and Okayama (1987) (45) with the following modifications. Generation of recombinant ILT virus is dependent upon homologous recombination between ILT viral DNA and the plasmid homology vector containing the desired foreign DNA flanked by the appropriate herpesvirus cloned sequences. Plasmid DNA (10-40 mg) was added to 250 ml of a solution having a final concentration of 0.25 M CaCl₂. An equal volume of a buffer containing 50 mM MOPS (pH 6.95), 280 mM NaCl, and 1.5 mM Na₂HPO₄ was added to the DNA/CaCl₂ solution. After 10 minutes at room temperature,
the mixture was added dropwise to a 6 cm dish of CEK cells on maintenance media, and placed at 39°C for 4 to 5 hours. The cells were rinsed once with PBS, once with 20% glycerol in PBS for 2 minutes, rinsed again with PBS and fed with maintenance media. 1.5 ml of ILT viral stock was added to the media, and the cells were incubated overnight. The next day, fresh maintenance media was added, and the cells were incubated for two more days. The transfection stock was harvested, aliquotted, and frozen at -70°C.

PROCEDURE FOR GENERATING ILTV SUBGENOMIC DNA FRAGMENTS.
The ability to generate herpesviruses by cotransfection of cloned overlapping subgenomic fragments has been demonstrated for pseudorabies virus (46). If deletions and/or insertions are engineered directly into the subgenomic fragments prior to the cotransfection, this procedure results in a high frequency of viruses containing the genomic alteration, greatly reducing the amount of screening required to purify the recombinant virus. We have used the procedure of overlapping cosmids to map restriction enzyme sites.

A library of subclones containing overlapping ILTV subgenomic fragments was generated as follows. USDA ILTV Strain 83-2 has been designated S-ILT-001. Approximately 20 μg of ILTV DNA (obtained from S-ILT-001) in 0.5 ml of 10 mM Tris-HCl pH 8.0, 1 mM EDTA (TE) was sheared by
passing it twice through a 25 gauge needle as previously described (46). The DNA was centrifuged through a 15-40% glycerol gradient in 50 mM Tris-HCl pH 8.0, 1 mM EDTA, and 0.3 M NaCl for 5.5 hours at 274,000 x g. Fractions were analyzed on a 0.3% agarose gel, and those containing DNA of 35-50 kb were pooled, diluted twofold with TE, and precipitated with one tenth volume of 3 M sodium acetate and 2.5 volumes of ethanol. The tubes were centrifuged for one hour at 109,000 x g at 10°C. Pellets were resuspended, transferred to microfuge tubes, and precipitated with one tenth volume of 3 M sodium acetate and 2.5 volumes of ethanol. The DNA was resuspended in TE. DNA ends were made blunt ended by the POLYMERASE FILL-IN REACTION. The DNA was purified by extraction with both buffer saturated phenol and ether, precipitated with sodium acetate and ethanol as above, and resuspended in TE. Half of this material was ligated with 3 mg of vector, pSY1626, by the DNA ligation reaction. The vector used was pSY1626, which was made as follows. Cosmid pHC79 (Gibco BRL) was cut with HindIII and Avai to remove the tetracycline gene, and the ends were filled in with Klenow polymerase (FILL IN REACTION). The poly linker from pWE15 (Stratagene) was ligated into this vector. The poly linker was isolated by digestion with EcoRI, the ends were filled in with Klenow polymerase (FILL IN REACTION), and the fragment was purified on a LMP-agarose gel. DNA ligation was performed in the presence of melted agarose. The resulting cosmid, pSY1005, was modified at the EcoRI
site to create pSY1626 by blunt-ended insertion of a 1.5 kb HindIII–BamHI fragment from pNEO (P-L Biochemicals) containing the neomycin resistance gene. pSY1626 was cut and made blunt at the BamHI site, and ligated with sheared ILTV fragments as described above. The ligation mixture was packaged using Gigapack XL (Stratagene) according to the manufacturers instructions. The packaging mixture was added to AG1 cells (Stratagene) grown in the presence of maltose, and colonies were selected on LB plates containing kanamycin. Cosmid subclones containing ILTV DNA were identified by comparing restriction enzyme maps of individual cosmid clones to each other and to ILVTV genomic DNA to obtain a contiguous sequence of ILTV genomic DNA.

SCREEN FOR RECOMBINANT ILTV EXPRESSING ENZYMIC MARKER GENES. When the E. coli β-galactosidase or β-glucuronidase (uidA) marker gene was incorporated into a recombinant virus the plaques containing the recombinants were visualized by a simple assay. The enzymatic substrate was incorporated (300 μg/ml) into the agar overlay during the plaque assay. For the lacZ marker gene the substrate Bluogal™ (halogenated indolyl-β-D-galactosidase, Gibco BRL) was used. For the uidA marker gene the substrate X-Glucuro Chx (5-bromo-4-chloro-3-indolyl-β-D-glucuronic acid Cyclohexylammonium salt, Biosynth AG) was used. Plaques that expressed active marker enzyme turned blue. The blue plaques were
then picked onto fresh cells and purified by further blue plaque isolation. In recombinant virus strategies in which the enzymatic marker gene was removed, the assay involves plaque purifying white plaques from a background of parental blue plaques. Viruses were typically purified with five to ten rounds of plaque purification.

SCREEN FOR FOREIGN GENE EXPRESSION IN RECOMBINANT ILTV USING BLACK PLAQUE ASSAYS. To analyze expression of foreign antigens expressed by recombinant ILT viruses, monolayers of CEK cells were infected with recombinant ILT virus, overlaid with nutrient agarose media and incubated for 3-5 days at 39°C. Once plaques have developed, the agarose overlay was removed from the dish, the monolayer rinsed once with PBS, fixed with 100% methanol for 10 minutes at room temperature and the cells air dried. After re-hydrating the plate with PBS, the primary antibody was diluted to the appropriate dilution with PBS plus Blotto and incubated with the cell monolayer for 2 hours to overnight at room temperature. Unbound antibody was removed from the cells by washing four times with PBS at room temperature. The appropriate secondary antibody conjugate was diluted 1:500 with PBS and incubated with the cells for 2 hours at room temperature. Unbound secondary antibody was removed by washing the cells three times with PBS at room temperature. The monolayer was rinsed in color development buffer (100mM Tris pH 9.5/ 100mM NaCl/ 5mM MgCl2), and
incubated 10 minutes to overnight at room temperature with freshly prepared substrate solution (0.3 mg/ml nitro blue tetrazolium + 0.15 mg/ml 5-bromo-4-chloro-3-indolyl phosphatase in color development buffer). The reaction was stopped by replacing the substrate solution with TE (10mM Tris, pH7.5/1 mM EDTA). Plaques expressing the correct antigen stain black.

PURIFICATION OF ILTV gG FROM ILT VIRUS OR RECOMBINANT VIRUSES EXPRESSING ILTV gG. ILTV gG was purified from the media of cells infected with either wild type ILTV or with FPV or SPV vectors expressing ILTV gG. Cells were allowed to go to complete cytopathic effect (CPE), the media was poured off, and cell debris was pelleted in a table-top centrifuge. The media was concentrated in an Amicon concentrator using a YM30 ultrafiltration membrane at 15 psi. The concentrate was dialyzed against 20 mM Tris-HCl, pH 7.0 and loaded onto a DEAE-Sephacel (Pharmacia) column equilibrated with the same buffer. The material was eluted using a salt gradient from 0 to 1.5 M NaCl in 20 mM Tris-HCl, pH 7.0. Three ml fractions were collected and assayed by Western blot. A peptide antibody against ILTV gG was used to identify fractions containing ILTV gG. Fractions were pooled and further concentrated in a Centricon-10 microconcentrator (Amicon).

HOMOLOGY VECTOR 501-94. The plasmid 501-94 was constructed for the purpose of deleting a portion of the
thymidine kinase (TK) gene coding region from the ILT virus (28). It incorporates the HCMV IE promoter and a screenable marker, the *E. coli* lacZ gene, flanked by ILT virus DNA. The HCMV IE promoter-*E. coli* lacZ gene is inserted in the opposite transcriptional orientation to the ILTV TK gene. Upstream of the marker gene is an approximately 1087 base pair fragment of ILTV DNA which includes the first 77 amino acid codons of the ILTV TK gene. Downstream of the lacZ gene is an approximately 675 base pair fragment of ILTV DNA which includes 80 amino acid codons at the 3′ end of the ILTV TK gene. When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the DNA coding for amino acids 78 to 285 of the ILTV TK gene with DNA coding for the lacZ gene. The lacZ marker gene is under the control of the human cytomegalovirus (HCMV) immediate early (IE) gene promoter and also contains the pseudorabies virus (PRV) gX gene polyadenylation signal at the 3′ end of the gene. A detailed description of the plasmid is given in Figure 5. It was constructed from the indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector is derived from an approximately 3002 base pair *HindIII* fragment of pSP64/65 (Promega). Fragment 1 is an approximately 1087 base pair *HindIII* to BclI subfragment of the ILTV 2.4 kb *HindIII* fragment. Fragment 2 is an approximately 5017 base pair *SalI* to *SalI* fragment containing the HCMV IE promoter, β-
galactosidase (lacZ) marker gene, and PRV gX polyadenylation signal (see Figure 5). Fragment 3 is an approximately 675 base pair BclI to HindIII subfragment of the ILTV 2.4 kb HindIII fragment.

HOMOLOGY VECTOR 544-55.12. The plasmid 544-55.12 was constructed for the purpose of deleting a portion of the US2 gene coding region from the ILT virus and inserting a foreign DNA. It incorporates a screenable marker, the E. coli uidA gene flanked by ILT virus DNA. The PRV gX promoter-E. coli uidA gene is inserted in the opposite transcriptional orientation to the ILTV US2 gene. Upstream of the uidA gene is an approximately 2300 base pair fragment of ILTV DNA which includes 41 amino acid codons at the 3' end of the US2 gene (SEQ ID NO 2: aa. 188-229). Downstream of the uidA gene is an approximately 809 base pair fragment of ILTV DNA which includes 22 amino acid codons at the 5' end of the US2 gene (SEQ ID NO 2: aa. 1-22). When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the ILTV US2 DNA coding for amino acids 23 to 187 with DNA coding for the E. coli uidA gene. The uidA marker gene is under the control of the pseudorabies virus (PRV) gX promoter and also contains the herpes simplex virus type 1 thymidine kinase (HSV-1 TK) gene polyadenylation signal at the 3' end of the gene. A detailed description of the plasmid is given in Figure 6. It was constructed from the
indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector is derived from an approximately 2958 base pair Asp718I restriction fragment of a pSP18/pSP19 fusion such that the multiple cloning site is EcoRI/SacI/Asp718I/SacI/EcoRI. Fragment 1 is an approximately 2300 base pair Asp718I to DraI subfragment (SEQ ID NO 1: Nucl. 1-405) of the ILTV 2.5 kb Asp718I fragment. Fragment 2 is an approximately 3039 base pair XbaI fragment containing the PRV gX promoter, the E. coli uidA gene, and the HSV-1 TK polyadenylation site (See Figure 6). Fragment 3 is an approximately 809 base pair XbaI to Asp718I subfragment of the ILTV 1097 bp Asp718I fragment (SEQ ID NO 1: Nucl. 905-1714).

HOMOLOGY VECTOR 562-61.1F. The plasmid 562-61.1F was constructed for the purpose of deleting part of the gI gene from the ILT virus and inserting a foreign DNA. It incorporates a screenable marker, the E. coli uidA gene, flanked by ILT virus DNA. The PRV gX promoter-E. coli uidA gene is transcribed in the opposite direction to the ILTV gI gene promoter. The 983 base pair deletion begins 12 base pairs upstream of the translation initiation codon and deletes 324 of 363 amino acid codons at the 5' end of the ILTV gI gene (SEQ ID NO 11: aa. 325-363). When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the DNA coding for the ILTV gI gene with DNA coding for the E. coli uidA gene. A
detailed description of the plasmid is given in Figure 7. It was constructed from the indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector is derived from an approximately 2647 base pair Asp718I to HindIII fragment of pUC19. Fragment 1 is an approximately 1619 base pair Asp718I to XbaI subfragment of the ILTV 8.0 kb Asp718I fragment (SEQ ID NO 1: Nucl. 7556-9175). Fragment 2 is an approximately 691 base pair XbaI to XhoI fragment (SEQ ID NO 1: Nucl. 9175-9861) generated by the polymerase chain reaction (PCR). The template was the ILTV 8.0 kb Asp718I fragment. The upstream primer 92.09 (5'-CCTAGCACCTTTGTATCGCG-3'; SEQ ID NO. 55) sits down at a site 821 base pairs upstream of the ILTV gI gene and synthesizes DNA toward the 3' end of the gene. The downstream primer 92.11 (5'-CGCCTCGAGTCCCAATGAATAGGCATTGG-3'; SEQ ID NO. 56) sits down at a site 12 base pairs upstream of the translation start site of the ILTV gI gene and synthesizes DNA toward the 5' end of the gD gene. The product of the PCR reaction is 818 base pairs. This DNA fragment is digested with XbaI at the 5' end (a restriction enzyme site present in the ILTV DNA) and XhoI at the 3' end (a restriction enzyme site created in the PCR primer—see underlined sequence) to create an approximately 691 base pair XbaI to XhoI fragment. Fragment 3 is an approximately 3051 base pair SalI fragment containing the PRV gX promoter, the uidA gene, and the HSV-1 TK polyadenylation site (See Figure 6). Fragment 4 is an
approximately 624 base pair XhoI to HindIII fragment generated by PCR (SEQ ID NO 1: Nucl. 10,847-11,461). The template was the ILTV 8.0 kb Asp718I fragment. The upstream primer 92.10 (5'-CGCCCTCAGGGACCCATGTTGCGTGGC-3'; SEQ ID NO. 57) sits down at a site 117 base pairs upstream from the translation termination codon within the ILTV gI gene. The downstream primer 92.08 (5'-CTCGTCCGAACGAGTTACAG-3'; SEQ ID NO. 58) sits down at a site 604 base pairs downstream of the translation termination site of the ILTV gI gene and within the ILTV gE gene. The PCR product (729 base pairs) is digested with XhoI which is a unique site generated by the upstream PCR primer (underlined) and with HindIII at a site within the ILTV gE gene. Restriction endonuclease digestion with XhoI and HindIII creates an approximately 624 base pair Fragment 4. Fragment 5 is an approximately 2700 base pair HindIII subfragment of the ILTV 8.0 kb Asp718I fragment (SEQ ID NO 1: Nucl. 11,461-13,473 plus unsequenced DNA).

HOMOLOGY VECTOR 472-73.27. The plasmid 472-73.27 was constructed for the purpose of deleting a portion of the glycoprotein G (gG) gene coding region from the ILT virus and inserting a foreign DNA. It incorporates a screenable marker, the E. coli lacZ gene, flanked by ILT virus DNA. The HCMV IE promoter-E. coli lacZ gene is transcribed in the same direction to the ILTV gG gene promoter. The 874 base pair deletion of the ILTV gG gene extends from 60
nucleotides upstream of the translation initiation site to 814 nucleotides into the amino acid coding sequence, removing the coding capacity of 271 of 292 amino acids of the gG protein (SEQ ID NO 7). When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the DNA coding for amino acids 1 to 271 of the ILTV gG gene with DNA coding for the E. coli lacZ gene. A detailed description of the plasmid is given in Figure 4. It was constructed from the indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector is derived from an approximately 2686 base pair Asp718I restriction fragment of pUC 19 (Gibco, BRL). Fragment 1 is an approximately 2830 base pair Asp718I to NheI subfragment of the ILTV 5164 bp Asp718I fragment (SEQ ID NO 1: Nucl. 1714-4544). Fragment 2 is an approximately 5017 base pair SalI to SalI fragment containing the HCMV IE promoter, E. coli β-galactosidase (lacZ) marker gene, and PRV gX polyadenylation signal (see Figure 4). Fragment 3 is an approximately 1709 base pair SalI to Asp718I subfragment of the ILTV 5164 bp Asp718I fragment (SEQ ID NO 1: Nucl. 5419-6878).

HOMOLOGY VECTOR 560-52.F1. The plasmid 560-52.F1 was constructed for the purpose of deleting part of the UL47-like gene, all of ORF4, and part of the ILTV gG gene from the ILT virus and inserting a foreign DNA. It incorporates a screenable marker, the E. coli uidA gene,
flanked by ILT virus DNA. The PRV gX promoter-E. coli uidA gene is transcribed in the opposite direction to the ILTV UL47-like, ORF4, and gG gene promoters. The 2640 base pair deletion removes 442 of 511 amino acid codons at the 3' end of the UL47-like gene (SEQ ID NO 4), the entire coding sequence of the ORF4 gene (SEQ ID NO 5) and 271 of 293 amino acid codons at the 5' end of the ILTV gG gene (SEQ ID NO 7). When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the DNA coding for the ILTV UL47-like, ORF4 and gG genes with DNA coding for the PRV gX promoter-E. coli uidA gene. A detailed description of the plasmid is given in Figure 8. It was constructed from the indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector is derived from an approximately 2958 base pair Asp718I restriction fragment of pSP18/pSP19 such that the multiple cloning site is EcoRI/SacI/Asp718I/SacI/EcoRI. Fragment 1 is an approximately 1066 base pair Asp718I to BssHII subfragment of the ILTV 5164 bp Asp718I fragment (SEQ ID NO 1: Nuc1. 1714-2777). Fragment 2 is an approximately 123 base pair SalI to BclI subfragment of the ILTV 5164 bp Asp718I fragment. Fragment 3 is an approximately 3027 base pair BamHI fragment containing the PRV gX promoter, the uidA gene, and the HSV-1 TK polyadenylation site (See Figure 8). Fragment 4 is an approximately 1334 base pair BclI to Asp718I subfragment of the ILTV 5164 bp Asp718I fragment (SEQ ID NO 1: Nuc1.
HOMOLOGY VECTOR 579-14.G2. The plasmid 579-14.G2 was constructed for the purpose of deleting the entire gG gene and a portion of the g60 gene from the ILT virus and inserting a foreign DNA. It incorporates a PRV gX promoter and a screenable marker, the E. coli uidA gene, flanked by ILT virus DNA. The PRV gX promoter-E. coli uidA gene is transcribed in the same direction to the ILTV gG and g60 gene promoters. The 3351 base pair deletion includes the entire coding sequence of the ILTV gG gene (SEQ ID NO 7) and 733 of 986 amino acid codons from the 5' end of the g60 gene (SEQ ID NO 8). When this plasmid is used according to the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT HERPESVIRUS, it will replace the DNA coding for the ILTV gG gene and amino acids 1 to 733 of the ILTV g60 gene with DNA coding for the E. coli uidA gene. A detailed description of the plasmid is given in Figure 9. It was constructed from the indicated DNA sources utilizing standard recombinant DNA techniques (42, 43). The plasmid vector pUC19 (Gibco, BRL) is derived from an approximately 2677 base pair Asp718I to BamHI fragment. Fragment 1 is an approximately 2830 base pair Asp718I to NheI subfragment of the ILTV 5164 bp Asp718I fragment (SEQ ID NO 1: Nucl. 1714-4544). Fragment 2 is an approximately 3051 base pair SalI fragment containing the PRV gX promoter, E. coli β-glucuronidase (uidA) marker gene, and an HSV-1 TK
polyadenylation site (See Figure 9). Fragment 3 is an approximately 1709 base pair SalI to BamHI subfragment of the ILTV 4545 base pair BamHI fragment (SEQ ID NO 1: Nucl. 7895-9604).

PLASMID 544-39.13. Plasmid 544-39.13 contains the β-glucuronidase expression cassette consisting of the PRV gX promoter, E. coli β-glucuronidase (uidA) marker gene, and an HSV-1 TK polyadenylation site. A detailed description of the marker gene is given in FIGURE 10. It was constructed utilizing standard recombinant DNA techniques (42, 43) by joining restriction fragments from the following sources with the synthetic DNA sequences indicated in FIGURE 10. The plasmid vector pSP71 (Promega) is derived from an approximately 3066 base pair XmaI to SmaI fragment. Fragment 1 is an approximately 422 base pair SalI to EcoRI restriction subfragment of the PRV BamHI restriction fragment #10 (47). Note that the EcoRI site was introduced at the location indicated in FIGURE 12 by PCR cloning. Fragment 2 is an approximately 1826 base pair EcoRI to SmaI fragment of the plasmid pRAJ260 (Clonetech). Note that the EcoRI and XmaI sites were introduced at the locations indicated in FIGURE 10 by PCR cloning. Fragment 3 is an approximately 784 base pair XmaI subfragment of the HSV-1 BamHI restriction fragment Q (48). Note that this fragment is oriented such that the polyadenylation sequence (AATAAA) is located closest to the junction with the E. coli uidA gene.
PLASMID 388-65.2. Plasmid 388-65.2 contains the β-galactosidase expression cassette consisting of the HCMV immediate early (IE) promoter, the E. coli lacZ marker gene, and the PRV γ1 gene polyadenylation site. A detailed description of the β-galactosidase expression cassette is given in FIGURE 11. It was constructed utilizing standard recombinant DNA techniques (42, 43) by joining restriction fragments from the following sources with the synthetic DNA sequences indicated in FIGURE 11. The plasmid vector pSP72 (Promega) is derived from an approximately 3076 base pair PstI to PstI fragment. Fragment 1 is a 1154 base pair PstI to AvaII fragment derived from a HCMV 2.1 kb PstI fragment containing the HCMV IE promoter. Fragment 2 is a 3010 base pair BamHI to PvuII fragment derived from plasmid pJF751 (49) containing the E. coli lacZ gene. Fragment 3 is an approximately 750 base pair NdeI to SalI fragment derived from PRV BamHI #7 which contains the carboxy-terminal 19 amino acids and the polyadenylation signal of the PRV γ1 gene.
EXAMPLES

Example 1

Complete sequence of the unique short region
of Infectious Laryngotracheitis Virus (ILT Virus)

We have determined the sequence of 13,473 base pairs of
contiguous DNA from the short region of the ILT virus
(SEQ. ID. NO. 1). This sequence contains the entire
13,098 base pair unique short region as well as 273 base
pairs of repeat region at one end and 102 base pairs of
repeat region at the other end. The unique short region
contains 13 methionine initiated open reading frames
(ORF) of greater than or equal to 110 amino acids
(excluding smaller nested ORFs). All 13 ORFs were aligned
to the Entrez release 6.0 virus division of the Genbank
DNA database utilizing the IBI MacVector Protein to DNA
alignment option (default settings). Eight of the ORFs
exhibited significant homology to one or more other virus
genes (see table). The nucleotide sequence numbers
referred to below begin within the internal repeat
sequence and end within the terminal repeat sequence. The
unique short region begins at base pair 274 of SEQUENCE
ID NO. 1.
Sequence Homology between Infectious Laryngotracheitis Virus (ILTV) Open Reading Frames in the Unique Short Region and other Viral Proteins

<table>
<thead>
<tr>
<th>Open Reading Frame (ORF)</th>
<th>Start (BP)</th>
<th>End (BP)</th>
<th>Length (aa)</th>
<th>Genbank Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Rc) b</td>
<td>970</td>
<td>281</td>
<td>229</td>
<td>EHV-1 US2</td>
</tr>
<tr>
<td>2</td>
<td>1059</td>
<td>2489</td>
<td>476</td>
<td>MDV PK</td>
</tr>
<tr>
<td>3</td>
<td>2575</td>
<td>4107</td>
<td>510</td>
<td>HSV-1 UL47</td>
</tr>
<tr>
<td>4</td>
<td>4113</td>
<td>4445</td>
<td>110</td>
<td>NS</td>
</tr>
<tr>
<td>4 (RC)</td>
<td>4519</td>
<td>4139</td>
<td>126</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>4609</td>
<td>5487</td>
<td>292</td>
<td>PRV gX</td>
</tr>
<tr>
<td>6</td>
<td>5597</td>
<td>8654</td>
<td>985</td>
<td>ILTV g60</td>
</tr>
<tr>
<td>6 (RC)</td>
<td>7826</td>
<td>6948</td>
<td>292</td>
<td>HSV-2 UL39</td>
</tr>
<tr>
<td>7</td>
<td>8462</td>
<td>9766</td>
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<td>PRV g50</td>
</tr>
<tr>
<td>8</td>
<td>9874</td>
<td>10862</td>
<td>362</td>
<td>VZV g1</td>
</tr>
<tr>
<td>8 (RC)</td>
<td>11150</td>
<td>10617</td>
<td>177</td>
<td>NS</td>
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<tr>
<td>9</td>
<td>11159</td>
<td>12658</td>
<td>499</td>
<td>VZV gE</td>
</tr>
<tr>
<td>10</td>
<td>12665</td>
<td>13447</td>
<td>260</td>
<td>NS</td>
</tr>
</tbody>
</table>

a Sequence alignment scored to the Entrez Release 6.0 of Genbank Virus Database.
b RC=Reverse Complement.
c NS=No score above 120 was found.
Other Abbreviations: EHV= Equine herpesvirus; MDV= Mareks disease virus; HSV-1= Herpes Simplex virus 1; PRV= Pseudorabies virus; ILTV= Infectious laryngotracheitis virus; HSV-2= Herpes Simplex virus 2; VZV= Varicella-Zoster virus; BP= base pairs; aa= amino acids.

US2 gene

The US2 gene consists of 690 base pairs and codes for a protein 229 amino acids in length and molecular weight approximately 25,272 daltons (SEQ. ID. NO. 12, 13). The ILTV US2 is homologous to the Equine herpesvirus(EHV)-1 and EHV-4 US2 proteins. The US2 gene is transcribed from nucleotide 970
to 281 on the reverse complement strand of the ILTV unique short region (SEQ. ID. NO. 1). The function of the US2 gene product is unknown.

5

Protein kinase gene

The protein kinase gene consists of 1431 base pairs from nucleotide 1059 to 2489 and codes for a protein 476 amino acids in length and molecular weight approximately 54,316 daltons (SEQ. ID. NO. 2). The ILTV protein kinase is homologous to the protein kinases from Mareks disease virus (MDV), Equine herpesvirus(EHV)-1 and -4, Pseudorabies virus (PRV), Varicella-Zoster virus (VZV), Simian varicella virus (SVV), and Herpes Simplex virus(HSV)-1 and -2.

10

UL47-like gene

The UL47-like gene is unique in its location within the unique short region of ILT virus. The UL47-like gene in all other known herpesviruses is located within the unique long sequence. The UL47-like gene consists of 1533 base pairs from nucleotide 2575 to 4107 and codes for a protein 510 amino acids in length and molecular weight approximately 57,615 daltons (SEQ. ID. NO. 3).

20

ORF4

ORF4 codes for a protein of unknown function. ORF4
consists of 333 base pairs from nucleotide 4113 to 4445 and codes for an open reading frame 110 amino acids in length and molecular weight approximately 12,015 daltons (SEQ. ID. NO. 4).

ORF4 Reverse Complement

ORF4 Reverse Complement (RC) codes for a protein of unknown function. ORF4 RC consists of 380 base pairs from nucleotide 4519 to 4139 and codes for an open reading frame 126 amino acids in length and molecular weight approximately 13,860 daltons (SEQ. ID. NOS. 14, 15).

gG gene

The gG gene consists of 879 base pairs from nucleotide 4609 to 5487 and codes for a glycoprotein 292 amino acids in length and molecular weight approximately 31,699 daltons (SEQ. ID. NO. 5). ILTV gG glycoprotein is homologous to PRV gX, Bovine herpesvirus(BHV)-1.3 gG, EHV-1 gG and EHV-4 gG. Recombinant ILTV gG protein produced in a Swinepox virus vector or a Fowlpox virus vector can be purified (see Materials and Methods) and reacts to peptide antisera to ILTV gG. The peptide antisera reacts to ILTV gG from wild type virus, but not to viruses deleted for the ILTV gG gene. Deletion of the gG gene results in an attenuated I LT virus that is useful
as a vaccine against ILT disease in chickens (see table in Example 6) and also serves as a negative marker to distinguish vaccinated from infected animals.

**g60 gene**

The g60 gene has been identified as glycoprotein 60 (33, 53). The g60 gene consists of 2958 base pairs from nucleotide 5697 to 8654 and codes for a glycoprotein 985 amino acids in length and molecular weight approximately 106,505 daltons (SEQ. ID. NO. 6).

**ORF6 Reverse Complement**

ORF6 RC consists of 878 base pairs from nucleotide 7826 to 6948 and codes for an open reading frame 292 amino acids in length and molecular weight approximately 32,120 daltons (SEQ. ID. NO. 16, 17). The ILTV ORF6 RC shares limited homology to portions of the HSV-1 and HSV-2 ribonucleotide reductase large subunit (UL39).

**gD gene**

The expression of the gD glycoprotein in vectored fowlpox virus or herpesvirus of turkeys (33) is sufficient to raise a protective immune response in the chicken. The gD gene consists of 1305 base pairs from nucleotide 8462 to 9766 and codes for a glycoprotein 434 amino acids in
length and molecular weight approximately 48,477 daltons (SEQ. ID. NO. 10, 11). The ILTV gD glycoprotein is homologous to the PRV g50, and the gD from HSV-1, MDV, IPV, and BHV-1.1. Monoclonal antibodies raised to ILT virus react specifically with gD protein from ILTV and also react to ILTV gD protein expressed in a Herpesvirus of Turkeys (HVT) virus vector. ILTV gD expressed in the HVT vector is useful as a subunit vaccine.

\[ gI \text{ gene} \]

The \( gI \) gene consists of 1089 base pairs from nucleotide 9874 to 10,962 and codes for a glycoprotein 362 amino acids in length and molecular weight approximately 39,753 daltons (SEQ. ID. NO. 7). The ILTV \( gI \) glycoprotein is homologous to the VZV \( gI \). Recombinant ILTV \( gI \) protein expressed in a swinepox virus vector reacts to convalescent sera from ILTV-infected chickens. Deletion of the \( gI \) gene results in an attenuated IILT virus that is useful as a vaccine against IILT disease in chickens. Recombinant viruses deleted for \( gI \) are safe in animal trials when vaccinated by a natural route directly into the respiratory tract, whereas parental virus causes lesions in 90% of the birds inoculated via the same route. Deletion of the \( gI \) gene serves as a negative marker to distinguish vaccinated from infected animals.
ORF8 Reverse Complement

ORF8 Reverse Complement codes for a protein of unknown function. ORF8 RC consists of 533 base pairs from nucleotide 11,150 to 10,617 and codes for an open reading frame 177 amino acids in length and molecular weight approximately 19,470 daltons (SEQ. ID. NO. 18, 19).

gE Gene

The gE gene consists of 1500 base pairs from nucleotide 11,159 to 12,658 and codes for a glycoprotein 499 amino acids in length and molecular weight approximately 55,397 daltons (SEQ. ID. NO. 8). The ILTV gE glycoprotein is homologous to the gE glycoproteins from VZV, Simian herpesvirus (SHV), EHV-1, HSV-1, and PRV. The ILTV gE is a neutralizing antigen useful as a subunit vaccine.
ORF10

ORF10 consists of 783 base pairs from nucleotide 12,665 to 13,447 and codes for a protein 261 amino acids in length and molecular weight approximately 27,898 daltons (SEQ. ID. NO. 9).
Example 2

S-ILT-004

S-ILT-004 is an infectious laryngotracheitis virus (ILTV) that has an approximately 620 base pair deletion of the thymidine kinase (TK) gene (28). The gene for E. coli β-galactosidase (lacZ) was inserted in the place of the TK gene and is under the control of the HCMV immediate early (IE) promoter. Transcription of the HCMV IE promoter-lacZ gene is in the opposite orientation to the TK promoter.

S-ILT-004 was constructed using homology vector 501-94 (see Materials and Methods) and S-ILT-001 (USDA ILTV Strain 83-2) in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock was screened by the Bluogal™ SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The result of blue plaque purification was recombinant virus S-ILT-004. This virus was characterized by restriction mapping and the SOUTHERN BLOTTING OF DNA procedure. This analysis confirmed the presence of the β-galactosidase (lacZ) marker gene and the deletion of approximately 619 base pairs of the TK gene. The remaining TK gene sequence codes for protein including amino acids 1 to 77, and amino acids 286 to 363. The HCMV IE promoter-lacZ gene is in the opposite orientation to the TK gene transcription.
S-ILT-004 is attenuated by deletion of the ILTV TK gene, but retains other genes known to be involved in the immune response in chickens to ILT virus. Therefore, S-ILT-004 may be useful as a killed vaccine to protect chickens from ILT disease.
Example 3

S-ILT-009

S-ILT-009 is an infectious laryngotracheitis virus (ILTV) that has an approximately 498 base pair deletion of the ILTV US2 gene and an approximately 874 base pair deletion of the ILTV gG gene. The gene for *E. coli* β-glucuronidase (uidA) was inserted in the place of the US2 gene and is under the control of the pseudorabies virus (PRV) gX promoter.

S-ILT-009 was constructed using homology vector 544-55.12 (see Materials and Methods) and S-ILT-002 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. S-ILT-002 was constructed as described in Example 5 (S-ILT-014). The transfection stock was screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The resulting purification of a blue plaque was recombinant virus S-ILT-009. This virus was characterized by restriction mapping and the SOUTHERN BLOTTING OF DNA procedure. This analysis confirmed the presence of the PRV gX promoter-β-glucuronidase (uidA) marker gene and the deletion of approximately 498 base pairs of the ILTV US2 gene and an approximately 874 base pair deletion of the ILTV gG gene.

However, during the Bluogal™ SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES, a deletion of the HCMV IE promoter-lacZ gene was detected within the existing ILTV gG deletion. The remaining insert into the
ILTV gg deletion contains approximately 2000 base pairs of DNA of which all of the lacZ gene and part of the PRV gX polyadenylation site are missing. The deletion was characterized by detailed restriction mapping and determined to be slightly different from the S-ILT-014 deletion (See Example 5).

S-ILT-009 is attenuated by deletion of the ILTV US2 and gg genes, but retains other genes known to be involved in the immune response in chickens to ILT virus. Therefore, S-ILT-009 is useful as an attenuated live vaccine or as a killed vaccine to protect chickens from ILT disease as shown in the table. Since S-ILT-009 does not express the ILTV gg genes, it is utilized as a negative marker to distinguish vaccinated animals from infected animals as described previously.
EFFICACY OF RECOMBINANT LIVE ILT VIRUS S-ILT-009
AGAINST VIRULENT INFECTIOUS LARYNGOTRACHEITIS VIRUS

CHALLENGE

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Gene(s) Deleted</th>
<th>Dose</th>
<th>Route</th>
<th>Challenge</th>
<th>Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-ILT-009</td>
<td>gG-, US2-</td>
<td>$7.8 \times 10^3$</td>
<td>IO</td>
<td>OS</td>
<td>70%</td>
</tr>
<tr>
<td>S-ILT-009</td>
<td>gG-, US2-</td>
<td>$1.56 \times 10^3$</td>
<td>IO</td>
<td>OS</td>
<td>77%</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
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</tr>
<tr>
<td>ASL embryo</td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>90%</td>
</tr>
</tbody>
</table>

14 day old chicks

a: USDA Challenge virus = $1.0 \times 10^4.5$ pfu
b: Protection = \# healthy birds/total (%).
c: Intraocular
d: Orbital Sinus
Example 4
S-ILT-011

S-ILT-011 is an infectious laryngotracheitis virus (ILTV) that has an approximately 983 base pair deletion of the ILTV gI gene. The gene for E. coli β-glucuronidase (uidA) was inserted in the place of the gI gene and is under the control of the pseudorabies virus (PRV) gX promoter. The PRV gX promoter-uidA gene is in the opposite orientation to the direction of transcription of the ILTV gI promoter.

S-ILT-011 was constructed using homology vector 562-61.1P (see Materials and Methods) and S-ILT-001 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock was screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The result of blue plaque purification was recombinant virus S-ILT-011. This virus was characterized by restriction mapping and the SOUTHERN BLOTTING OF DNA procedure. This analysis confirmed the presence of the β-glucuronidase (uidA) marker gene and the deletion of approximately 983 base pairs of the ILTV gI gene which deletes 325 of 363 amino acid codons from the 5' end of the gI gene.

S-ILT-011 is attenuated and is useful as a killed vaccine to protect chickens from ILT disease. S-ILT-011 shows a small plaque phenotype in tissue culture which is indicative of slow viral growth and attenuation. Since S-ILT-011 does not express the ILTV gI gene, it may be utilized as a negative marker to distinguish vaccinated animals from infected animals. As indicated in Example 1, ILTV-infected chickens make antibodies against ILTV gI protein.
Example 5

S-ILT-013

S-ILT-013 is an infectious laryngotracheitis virus (ILTV) that has an approximately 983 base pair deletion of the ILTV gI gene and an approximately 874 base pair deletion of the ILTV gG gene (and a deletion of the HCMV IE promoter lacZ marker gene making the lacZ gene nonfunctional). The gene for E. coli β-glucuronidase (uidA) was inserted in the place of the gI gene and is under the control of the pseudorabies virus (PRV) gX promoter.

S-ILT-013 was constructed using homology vector 562-61.1F (see Materials and Methods) and S-ILT-014 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock was screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The result of blue plaque purification was recombinant virus S-ILT-013. This virus was characterized by restriction mapping and the SOUTHERN BLOTTING OF DNA procedure. This analysis confirmed the presence of the β-glucuronidase (uidA) marker gene and the deletion of approximately 983 base pairs of the ILTV gI gene which removes 325 of 363 amino acid codons from the 5' end of the gI gene. This analysis also confirmed an approximately 874 base pair deletion of the ILTV gG gene and an approximately 1906 base pair insertion of a partial HCMV IE promoter-lacZ marker gene DNA, of which a portion of the HCMV IE promoter and almost none of the lacZ gene remains (see Example 6).

S-ILT-013 is attenuated and is useful as a killed vaccine to protect chickens from ILT disease. S-ILT-013 shows a small plaque phenotype in tissue culture which is indicative of slow viral growth and attenuation. Since S-ILT-013 does not express the ILTV gI or gG genes, ILTV gI and gG may be utilized as negative markers to distinguish vaccinated animals from infected animals.
Example 6

5 S-ILT-014 is an infectious laryngotracheitis virus (ILTV) that has an approximately 874 base pair deletion of the ILTV gG gene and a deletion of the inserted HCMV IE promoter lacZ marker gene making the lacZ gene nonfunctional. S-ILT-014 was derived from a purified S-ILT-002 virus stock in which a deletion of the HCMV IE promoter lacZ marker gene occurred.

S-ILT-002 was constructed using homology vector 472-73.27 (See Materials and Methods) and S-ILT-001 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The virus S-ILT-002 has a 874 base pair deletion within the ILTV gG gene and an insertion of the E. coli β-galactosidase (lacZ) gene in place of the ILTV gG gene. However, during the Bluogal™ SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES, a white plaque was picked which contained a deletion of the lacZ gene within the ILTV gG deletion.

This virus, S-ILT-014, was characterized by restriction mapping, DNA SEQUENCING and the SOUTHERN BLOTTING OF DNA procedure. This analysis confirmed the presence of an approximately 874 base pair deletion of the ILTV gG gene and approximately 1956 base pair insertion of a partial HCMV IE promoter lacZ marker gene DNA (2958 base pairs deleted). The remaining HCMV IE promoter lacZ marker gene DNA consists of an approximately 686 base pair DNA fragment of the approximately 1154 base pair HCMV IE promoter and an approximately 1270 base pair DNA fragment containing approximately 520 base pairs of the 3010 base pair β-galactosidase (lacZ) marker gene and all of the approximately 750 base pair PRV gX polyadenylation signal.
S-ILT-014 is useful as an attenuated live vaccine or as a killed vaccine to protect chickens from ILT disease as indicated in the table below. Since S-ILT-014 does not express the ILTV gG gene and ILTV-infected chickens make antibodies to gG as indicated in Example 1, ILTV gG is utilized as a negative marker to distinguish vaccinated animals from infected animals.

**EFFICACY OF RECOMBINANT LIVE ILT VIRUS S-ILT-014 AGAINST VIRULENT INFECTIOUS LARYNGOTRACHEITIS VIRUS CHALLENGE**

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<th>Route</th>
<th>Challenge</th>
<th>Protection</th>
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14 day old chicks
a: USDA Challenge virus =1.0x10⁴³ pfu
b: Protection = # healthy birds/total (%).
c: Intracocular
d: Orbital Sinus
Example 7

S-ILT-015

5 S-ILT-015 is an infectious laryngotracheitis virus (ILTV) that has an approximately 2640 base pair deletion of the UL47-like gene, the ORF4 gene, and ILTV gG gene. The gene for E. coli β-glucuronidase (uidA) was inserted in the place of the UL47-like, ORF4, and gG genes and is under the control of the pseudorabies virus (PRV) gX promoter. The PRV gX promoter-uidA gene is in the opposite orientation to the direction of transcription of the ILTV UL47-like, ORF4, and gG promoters.

15 S-ILT-015 was constructed using homology vector 560-52.F1 (see Materials and Methods) and S-ILT-001 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock was screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The result of blue plaque purification was recombinant virus S-ILT-015. This virus was characterized by restriction mapping and the SOUTHERN BLOTTING OF DNA procedure. These results confirmed the presence of a 2640 base pair deletion which includes 442 of a total 511 amino acid codons at the 3' end of the UL47-like gene, all of the ORF4 gene and 271 of 293 amino acid codons of the 5' end of the gG gene.

S-ILT-015 is useful as an attenuated live vaccine or as a killed vaccine to protect chickens from ILT disease as indicated in the table below. Since S-ILT-015 does not express the ILTV gG gene, ILTV gG is utilized as a negative marker to distinguish vaccinated animals from infected animals.
EFFICACY OF RECOMBINANT LIVE ILT VIRUS S-ILT-015 AGAINST VIRULENT INFECTIOUS LARYNGOTRACHEITIS VIRUS CHALLENGE

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<td>ASL embryo</td>
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14 day old chicks

a: USDA Challenge virus = 1.0x10^4 pfu
b: Protection = # healthy birds/total (%).
c: Intraocular
d: Orbital Sinus
Example 8

S-ILT-017 is an infectious laryngotracheitis virus (ILTV) that has an approximately 3351 base pair deletion of the ILTV gG gene and the g60 gene. The gene for E. coli β-glucuronidase (uidA) was inserted in the place of the ILTV gG and g60 genes and is under the control of the pseudorabies virus (PRV) gX promoter.

S-ILT-017 was constructed using homology vector 579-14.G2 (see Materials and Methods) and S-ILT-001 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock was screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES. The result of blue plaque purification was recombinant virus S-ILT-017.

S-ILT-017 is attenuated by deletion of the ILTV g60 and gG genes, but retains other genes known to be involved in the immune response in chickens to ILT virus. Therefore, S-ILT-017 may be used as a killed vaccine to protect chickens from ILT disease. Since S-ILT-017 does not express the ILTV gG or g60 genes, it is used as a negative marker to distinguish vaccinated animals from infected animals.
Example 9

Recombinant infectious laryngotracheitis viruses that express infectious bronchitis virus (IBV) spike and matrix protein genes.

A homology vector is used to generate ILT viruses containing the IBV Arkansas spike protein gene. The recombinant ILT virus contains a deletion of one or more ILTV genes, including gG, US2, UL47-like, and ORF4, and the insertion of two foreign genes: the E. coli β-glucuronidase gene (uidA) and the IBV Arkansas spike protein gene. The uidA gene is under the control of the PRV gX promoter and the IBV Arkansas spike protein gene is under the control of the HCMV IE promoter.

To construct a homology vector containing the foreign genes inserted into the ILT virus, a DNA fragment containing the HCMV-IE promoter, the IBV Arkansas spike protein and the HSV-1 TK polyadenylation signal is inserted into a restriction enzyme site at the position of the deletion of the ILTV gG gene in the ILTV homology vector. A DNA fragment containing the PRV gX promoter and the E. coli β-glucuronidase (uidA) gene is inserted into a unique restriction enzyme site within the ILTV homology vector. A recombinant virus is constructed by combining the final homology vector containing the IBV Arkansas spike gene and the E. coli β-glucuronidase (uidA) gene and S-ILT-001 in the HOMOLOGOUS RECOMBINATION PROCEDURE FOR GENERATING RECOMBINANT VIRUS. The transfection stock is screened by the X-Gluc SCREEN FOR RECOMBINANT HERPESVIRUS EXPRESSING ENZYMATIC MARKER GENES to detect the presence of the uidA gene and by the BLACK PLAQUE ASSAY FOR FOREIGN GENE EXPRESSION to detect the presence of the IBV Arkansas spike protein.
A similar strategy is used to construct recombinant ILT viruses carrying the IBV S1 protein from Arkansas, Massachusetts, or Connecticut serotypes, IBV matrix protein from Arkansas, Massachusetts, or Connecticut serotypes, and IBV nucleocapsid from Arkansas, Massachusetts, or Connecticut serotypes. The strategy is also used to construct recombinant ILT viruses carrying the Newcastle Disease virus (NDV) HN and F genes and the Infectious Bursal Disease virus (IBDV) polyprotein or portions thereof. The strategy is also used to construct recombinant ILT viruses carrying the Mareks Disease virus (MDV) gA, gD, and gB genes.

Recombinant ILT virus carrying these antigens are valuable as a multivalent vaccine to protect chickens from diseases caused by ILTV and one or more of the viruses IBV, NDV, IBDV, or MDV. Since the ILTV vaccines described here do not express ILTV gG, it is useful as a negative marker to distinguish vaccinated animals from infected animals.

Example 10

Vaccines utilizing ILTV to express antigens from various disease causing microorganisms.

REFERENCES:


5. B. Roizman, et. al., Cold Spring Harbor Conference on New Approaches to Viral Vaccines (September 1983).


33. Y. M. Saif, et. al., AVMA 130th Annual Meeting, July 17-21, 1993, Minneapolis, MN.


54. T. Honda, et. al., U.S. Patent No. 4,980,162.

55. Federal Register, Vol. 55, No. 90, pp. 19245-19253


SEQUENCE LISTING

(i) APPLICANT: Cochran, Mark D.
    Wild, Martha A.

(ii) TITLE OF INVENTION: RECOMBINANT INFECTIOUS LARYNGOTRACHEITIS VIRUS AND USES THEREOF

(iii) NUMBER OF SEQUENCES: 58

(iv) CORRESPONDENCE ADDRESS:
    (A) ADDRESSEE: John P. White, c/o Cooper & Dunham
    (B) STREET: 30 Rockefeller Plaza
    (C) CITY: New York
    (D) STATE: New York
    (E) COUNTRY: USA
    (F) ZIP: 10112

(v) COMPUTER READABLE FORM:
    (A) MEDIUM TYPE: Floppy disk
    (B) COMPUTER: IBM PC compatible
    (C) OPERATING SYSTEM: PC-DOS/MS-DOS
    (D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
    (A) APPLICATION NUMBER: US
    (B) FILING DATE: 23-SEP-1993
    (C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
    (A) NAME: White, John P.
    (B) REGISTRATION NUMBER: 28,678
    (C) REFERENCE/DOCKET NUMBER: 39116/JPW/JEL

(ix) TELECOMMUNICATION INFORMATION:
    (A) TELEPHONE: (212) 977-9550
    (B) TELEFAX: (212) 664-0525
    (C) TELEX: 422523 COOP UI

(2) INFORMATION FOR SEQ ID NO:1:
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| TTA CGG ACC AGA CTG CGT GCC ACC GGT AAG AAA ACT GCC GGA TTG TCC |
|----------------------|--------------------|
| Leu Pro Thr Arg Leu Arg Gly Thr Gly Lys Thr Ala Gly Leu Ser |
| 30 | 35 | 40 |

| AAT TAT ACC CAG CCT ATT CCC TGG AAC CCT AAA TCC TGC AGC GCG GCC |
|----------------------|--------------------|
| Asn Tyr Thr Gln Pro Ile Pro Trp Asn Pro Lys Phe Cys Ser Ala Arg |
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| GGG GAA TCT GAC AAC CAC GGC TGT AAA GAC ACT TTT TAT CGC AGG ACG |
|----------------------|--------------------|
| Gly Glu Ser Asp Asn His Ala Cys Lys Asp Thr Tyr Phe Arg Thr |
| 60 | 70 |

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|----------------------|--------------------|
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| 80 | 85 | 90 |

| ACA CCC ATG CCT ACT GAG TAT GGG CGC TGT CCC TCC GCA AAG GCC AAA |
|----------------------|--------------------|
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| 95 | 100 | 105 |

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|----------------------|--------------------|
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| TGT AAA CTT CGG GAT TCT CAA GCA GCA CCC CGG GCA ACC TAT AGT TCT |
|----------------------|--------------------|
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| GCG CAA AGA TAT ACT GTT GAC GAG GTT TCG TCC CCA ACT CCG CCA GGC |
|----------------------|--------------------|
| Ala Glu Arg Tyr Thr Val Asp Glu Val Val Ser Pro Thr Pro Pro Gly |
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| TGG CAC GCT GTT GCC GCC GAC TTT GAA AGC CGC GGC GAA CTT CTT GCC GTC |
|----------------------|--------------------|
| Val Asp Ala Val Ala Asp Leu Glu Thr Arg Ala Glu Leu Pro Gly Ala |
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Thr Thr Gln Glu Thr Glu Ser Lys Asn Lys Leu Pro Asn Gln Glu Lys
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GTC GGG GCA GGC ATA GCA AAC GAG CTG GCT GCT ATG CGG AGG GCG TGT
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CTT CCG CTC GCC GCG TCG GCC GCC GAA ATA GTG GCC TGG GCC
Leu Pro Leu Ala Ala Ala Ala Ala Gly Ile Val Ala Trp Ala
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GCC GCG AGG GCC TGG CAG AAA CAA GGG CCG TAG CAGTAATAATA ACCACACAA
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13270

13318

13366

13414

13467

13473

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 476 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Arg Thr Thr Glu Asn Pro Leu Thr Ser Lys Arg Val Cys Val Leu Asp
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Ser Phe Ser Arg Thr Met Ser Leu Arg Pro Tyr Ala Glu Ile Leu Pro
35 . 40 45

Thr Ala Glu Gly Val Glu Arg Leu Ala Glu Leu Val Ser Val Thr Met
50 . 55 60

Thr Glu Arg Ala Glu Pro Val Thr Glu Asn Thr Ala Val Asn Ser Ile
65 . 70 75 80

55

Pro Pro Ala Asn Glu Asn Gly Gin Asn Phe Ala Tyr Ala Gly Asp Gly
85 . 90

95

Pro Ser Thr Thr Glu Lys Val Asp Gly Ser His Thr Asp Phe Asp Glu
100 . 105 110

60

Ala Ser Ser Asp Tyr Ala Gly Pro Val Pro Leu Ala Gln Thr Arg Leu
115 . 120 125

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(2) INFORMATION FOR SEQ ID NO:3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 510 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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20  Asn Lys Thr Met Leu Leu Tyr Arg Pro Asp Ser Thr Met Arg His Ser
35  Gly Gly Asp Ala Asn His Arg Gly Ile Arg Pro Arg Arg Lys Ser Ile
50  Gly Ala Phe Ser Ala Arg Glu Lys Thr Gly Lys Arg Asn Ala Leu Thr
65  Glu Ser Ser Ser Ser Ser Asp Met Leu Asp Pro Phe Ser Thr Asp Lys
80  Glu Phe Gly Gly Lys Tryr Thr Val Asp Gly Pro Ala Asp Ile Thr Ala
100  Glu Val Leu Ser Gln Ala Trp Val Leu Gln Leu Val Lys His Glu
115  Asp Ala Glu Glu Glu Arg Val Thr Tyr Glu Ser Lys Pro Thr Pro Ile
130  Gln Pro Phe Asn Ala Trp Pro Asp Gly Pro Ser Trp Asn Ala Gln Asp
145  Phe Thr Arg Ala Pro Ile Val Tyr Pro Ser Ala Glu Val Leu Asp Ala
160  Glu Ala Leu Lys Val Gly Ala Phe Val Ser Arg Val Leu Gln Cys Val
175  Pro Phe Thr Arg Ser Lys Ser Val Thr Val Arg Asp Ala Gln Ser
190  Phe Leu Gly Asp Ser Phe Trp Arg Ile Met Glu Val Tyr Thr Val
205  Cys Leu Arg Glu His Ile Thr Arg Leu Arg His Pro Ser Ser Lys Ser
220  Ile Val Asn Cys Asn Asp Pro Leu Trp Tyr Ala Tyr Ala Asn Gln Phe
235  His Trp Arg Gly Met Arg Val Pro Ser Leu Lys Leu Ala Ser Pro
250  Glu Glu Ile Gln His Gly Pro Met Ala Ala Val Phe Arg Asn Ala
265  Gly Ala Gly Leu Phe Leu Trp Pro Ala Met Arg Ala Ala Phe Glu Glu
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Arg Asp Arg Leu Leu Arg Ala Cys Leu Ser Ser Leu Asp Ile Met
305 310 315 320
Asp Ala Ala Val Leu Ala Ser Phe Pro Phe Tyr Trp Arg Gly Val Gln
325 330 335
Asp Thr Ser Arg Phe Glu Pro Ala Leu Gly Cys Leu Ser Glu Tyr Phe
340 345 350
Ala Leu Val Val Leu Ala Glu Thr Val Leu Ala Thr Met Phe Asp
355 360 365
His Ala Leu Val Phe Met Arg Ala Leu Ala Asp Gly Asn Phe Asp Asp
370 375 380
Tyr Asp Glu Thr Arg Tyr Ile Asp Pro Val Lys Asn Glu Tyr Leu Asn
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Gly Ala Glu Gly Thr Leu Leu Arg Gly Ile Val Ala Ser Asn Thr Ala
405 410 415
Leu Ala Val Val Cys Ala Asn Thr Tyr Ser Thr Ile Arg Lys Leu Pro
420 425 430
Ser Val Ala Thr Ser Ala Cys Asn Val Ala Tyr Arg Thr Glu Thr Leu
435 440 445
Lys Ala Arg Arg Pro Gly Met Ser Asp Ile Tyr Arg Ile Leu Gln Lys
450 455 460
Glu Phe Phe Phe Tyr Ile Ala Trp Leu Gln Arg Val Ala Thr His Ala
465 470 475 480
Asn Phe Cys Leu Asn Ile Leu Lys Arg Ser Val Asp Thr Gly Pro Arg
485 490 495
His Phe Cys Ser Gly Pro Ala Arg Arg Ser Gly Cys Ser Ser
500 505 510

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 110 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Cys Pro Leu Leu Val Pro Ile Gln Tyr Glu Asp Phe Ser Lys
1 5 10 15
Ala Met Gly Ser Glu Leu Lys Arg Glu Lys Leu Glu Thr Phe Val Lys
20 25 30
Ala Ile Ser Arg Arg Arg Asp Arg Pro Arg Gly Ser Leu Arg Phe Leu Ile
35 40 45
Ser Asp His Ala Arg Glu Ile Ile Ala Asp Gly Val Arg Phe Lys Pro
50 55 60
Val Ile Asp Glu Pro Val Arg Ala Ser Val Ala Leu Ser Thr Ala Ala
65 70 75 80
Ala Gly Lys Val Lys Ala Arg Arg Leu Thr Ser Val Arg Ala Pro Val
85 90
Pro Pro Ala Gly Ala Val Ser Ala Arg Arg Lys Ser Glu Ile
100 105 110

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 292 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(x) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ser Gly Phe Ser Asn Ile Gly Ser Ile Ala Thr Val Ser Leu Val
1 5 10 15
Cys Ser Leu Leu Cys Ala Ser Val Leu Gly Ala Pro Val Leu Asp Gly
20 25 30
Leu Glu Ser Ser Pro Phe Pro Phe Gly Gly Lys Ile Ile Ala Gln Ala
35 40 45
Cys Asn Arg Thr Thr Ile Glu Val Thr Val Pro Trp Ser Asp Tyr Ser
50 55 60
Gly Arg Thr Glu Val Ser Val Glu Val Lys Trp Phe Tyr Gly Asn
65 70 75 80
Ser Asn Pro Glu Ser Phe Val Phe Gly Val Asp Ser Glu Thr Ser
85 90
Gly His Glu Asp Leu Ser Thr Cys Trp Ala Leu Ile His Asn Leu Asn
100 105 110
Ala Ser Val Cys Arg Ala Ser Asp Ala Gly Ile Pro Asp Phe Asp Lys
115 120 125
Gln Cys Glu Lys Val Gln Arg Arg Leu Arg Ser Gly Val Glu Leu Gly
130 135 140
Ser Tyr Val Ser Gly Asn Gly Ser Leu Val Leu Tyr Pro Gly Met Tyr
145 150 155 160
Asp Ala Gly Ile Tyr Ala Tyr Gln Leu Ser Val Gly Gly Lys Gly Tyr
165 170 175
Thr Gly Ser Val Tyr Leu Asp Val Gly Pro Asn Pro Gly Cys His Asp
180 185 190 195
Gln Tyr Gly Tyr Thr Tyr Tyr Ser Leu Ala Asp Glu Ala Ser Asp Leu
200 205
Ser Ser Tyr Asp Val Ala Ser Pro Glu Leu Asp Gly Pro Met Glu Glu
210 215 220
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**INFORMATION FOR SEQ ID NO:6:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 985 amino acids
(B) **TYPE:** amino acid
(D) **TOPOLOGY:** linear

(ii) **MOLECULE TYPE:** protein

(xi) **SEQUENCE DESCRIPTION:** SEQ ID NO:6:

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15 645 650 655
Thr Glu Thr Pro Ser Ala Ala Pro Glu Val Tyr Thr Arg Ser Ser Ser
20 660 665 670
Thr Met Pro Glu Thr Ala Gln Ser Thr Pro Leu Ala Ser Gln Asn Pro
25 675 680 685
Thr Ser Ser Gly Thr Gly Thr His Asn Thr Glu Pro Arg Thr Tyr Pro
30 690 695 700
Val Gln Thr Thr Pro His Thr Gln Lys Leu Tyr Thr Glu Asn Lys Thr
35 705 710 715 720
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40 725 730 735
Glu Ser Gln Thr Pro Leu Leu Asp Val Lys Ile Val Glu Val Lys Phe
45 740 745 750
Ser Asn Asp Gly Glu Val Thr Ala Thr Cys Val Ser Thr Val Lys Ser
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Pro Tyr Arg Val Glu Thr Asn Trp Lys Val Asp Leu Val Asp Val Met
55 770 775 780
Asp Glu Ile Ser Gly Asn Ser Pro Ala Gly Val Phe Asn Ser Asn Glu
60 785 790 795 800
Lys Trp Gln Lys Glu Tyr Tyr Arg Val Thr Asp Gly Arg Thr Ser
65 805 810
Val Gln Leu Met Cys Leu Ser Cys Thr Ser His Ser Pro Glu Pro Tyr
70 820 825 830
Cys Leu Phe Asp Thr Ser Leu Ile Ala Arg Glu Lys Asp Ile Ala Pro
75 835 840 845
Glu Leu Tyr Phe Thr Ser Asp Pro Gln Thr Ala Tyr Cys Thr Ile Thr
80 850 855 860
Leu Pro Ser Gly Val Val Pro Arg Phe Glu Trp Ser Leu Asn Asn Val
85 865 870 875 880
Ser Leu Pro Glu Tyr Leu Thr Ala Thr Val Val Ser His Thr Ala
90 885 890 895
Gly Gln Ser Thr Val Trp Lys Ser Ser Ala Arg Ala Gly Glu Ala Trp
95 900 905 910
Ile Ser Gly Arg Gly Gly Asn Ile Tyr Glu Cys Thr Val Leu Ile Ser
100 915 920 925
Asp Gly Thr Arg Val Thr Thr Arg Lys Glu Arg Cys Leu Thr Asn Thr
105 930 935 940
-102-

Trp Ile Ala Val Glu Asn Gly Ala Ala Ala Gln Ala Gln Leu Tyr Ser Leu
945 950 955 960

Phe Ser Gly Leu Val Ser Gly Leu Cys Gly Ser Ile Ser Ala Leu Tyr
965 970

Ala Thr Leu Trp Thr Ala Ile Tyr Phe
980 985

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 362 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Ala Ser Leu Leu Gly Thr Leu Ala Leu Ala Ala Ala Thr Leu Ala
1 5 10 15

Pro Phe Gly Ala Met Gly Ile Val Ile Thr Gly Asn His Val Ser Ala
20 25 30

Arg Ile Asp Asp Asp His Ile Val Ile Val Ala Pro Arg Pro Glu Ala
35 40 45

Thr Ile Gln Leu Gln Leu Phe Phe Met Pro Gly Gln Arg Pro His Lys
50 55

Pro Tyr Ser Gly Thr Val Arg Val Ala Phe Arg Ser Asp Ile Thr Asn
65 70 75 80

Gln Cys Tyr Gln Glu Leu Ser Glu Glu Arg Phe Glu Asn Cys Thr His
85 90 95

Arg Ser Ser Ser Val Phe Val Gly Cys Lys Val Thr Glu Tyr Thr Phe
100 105 110

Ser Ala Ser Asn Arg Leu Thr Gly Pro Pro His Pro Phe Lys Leu Thr
115 120 125

Ile Arg Asn Pro Arg Pro Asp Asp Gly Ser Gly Met Phe Tyr Val Ile Val
130 135 140

Arg Leu Asp Asp Thr Lys Glu Pro Ile Asp Val Phe Ala Ile Gln Leu
145 150 155 160

Ser Val Tyr Gln Phe Ala Asn Thr Ala Ala Thr Arg Gly Leu Tyr Ser
165 170 175

Lys Ala Ser Cys Arg Thr Phe Gly Leu Pro Thr Val Gln Leu Glu Ala
180 185 190

Tyr Leu Arg Thr Glu Glu Ser Trp Arg Asn Trp Gln Ala Tyr Val Ala
195 200 205

Thr Glu Ala Thr Thr Ser Ala Glu Ala Thr Thr Pro Thr Pro Val
210 215 220

Thr Ala Thr Ser Ala Ser Glu Leu Glu Ala Glu His Phe Thr Phe Pro
225 230 235 240
Trp Leu Glu Asn Gly Val Asp His Tyr Glu Pro Thr Pro Ala Asn Glu 245 255
Asn Ser Asn Val Thr Val Arg Leu Gly Thr Met Ser Pro Thr Leu Ile 260 265 270
Gly Val Thr Val Ala Ala Val Val Ser Ala Thr Ile Gly Leu Val Ile 275 280 285
Val Ile Ser Ile Val Thr Arg Asn Met Cys Thr Pro His Arg Lys Leu 290 295 300
Asp Thr Val Ser Gln Asp Glu Arg Ser Gln Thr Arg Arg Glu 305 310 315 320
Ser Arg Lys Phe Gly Pro Met Val Ala Cys Glu Ile Asn Lys Gly Ala 325 330 335
Asp Gln Asp Ser Glu Leu Val Glu Leu Val Ala Ile Val Asp Ser 340 345 350
Ala Leu Ser Ser Pro Asp Ser Ile Lys Met 355 360

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
Met Asn Met Leu Val Ile Val Leu Ala Ser Cys Leu Ala Arg Leu Thr 1 5 10 15
Phe Ala Thr Arg His Val Leu Phe Leu Glu Gly Thr Gln Ala Val Leu 20 25 30
Gly Glu Asp Pro Arg Asn Val Pro Glu Gly Thr Val Ile Lys Trp 35 40 45
Thr Lys Val Leu Arg Asn Ala Cys Lys Met Lys Ala Ala Asp Val Cys 50 55 60
Ser Ser Pro Asn Tyr Cys Phe His Asp Leu Ile Tyr Asp Gly Lys 65 70 75 80
Lys Asp Cys Pro Pro Ala Gly Pro Leu Ser Ala Asn Leu Val Ile Leu 85 90 95
Leu Lys Arg Gly Glu Ser Phe Val Leu Gly Ser Gly Leu His Asn 100 105 110
Ser Asn Ile Thr Asn Ile Met Trp Thr Glu Tyr Gly Gly Leu Leu Phe 115 120 125
Asp Pro Val Thr Arg Ser Asp Glu Gly Ile Tyr Phe Arg Arg Ile Ser 130 135 140
Gln Pro Asp Leu Ala Met Glu Thr Thr Ser Tyr Asn Val Ser Val Leu 145 150 155 160
Ser His Val Asp Glu Lys Ala Pro Ala Pro His Glu Val Glu Ile Asp
   165                   170                  175
Thr Ile Lys Pro Ser Glu Ala His Ala His Val Glu Leu Gln Met Leu
   180                   185                    190
Pro Phe His Glu Leu Asn Asp Asn Ser Pro Thr Tyr Val Thr Pro Val
   195                   200                     205
Leu Arg Val Phe Pro Pro Thr Glu His Val Lys Phe Asn Val Thr Tyr
   210                   215                     220
Ser Trp Tyr Gly Phe Asp Val Lys Glu Glu Cys Glu Glu Val Lys Leu
   225                   230                     235                    240
Phe Glu Pro Cys Val Tyr His Pro Thr Asp Gly Lys Cys Gln Phe Pro
   245                   250                     255
 Ala Thr Asn Gln Arg Cys Leu Ile Gly Ser Val Leu Met Ala Glu Phe
   260                   265                     270
Leu Gly Ala Ala Ser Leu Leu Asp Cys Ser Arg Asp Thr Leu Glu Asp
   275                   280                     285
Cys His Glu Asn Arg Val Pro Asn Leu Arg Phe Asp Ser Arg Leu Ser
   290                   295                     300
Glu Ser Arg Ala Gly Leu Val Ile Ser Pro Leu Ile Ala Ile Pro Lys
   305                   310                     315                    320
Val Leu Ile Ile Val Val Ser Asp Gly Asp Ile Leu Gly Trp Ser Tyr
   325                   330                     335
Thr Val Leu Gly Lys Arg Asn Ser Pro Arg Val Val Val Glu Thr His
   340                   345                     350
 Met Pro Ser Lys Val Pro Met Asn Lys Val Val Ile Gly Ser Pro Gly
   355                   360                     365
Pro Met Asp Glu Thr Gly Asn Tyr Lys Met Tyr Phe Val Val Ala Gly
   370                   375                     380
Val Ala Ala Thr Cys Val Ile Leu Thr Cys Ala Leu Leu Val Gly Lys
   385                   390                     395                    400
Lys Lys Cys Pro Ala His Gln Met Gly Thr Phe Ser Lys Thr Glu Pro
   405                   410                     415
Leu Tyr Ala Pro Leu Pro Lys Asn Glu Phe Glu Ala Gly Gly Leu Thr
   420                   425                     430
Asp Asp Glu Glu Val Ile Tyr Asp Glu Val Tyr Glu Pro Leu Phe Arg
   435                   440                     445
Gly Tyr Cys Lys Gln Glu Phe Arg Glu Asp Val Asn Thr Phe Phe Gly
   450                   455                     460
Ala Val Val Glu Gly Glu Arg Ala Leu Asn Phe Lys Ser Ala Ile Ala
   465                   470                     475                    480
Ser Met Ala Asp Arg Ile Leu Ala Asn Lys Ser Gly Arg Arg Asn Met
   485                   490                     495
Asp Ser Tyr
(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 260 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(x) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Pro Phe Lys Thr Arg Gly Ala Ala Glu Asp Ala Ala Gly Lys Asn  
1      5          10         15

Arg Phe Lys Lys Ser Arg Asn Arg Glu Ile Leu Pro Thr Arg Leu Arg  
20     25          30

Gly Thr Gly Lys Thr Ala Gly Leu Ser Asn Tyr Thr Gln Pro Ile  
35     40          45

Pro Trp Asn Pro Lys Phe Cys Ser Arg Gly Glu Ser Asp Asn His  
50     55          60

Ala Cys Lys Asp Thr Phe Tyr Arg Thr Cys Cys Ala Ser Arg Ser  
65     70          75         80

Thr Val Ser Ser Gln Pro Asp Ser Pro His Thr Pro Met Pro Thr Glu  
85     90          95

Tyr Gly Arg Val Pro Ser Ala Lys Arg Lys Lys Leu Ser Ser Ser Asp  
100    105         110

Xaa Glu Gly Ala His Gln Pro Leu Val Ser Cys Lys Leu Pro Asp Ser  
115    120         125

Gln Ala Ala Pro Ala Arg Thr Tyr Ser Ser Ala Gln Arg Tyr Thr Val  
130    135         140

Asp Glu Val Ser Ser Pro Thr Pro Pro Gly Val Asp Ala Val Ala Asp  
145    150         155         160

Leu Glu Thr Arg Ala Glu Leu Pro Gly Ala Thr Thr Glu Gln Thr Glu  
165    170         175

Ser Lys Asn Lys Leu Pro Asn Gln Gln Ser Arg Leu Lys Pro Lys Pro  
180    185         190

Thr Asn Glu His Val Gly Gly Glu Arg Cys Pro Ser Glu Gly Thr Val  
195    200         205

Glu Ala Pro Ser Leu Gly Ile Leu Ser Arg Val Gly Ala Ala Ile Ala  
210    215         220

Asn Glu Leu Ala Arg Met Arg Ala Cys Leu Pro Leu Ala Ala Ser  
225    230         235         240

Ala Ala Ala Gly Ile Val Ala Trp Ala Ala Ala Arg Ala Leu Gln  
245    250         255

Lys Glu Gly Arg  
260

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
-106-

(A) LENGTH: 1305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1305

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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ATG CAC CGT CCT CAT AGA CGG CAC TCG GTG TAC TAC GCG AAA GGA
Met His Arg Pro His Leu Arg Arg His Ser Arg Tyr Tyr Ala Lys Gly
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GAG GTG CTT AAG AAA CAC ATG GAT TGG GTT GGA AAA CGG TGG TGC TCA
Glu Val Leu Arg Lys His Met Asp Cys Gly Gly Gly Lys Arg Cys Cys Ser
20   25   30
GAG CCA GCT GTA TTT TGC ACT CTT TCC TGG ACT TGT GTC AGG ATT ATG CGG
Gly Ala Ala Val Phe Thr Leu Phe Trp Thr Cys Val Arg Ile Met Arg
30   35   40   45
GAG CAT ATC TGC TTT GTA CGG AAC GCT ATG GAC CGC CAT TTA TTT TTG
Glu His Ile Cys Phe Val Arg Asn Ala Met Asp Arg His Leu Phe Leu
50   55   60
AGG AAT GCT TTT TGG ACT ATC GTA CTT TCC TCC TGC GCT AGC CAG
Arg Asn Ala Phe Trp Thr Ile Val Leu Leu Ser Ser Phe Ala Ser Gln
65   70   75   80
AGC ACC GCC GGC GTC ACG TAC GAC TAC ATT TTA GCC GCT CGC GGC CTC
Ser Thr Ala Ala Val Thr Tyr Asp Tyr Ile Leu Gly Arg Arg Ala Leu
85   90   95
GAC GCG CTA ACC ATA CGG GCC GTC GGT GCC CCG TAT AAC AGA TAC CTC ACT
Asp Ala Leu Thr Ile Pro Ala Val Gly Pro Tyr Asn Arg Tyr Leu Thr
100  105  110
AGG GTA TCA AAG GCC TGC GAC GTT GTC GAG CTC AAG CCG ATT TCT AAC
Arg Val Ser Arg Gly Cys Asp Val Val Glu Leu Asn Pro Ile Ser Asn
115  120  125
GTG GAC GAC ATG ATA TCG GCC GGC AAA AAA AAG AAG GGG GCC CCT
Val Asp Asp Met Ile Ser Ala Ala Lys Glu Lys Gly Gly Gly Pro
130  135  140
TTC GAC GCC TCC GTT GTC TGC TGC TAC ATG ATT TAC TAC GAC GAC GGC
Phe Glu Ala Ser Val Val Trp Phe Tyr Val Ile Lys Gly Asp Asp Gly
145  150  155  160
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Glu Asp Lys Tyr Cys Pro Ile Tyr Arg Lys Glu Tyr Arg Cys Gly
165  170  175
GAC GTA CTA CTG CTA TCT GAA TGC GCC GTT CAA TCT GCA CAG ATG TGG
Asp Val Glu Leu Leu Ser Gly Cys Ala Val Gln Ser Ala Gln Met Trp
180  185  190
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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 434 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:11:

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10 Glu Val Leu Asn Lys His Met Asp Cys Gly Gly Lys Arg Cys Cys Ser
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20 Gly Ala Ala Val Phe Thr Leu Phe Trp Thr Cys Val Arg Ile Met Arg
   25 30
30 Glu His Ile Cys Phe Val Arg Asn Ala Met Asp Arg His Leu Phe Leu
   35 40
40 Arg Asn Ala Phe Trp Thr Ile Val Leu Leu Ser Ser Phe Ala Ser Gln
   45 50
50 Ser Thr Ala Ala Val Thr Tyr Asp Tyr Ile Leu Gly Arg Arg Ala Leu
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60 Asp Ala Leu Thr Ile Pro Ala Val Gly Pro Tyr Asn Arg Tyr Leu Thr
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70 Arg Val Ser Arg Gly Cys Asp Val Val Glu Leu Asn Pro Ile Ser Asn
   75 80
80 Val Asp Asp Met Ile Ser Ala Ala Lys Glu Lys Glu Lys Gly Gly Pro
   85 90
90 Phe Glu Ala Ser Val Val Trp Phe Tyr Val Ile Lys Gly Asp Asp Gly
   95 100
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140 Thr Leu Lys Ile Gly Arg Phe Ala Gln Thr Ala Leu Val Thr Leu Glu
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160 Ser Lys Cys Trp Thr Thr Glu Gln Tyr Glu Thr Gly Phe Gln Gly Glu
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180 Tyr Arg Gly Tyr Glu Asp Ile Leu Gln Arg Trp Asn Asn Leu Leu Arg
   185 190
190
| Lys | Lys | Asn | Pro | Ser | Ala | Pro | Asp | Pro | Arg | Pro | Asp | Ser | Val | Pro | Gln |
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(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 690 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..689

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

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(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 690 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..689

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:
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Leu  Phe  Ser  Leu  Pro  Arg  Met  Cys  Arg  Pro  Val  Ile  Arg  Phe  Gly  Glu  
   65  70  75  80  
Gly  Gly  Asp  Pro  Pro  Gly  Val  Ser  Pro  Glu  Trp  Ser  Gly  Leu  Asp  Ala  
   85  90  95  
Leu  Tyr  Thr  His  Ser  Ser  Thr  Ser  Ala  Tyr  Ala  Ala  Lys  Gly  Phe  His  
   100  105  110  
TTG  TGG  GTG  CTG  GGT  ACC  GCT  GAC  ATA  TGC  ATG  GCA  GCT  TTA  AAC  CTC  
Leu  Thr  Val  Gly  Thr  Ala  Asp  Ile  Cys  Met  Ala  Ala  Leu  Asn  Leu  
   115  120  125  
CCT  GCG  CCA  AAA  ACT  TTC  CTA  ATT  ACC  GAA  ACC  GGA  GGT  AAA  AAT  TTT  
Pro  Ala  Pro  Lys  Thr  Phe  Leu  Ile  Thr  Thr  Gly  Thr  Glu  Asn  Phe  
   130  135  140  
GAG  AGA  GGA  GTG  GAA  ATA  TTT  TTG  GTA  AAC  GGA  GAC  AAG  ACA  ACG  CTG  
Glu  Arg  Gly  Val  Glu  Ile  Phe  Leu  Val  Asn  Gly  Asp  Lys  Thr  Leu  
   145  150  155  160  
TCT  CGT  AGT  CAC  CCA  TCA  GTG  AGA  ACT  CTT  GCC  CCT  TCG  AGC  CTG  
Ser  Leu  Ser  His  Pro  Ser  Val  Trp  Thr  Thr  Leu  Ala  Pro  Ser  Ser  Leu  
   165  170  175  
AGA  ACG  CCC  TGG  CCG  TAC  AGC  AGC  GTA  AAG  TTT  TTA  AAA  GTG  AAA  CCT  
Arg  Thr  Pro  Pro  Trp  Pro  Phe  Ser  Thr  Val  Ser  Lys  Phe  Leu  Lys  Val  Lys  Pro  
   180  185  190  
AAC  TCG  GCC  TAC  TGT  GTT  TCC  GAC  TCG  GAT  GAT  GGC  GAA  CGG  CAG  
Asn  Ser  Ala  Ala  Tyr  Val  Ser  Asp  Ser  Asp  Asp  Gly  Arg  Glu  Arg  Glu  
   195  200  205  
CCA  AAA  TTT  TTT  TCC  GGG  AGT  CTA  TTT  AAG  TCG  AAG  AAA  CCC  CGC  TCC  
Pro  Lys  Phe  Phe  Leu  Gly  Ser  Leu  Phe  Lys  Ser  Lys  Lys  Pro  Arg  Ser  
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Pro  Arg  Arg  Arg  Arg  225  

(2) INFORMATION FOR SEQ ID NO:13:  

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 229 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear  

(ii) MOLECULE TYPE: protein  

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:13:  

Met  Ala  Pro  Val  Lys  Val  Thr  Ile  Val  Ser  Ala  Val  Asp  Ser  His  Tyr  
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Lys  Leu  Pro  Asn  Ser  Arg  Phe  Glu  Leu  Ser  Asp  Ser  Gly  Trp  Lys  Glu  
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Leu  Val  His  Ala  Val  Lys  Thr  Met  Ala  Ser  Tyr  Asp  Arg  Pro  Ser  Thr  
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Leu  Ser  Val  Ile  Val  Arg  Pro  Ala  Ser  Leu  Tyr  Glu  Val  Ser  Gly  Glu  
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Gly Gly Asp Pro Pro Gly Val Ser Pro Glu Trp Ser Gly Leu Asp Ala
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Gly Phe Tyr His Leu Ser Ser Gly Ala Tyr Ala Ala Lys Glu Phe His
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Pro Ala Pro Lys Thr Phe Leu Ile Thr Glu Thr Gly Gly Lys Asn Phe
130
Glu Arg Gly Val Glu Ile Phe Leu Val Asn Gly Asp Lys Thr Thr Leu
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Ser Leu Ser His Pro Ser Val Thr Thr Leu Ala Pro Ser Ser Leu
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Arg Thr Pro Trp Pro Tyr Ser Thr Val Lys Phe Leu Lys Val Lys Pro
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Pro Lys Phe Phe Leu Gly Ser Leu Phe Lys Ser Lys Lys Pro Arg Ser
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Pro Arg Arg Arg Arg
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(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 381 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
   (A) NAME/KEY: CDS
   (B) LOCATION: 1..380

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

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TCG CCC GCA AAT GCC AAG CAT TTT TAT CAT ATT TCC GAT TTC CGG GCC
Ser Pro Ala Asn Ala Tyr His Phe Tyr His Ile Ser Asp Phe Arg Arg
20 25 30

GCG GAA ACG GCG CCT GCG GCC GGT AGC GGC GCC CGA ACT GAG GTT AAG
Ala Glu Thr Ala Pro Ala Gly Gly Thr Gly Ala Arg Thr Glu Val Lys
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CGT CGC GCT TTC ACT TTC CCA GCG GCA GCG GTA CTC AGC GCA ACT GAA
Arg Arg Ala Phe Thr Phe Pro Ala Ala Ala Val Leu Ser Ala Thr Glu
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GCC CGA ACC GGC TCG TCT ATC ACC GGC TAA AAC CGT ACT CGG TCT GCA
Ala Arg Thr Gly Ser Ser Ser Ile Thr Gly Leu Asn Arg Thr Pro Ser Ala
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ATA ATT TCC CTT GCA TGG TCC GAA ATG AGA AAT CTT AAG GAC CCC CTC
Ile Ile Ser Leu Ala Trp Ser Glu Met Arg Asn Leu Lys Asp Pro Leu
85 90 95
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Gly Ser Leu Ser Leu Glu Ile Ala Leu Thr Asn Val Ser Asn Phe Ser
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(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 126 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

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Ser Pro Ala Asn Ala Lys His Phe Tyr His Ile Ser Asp Phe Arg Arg
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Ala Glu Thr Ala Pro Ala Gly Gly Thr Gly Ala Arg Thr Glu Val Lys
35 40 45
Arg Arg Ala Phe Thr Phe Pro Ala Ala Ala Val Leu Ser Ala Thr Glu
50 55 60
Ala Arg Thr Gly Ser Ser Ile Thr Gly Leu Asn Arg Thr Pro Ser Ala
65 70 75 80
Ile Ile Ser Leu Ala Trp Ser Glu Met Arg Asn Leu Lys Asp Pro Leu
85 90 95
Gly Ser Leu Ser Leu Glu Ile Ala Leu Thr Asn Val Ser Asn Phe Ser
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Leu Leu Ser Ser Asp Pro Met Ala Phe Glu Lys Ser Ser Tyr
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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 879 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..878

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

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1 5 10 15

CCC GGT TCC CGA ACT AGT AGG GTT TTG CGA GGC CAG GGG TGT GCT CTG
Pro Gly Ser Arg Thr Gly Arg Val Leu Arg Gly Glu Cys Ala Leu
20 25 30

TGC AGT TCC TTC CAT CGT ACT CGA ACT CGG AGT ATA AAC CTC CGG TGC
Cys Ser Phe Trp His Arg Thr Arg Thr Pro Ser Ile Asn Leu Arg Cys
35 40 45

CGC GCT CGG GTG AGT AAT TTC CGC TGC GGC CAG AGT CGG GGT
Arg Ala Arg Gly Leu Ser Asn Phe Arg Leu Cys Ala Gln Ser Pro Gly
50 55 60

GAA AGG CAC AGG TTC AGT CGG ACT CGG AGT CAA CAC CTC CGG CTC
Glu Arg His Arg Arg Thr Cys Arg Gly Thr Arg Thr Leu Ser Gln His Leu Arg Leu
65 70 75 80

TGT ACT CGG AGT CTG AGT AGG GTT TGG TCG TAC CGT ACT CGG GGC CTG AGT
Cys Thr Arg Ser Leu Ser Ser Phe Arg Tyr Arg Thr Arg Gly Leu Ser
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GAA AAA GTG TGT TTC AGT ACT CTG AGT TCG CAT AGT GTC CGG CTC GGC
Glu Lys Val Cys Phe Ser Thr Leu Ser Ser His Ser Val Arg Leu Gly
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ACT CGA AGT CTG AGT AAA GGC CTC AGT TCC CGC GCT CTG AGT CGG AGT
Thr Arg Ser Leu Ser Lys Gly Leu Ser Ser Arg Ala Leu Ser Pro Ser
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Ala Thr Arg Leu Ser Tyr Leu Gly Tyr Thr Arg Ala Gly Leu Gly
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Arg Cys Leu Gly Phe Cys Thr Arg Ser Leu Ser Lys Ser His Leu Phe
195 200 205
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CTG AGT AAG AGC CGC CTG ACT CTG ACT CGG ACT CTG GAT CTG GAT AAG ATA CCA Leu Ser Lys Ser Arg Leu Phe Ser Thr Arg Ser Leu Ser Lys Ile Pro
225 230 235 240
CGG TTC CTG ACT CTG GGA CGG CGC GGT TTC CGA CTG GGT ACT CGG ACT Arg Phe Leu Thr Leu Gly Pro Arg Gly Phe Arg Leu Gly Thr Arg Thr
245 250 255
CTG AGT AAA GAC CAC CGT TCC ACT CTG GGT CTG TGT AGT TCC ATG Leu Ser Lys Asp His Arg Phe Cys Thr Leu Gly Leu Cys Ser Phe Met
260 265 270
TGC CGC GCT CGG CTG GTC GCT AGA AAT CCC CGC GGT GGT AGG AAA Cys Arg Ala Arg Gly Leu Gly Arg Asn Pro Arg Arg Gly Arg Arg Arg Lys
275 280 285
CAG TGT ATT TTC TG A Gln Cys Ile Phe
290

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Trp Cys Arg Leu His Trp Ile Ser Pro Arg Phe Ser Ile Met Arg
1 5 10 15
Pro Gly Ser Arg Thr Gly Arg Val Leu Arg Gly Gln Gly Cys Ala Leu
20 25 30
Cys Ser Phe Trp His Arg Thr Arg Thr Pro Ser Ile Asn Leu Arg Cys
35 40 45
Arg Ala Arg Gly Leu Ser Asn Phe Arg Leu Cys Ala Gln Ser Pro Gly
50 55 60
Glu Arg His Arg Phe Gly Thr Arg Thr Leu Ser Gln His Leu Arg Leu
65 70 75 80
Cys Thr Arg Ser Leu Ser Ser Phe Arg Tyr Arg Thr Arg Gly Leu Ser
85 90
Glu Lys Val Cys Phe Ser Thr Leu Ser Ser His Ser Val Arg Leu Gly
100 105 110
Thr Arg Ser Leu Ser Lys Gly Leu Ser Ser Arg Ala Leu Ser Pro Ser
115 120 125
Lys Asn Arg Arg Phe Ser Thr Arg Gln Ser Ser Phe Arg Tyr Arg
130 135 140
Ala Arg Gly Leu Ser Lys His Leu Arg Tyr Arg Thr Arg Thr Leu Cys
145 150 155 160
-115-

Lys Asn Leu Arg Arg Arg Ala Arg Ser Ala Ser Gly Phe Gly Gly Arg
165 170

Ala Thr Arg Leu Ser Lys Tyr Leu Gly Tyr Arg ...a Arg Gly Leu Gly
180 185 190

Arg Cys Leu Gly Phe Cys Thr Arg Ser Leu Ser Lys Ser His Leu Phe
195 200 205

Ser Thr Arg Ser Leu Ser Lys Gln Arg Leu Arg Phe Cys Asp Leu Arg
210 215 220

Leu Ser Lys Ser Arg Leu Phe Ser Thr Arg Ser Leu Ser Lys Ile Pro
225 230 235 240

Arg Phe Leu Thr Leu Gly Pro Arg Gly Phe Arg Leu Gly Thr Arg Thr
245 250 255

Leu Ser Lys Asp His Arg Phe Cys Thr Leu Gly Leu Cys Ser Phe Met
260 265 270

Cys Arg Ala Arg Gly Leu Gly Arg Asn Pro Arg Arg Gly Arg Arg Lys
275 280 285

Gln Cys Ile Phe
290

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..533

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
ATG CTC CCA AGC CTA CTC AAC AAG GCC TCT CCC CGG CTG AAT TCT CCT
Met Leu Pro Ser Leu Leu Asn Arg Gly Ser Pro Arg Leu Asn Ser Pro
1  5 10 15

CCT AAG TGT TCA GAG GCC TCT GCT GTA CCA TAT AAC TAT CGT GTA GTA
Pro Lys Cys Ser Glu Ala Ser Ala Val Pro Tyr Asn Tyr Arg Val Val
20 25 30

CGC CCC TCC CAG TCC GTG TCC GAT ACT GCC CCT TTT GAG AGG ATT GGG
Arg Pro Ser Glu Ser Val Ser Asp Thr Ala Pro Phe Glu Arg Ile Gly
35 40 45

AGA TTA GAG AAT CGA AAT GAT TGG AGA GCC ACA TTC AGA CTT AAT CAC
Arg Leu Gly Asn Arg Asn Asp Trp Arg Ala Thr Phe Arg Leu Asn His
50 55 60

ATT TTT ATT TAG TCG GCC GAG CTT AGC GCA GAC GGG TTA ACA ATC GCA
```

240
Ile Phe Ile Glu Ser Gly Glu Leu Ser Ser Ala Asp Gly Leu Thr Ile Ala
65

Thr Ser Thr Ser Thr Ser Leu Ser Trp Ser Ala Pro Leu Phe Ile Ser
85

His Ala Thr Met Gly Pro Asn Phe Arg Asp Ser Leu Leu Val Trp Glu
100

Arg Ser Ser Ser Ser Cys Glu Thr Val Ser Asn Phe Arg Cys Gly Val
115

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Leu Pro Ser Leu Leu Asn Arg Gly Ser Pro Arg Leu Asn Ser Pro
1

Pro Lys Cys Ser Glu Ala Ser Ala Val Pro Tyr Asn Tyr Arg Val Val
20

Arg Pro Ser Glu Ser Val Ser Asp Thr Ala Pro Phe Glu Arg Ile Gly
35

Arg Leu Glu Asn Arg Asn Asp Trp Arg Ala Thr Phe Arg Leu Asn His
50

Ile Phe Ile Glu Ser Gly Glu Leu Ser Ser Ala Asp Gly Leu Thr Ile Ala
65

Thr Ser Ser Thr Ser Ser Leu Ser Trp Ser Ala Pro Leu Phe Ile Ser
85

His Ala Thr Met Gly Pro Asn Phe Arg Asp Ser Leu Leu Val Trp Glu
100

Arg Ser Ser Ser Ser Cys Glu Thr Val Ser Asn Phe Arg Cys Gly Val
115
(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:
GAATTCGAGC TCGTAGCCG GATAATAAGT ACAATTTAAC GCAGAGGT

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:
GCTGACCGCT AGTGCAGCT GAGTGAATAA TAAAT

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TGTCCGTGCA GATCCCTCTAG AGTCGACGAA AGGTCAGAGA CGATGCC

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CGGATCAGAA ACTCTTGCGG TACCCGGGAT CCTCTAGA

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAATACAGC TTAGATGCA ATTTACTCGA GCC

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GGTTTGCGGG AGCCGATATG ATCTCGACCT GCAGTGAAATA ATAAAATGTG T
(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 48 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TGTCGGTCAA GATCCCTCTAG AGTCGAGATC AGCAAAATGT TCAGGGGGA

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 18 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AAGCTTGGCG TAATCATG

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 39 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGAATTCGAG CTCGACCTG CTTGGCGAGC GCAGGGGCG

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 51 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGCCGATTTA GGTITTTACTT TTCTAGAGGA TCCCCTCAGAC GTCTGGGGCG C

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 48 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TTGCTGCGTT CCCGGGGATC CTCTAGAATT AGGTAAGTTG TAGTGCGA

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 42 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TCAAGATCCA GGAAATCTTT CGGTACCGAG TCTGAATTG TA

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 33 base pairs
   (B) TYPE: nucleic acid
   (C) STRANDEDNESS: single
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
GAATTGCAGC TCGTACCGA AAGCTACTCA GAC

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
CGCAAACAGC TCTCGTACT CTGAGTGCCTA ACGATCGCTG TT

(2) INFORMATION FOR SEQ ID NO:34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:
GAATAGCATA CCAATGCCTA TTCATGGGA CTGACTCTA GAGGATCCCC GGAACG

(2) INFORMATION FOR SEQ ID NO:35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:
TCGAGGGGAT CCTCTAGAGT CGAGGACCC ATGGTTGCGT GC

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:
TTTACTAAAG CGCGCGGAAA GCTTCGCTGT GCTGGGTCTT GG

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:
AAGCTTGGCG TAATCATGCT C

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:
GGAATTCGAG CTCGGTACCC GGAATAACG TACATGTTAA CGCAGAGG

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

ATCTATTGGA GCCGTTAGCG CCGTCGACG AAAGGTAGA GACGA

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CTGCTTCATT TCTGATCCCC GGGAACG

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

ACCACCCCCG CGCCCCAGAC GTCGAGGGGA TCAATTATG CGTATTGAAT A

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

ATCAGAAACT CTTTCGTTAC CGAGCTGCAA TTC

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GAATTCCAGC TCGTACCGC GATAATACGT ACATGTTAAC GCAGAGGT

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GCTGACCGCT AGTGCAGCTT AAGGATCCC CTC

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
SEQUENCE DESCRIPTION: SEQ ID NO: 45:
CGTCCCGGG GATCCTCTAG AGTGCACGGC AGAGTCGCAG AC

INFORMATION FOR SEQ ID NO: 46:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

SEQUENCE DESCRIPTION: SEQ ID NO: 46:
TGATCCAAAC TGCGATCTTC TAGAGTCGAC

INFORMATION FOR SEQ ID NO: 47:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

SEQUENCE DESCRIPTION: SEQ ID NO: 47:
AAAGCTGGGC TGCAAGTCGA CTCTAGAGGA TCCCCTGAC CTCTGGG

INFORMATION FOR SEQ ID NO: 48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

SEQUENCE DESCRIPTION: SEQ ID NO: 48:
CACACCTTTG CGCATCTCCA CAGCTCAACA ATGAATTCCA TGTTAGTCC TGTAGRAACC

INFORMATION FOR SEQ ID NO: 49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:
CAGGGAGGCA AACAATGAAT CACCAACTCT CCGGGAGGAT GGGGAGGCT AACTGAAACA

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:
TGCTGCCGTC CCGGGATCC TCTAGACTCG ACCTGCAGCC CAAGC

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:
TCTAGACTCG ACCTGCAGTG AATATTAAA TGTGTGTGTG TCCGAAAT

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(x) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CTCCATAGAA GACCCGGGA CCATGGATCC GTCGTTTTA CAACG

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(x) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TCGGCGGAAA TCCAGCTGAG CGCCGGTGC TACCATACC AGTTGGTCTG GTGTCAAAAA

GATCTAGAAT AAGCTAGAGG ATCGATCCCC TATGGCGATC ATCAG

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(x) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CCGTCGAGAT CCTCTAGAGT CGACCTGAC GTCGAC

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: N
(iv) ANTI-SENSE: N

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

CCTAGCACCC TTGTATGCGG

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: N

(iv) ANTI-SENSE: N

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

CGCCTCGAGT CCCAATGAAT AGGCATGG

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: N

(iv) ANTI-SENSE: N

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CGCCTCGAGG ACCCATGTT GCGTGCG

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: N

(iv) ANTI-SENSE: N
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTCGTCGAA CCAGTTACAG

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What is claimed is:

1. A recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, where in the deletion is in the glycoprotein gG gene.

2. The recombinant infectious laryngotracheitis virus of claim 1, designated S-ILT-014.

3. The recombinant infectious laryngotracheitis virus of claim 1, designated S-ILT-002.

4. The recombinant infectious laryngotracheitis virus of claim 1, further characterized by a deletion in the US2 gene.

5. The recombinant infectious laryngotracheitis virus of claim 4, designated S-ILT-009.

6. The recombinant infectious laryngotracheitis virus of claim 1, further characterized by a deletion in the ORF: gene and a deletion in the UL47-like gene.

7. The recombinant infectious laryngotracheitis virus of claim 6, designated S-ILT-015.

8. The recombinant infectious laryngotracheitis virus of claim 1, further characterized by a deletion in the glycoprotein g60 gene.

9. The recombinant infectious laryngotracheitis virus of claim 8, designated S-ILT-017.
10. The recombinant infectious laryngotracheitis virus of claim 1, further characterized by a deletion in the glycoprotein gI gene.

11. The recombinant infectious laryngotracheitis virus of claim 1, further characterized by a deletion in the thymidine kinase (TK) gene.

12. The recombinant infectious laryngotracheitis virus of claim 1, which further comprises a foreign gene inserted within a non-essential site of the infectious laryngotracheitis viral genome, wherein the foreign gene is capable of being expressed in a recombinant infectious laryngotracheitis infected host cell.

13. The recombinant infectious laryngotracheitis virus of claim 12, wherein a foreign gene is inserted within the unique short region of the viral genome, provided, however, that the foreign gene is not inserted within the glycoprotein gD gene, the glycoprotein gI gene, the protein kinase gene and the ORF 10 gene.

14. The recombinant infectious laryngotracheitis virus of claim 13, wherein the foreign gene is inserted into a gene selected from a group consisting of the US2 gene, UL47-like gene, ORF4 gene, glycoprotein gG gene, glycoprotein g60 gene, and glycoprotein gI gene.

15. The recombinant infectious laryngotracheitis virus of claim 12, wherein the foreign gene encodes a screenable marker.
16. The recombinant infectious laryngotracheitis virus of claim 15, wherein the screenable marker is E. coli β-galactosidase.

17. The recombinant infectious laryngotracheitis virus of claim 15, wherein the screenable marker is E. coli β-glucuronidase.

18. The recombinant infectious laryngotracheitis virus of claim 12, wherein the foreign gene encodes an antigenic polypeptide.

19. The recombinant infectious laryngotracheitis virus of claim 18, wherein the antigenic polypeptide, when introduced into the host cell, induces production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable.

20. The recombinant infectious laryngotracheitis virus of claim 19, wherein the antigenic polypeptide is derived or derivable from a group consisting of infectious bronchitis virus, Newcastle disease virus, infectious bursal disease virus, and Marek's disease virus.

21. The recombinant infectious laryngotracheitis virus of claim 19, wherein the antigenic polypeptide is derived or derivable from a group consisting of avian encephalomyelitis virus, avian reovirus, avian paramyxovirus, avian influenza virus, avian adenovirus, fowl pox virus, avian coronavirus, avian rotavirus, chick anemia agent, Salmonella spp. E. coli, Pasteurella spp., Bordetella spp., Eimeria spp., Histomonas spp., Trichomonas spp., Poultry nematodes, cestodes, trematodes, poultry mites/lice, poultry protozoa.
22. The recombinant infectious laryngotracheitis virus of claim 12, wherein the foreign gene is under control of an endogenous upstream infectious laryngotracheitis virus promoter.

23. The recombinant infectious laryngotracheitis virus of claim 12, wherein the foreign gene is under control of a heterologous upstream promoter.

24. The recombinant infectious laryngotracheitis virus of claim 23, wherein the promoter is selected from a group consisting of the HCMV IE promoter, PRV gX promoter, and BHV-1.1 VP8 promoter.

25. A recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the glycoprotein gG gene, so that upon replication the recombinant infectious laryngotracheitis virus produces no glycoprotein gG.

26. A recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in the glycoprotein gI gene, so that upon replication, the recombinant infectious virus produces no glycoprotein gI.

27. A recombinant infectious laryngotracheitis virus of claim 26, which further comprises a deletion in the glycoprotein gG gene so that upon replication, the recombinant virus produces no glycoprotein gG.

28. The recombinant infectious laryngotracheitis virus comprising the infectious laryngotracheitis viral
-134-

genome which contains a deletion in the unique short region of the viral genome, wherein the deletion is in a gene selected from a group consisting of the US2 gene, the UL47-like gene, and the glycoprotein g60 gene.

29. The recombinant infectious laryngotracheitis virus of claim 28, wherein the deletion is in the US2 gene.

30. The recombinant infectious laryngotracheitis virus of claim 28, wherein the deletion is in the UL47-like gene.

31. The recombinant infectious laryngotracheitis virus of claim 28, wherein the deletion is in the glycoprotein g60 gene.

32. A recombinant infectious laryngotracheitis virus which comprises a foreign gene inserted within the unique short region of the infectious laryngotracheitis viral genome, provided, however, that the insertion is not in the protein kinase gene, the glycoprotein gD gene, the glycoprotein gE gene and the ORF10 gene, wherein the foreign gene is capable of being expressed in the recombinant infectious laryngotracheitis virus infected host cell.

33. A recombinant infectious laryngotracheitis virus of claim 32, wherein the foreign gene is inserted in the gene selected from a group consisting of the US2 gene, UL-47 like gene, ORF4 gene and glycoprotein g60 gene.
34. The recombinant infectious laryngotracheitis virus of claim 32, wherein the foreign gene encodes a screenable marker.

35. The recombinant infectious laryngotracheitis virus of claim 34, wherein the screenable marker is E. coli B-galactosidase.

36. The recombinant infectious laryngotracheitis virus of claim 34, wherein the screenable marker is E. coli B-glucuronidase.

37. The recombinant infectious laryngotracheitis virus of claim 32, wherein the foreign gene encodes an antigenic polypeptide.

38. The recombinant infectious laryngotracheitis virus of claim 37, wherein the antigenic polypeptide, when introduced into the host cell, induces production of protective antibodies against an avian disease causing agent from which the antigen is derived or derivable.

39. The recombinant infectious laryngotracheitis virus of claim 38, wherein the antigenic polypeptide is derived from or derivable from a group consisting of infectious bronchitis virus, Newcastle disease virus, infectious bursal disease virus, and Marek’s disease virus.

40. The recombinant infectious laryngotracheitis virus of claim 38, wherein the antigenic polypeptide is derived from or derivable from a group consisting of avian encephalomyelitis virus, avian reovirus, avian paramyxovirus, avian influenza virus, avian adenovirus, fowl pox virus, avian coronavirus, avian rotavirus, chick anemia agent, Salmonella spp., E.
41. The recombinant infectious laryngotracheitis virus of claim 32, wherein the foreign gene is under control of an endogenous upstream infectious laryngotracheitis virus promoter.

42. The recombinant infectious laryngotracheitis virus of claim 32, wherein the foreign gene is under control of a heterologous upstream promoter.

43. The recombinant infectious laryngotracheitis virus of claim 42, wherein the promoter is selected from a group consisting of HCMV IE promoter, PRV gX promoter, and BHV-1.1 VP8 promoter.

44. A vaccine for infectious laryngotracheitis virus comprising an effective immunizing amount of the recombinant infectious laryngotracheitis virus of claim 1 and a suitable carrier.

45. A vaccine for infectious laryngotracheitis virus comprising an effective immunizing amount of the recombinant infectious laryngotracheitis virus of claim 2 and a suitable carrier.

46. A vaccine for infectious laryngotracheitis virus comprising an effective immunizing amount of the recombinant infectious laryngotracheitis virus of claim 3 and a suitable carrier.

47. A vaccine for infectious laryngotracheitis virus comprising an effective immunizing amount of the
recombinant infectious laryngotracheitis virus of
claim 5 and a suitable carrier.

48. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
recombinant infectious laryngotracheitis virus of
claim 7 and a suitable carrier.

49. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
recombinant infectious laryngotracheitis virus of
claim 9 and a suitable carrier.

50. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
recombinant infectious laryngotracheitis virus claim
3, 4, 6, 8, 10, or 11 and a suitable carrier.

51. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
virus of claim 25 and a suitable carrier.

52. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
virus of claim 26 and a suitable carrier.

53. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
virus of claim 27 and a suitable carrier.

54. A vaccine for infectious laryngotracheitis virus
comprising an effective immunizing amount of the
recombinant, infectious laryngotracheitis virus of
claim 29, 30, or 31 and a suitable carrier.

55. A multivalent vaccine for infectious
laryngotracheitis and for one or more of other avian
diseases comprising an effective immunizing amount of the recombinant virus of claim 19, 20, or 21 and a suitable carrier.

56. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of the vaccine of claim 44.

57. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of the vaccine of claim 45.

58. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of the vaccine of claim 46.

59. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of the vaccine of claim 47.

60. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of the vaccine of claim 48.

61. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an
62. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of vaccine of claim 50.

63. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of vaccine of claim 51.

64. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of vaccine of claim 52.

65. A method of immunizing chickens or other poultry against infectious laryngotracheitis which comprises administering to said chickens or other poultry an effective immunizing amount of vaccine of claim 53.

66. A method of immunizing chickens or other poultry against infectious laryngotracheitis and one or more of other avian diseases which comprises administering to said chickens or other poultry an effective immunizing amount of vaccine of claim 55.

67. A method of distinguishing chickens or other poultry which are vaccinated with the vaccine of claim 26 from those which are infected with a naturally-occurring infectious laryngotracheitis virus which comprises analyzing samples of body fluids from chickens or other poultry for the presence of glycoprotein gG and at least one other antigen normally expressed in chickens or other poultry
infected by a naturally-occurring infectious laryngotracheitis virus, the presence of those antigens normally expressed in infected chickens but the absence of glycoprotein gG being indicative of vaccination with the vaccine of claim 25 and not infection with a naturally-occurring infectious laryngotracheitis virus.

68. A method of distinguishing chickens or other poultry which are vaccinated with the vaccine of claim 2, 3, 5, 7 or 9 from those which are infected with a naturally-occurring infectious laryngotracheitis virus which comprises analyzing samples of body fluids from chickens or other poultry for the presence of glycoprotein gG and at least one other antigen normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus, the presence of those antigens normally expressed in infected chickens but the absence of glycoprotein gG being indicative of vaccination with the vaccine of claim 2, 3, 5, 7 or 9 and not infection with a naturally-occurring infectious laryngotracheitis virus.

69. A method of distinguishing chickens or other poultry which are vaccinated with the vaccine of claim 27 from those which are infected with a naturally-occurring infectious laryngotracheitis virus which comprises analyzing samples of body fluids from chickens or other poultry for the presence of glycoprotein gI, glycoprotein gG, and at least one other antigen normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus, the presence of those antigens normally expressed in infected chickens but the absence of glycoprotein gG and glycoprotein gI being indicative vaccination with
the vaccine of claim 27 and not infection with a naturally-occurring infectious laryngotracheitis virus.

70. A method of distinguishing chickens or other poultry which are vaccinated with the vaccine of claim 26 from those which are infected with a naturally-occurring infectious laryngotracheitis virus which comprises analyzing samples of body fluids from chickens or other poultry for the presence of glycoprotein gI and at least one other antigen normally expressed in chickens or other poultry infected by a naturally-occurring infectious laryngotracheitis virus, the presence of those antigens normally expressed in infected chickens but the absence of glycoprotein gI being indicative of vaccination with the vaccine of claim 26 and not infection with a naturally-occurring infectious laryngotracheitis virus.

71. A homology vector for producing a recombinant infectious laryngotracheitis virus by inserting a foreign DNA into the unique short region of the infectious laryngotracheitis genomic DNA, which comprises a double-stranded DNA molecule consisting essentially of a double-stranded foreign gene, which is flanked on either side by a double-stranded DNA homologous to the DNA located in the unique short region of the genomic DNA, provided, however, that the flanking sequences are not homologous to the glycoprotein gD gene, the glycoprotein gE gene, the protein kinase gene, and the ORF10 gene.

72. The homology vector of claim 71, wherein the foreign gene encodes a screenable marker.
73. The homology vector of claim 72, wherein the screenable marker is *E. coli* β-galactosidase or *E. coli* β-glucuronidase.

74. A homology vector for producing a recombinant infectious laryngotracheitis virus by deleting DNA which encodes a screenable marker, which has been inserted into the infectious laryngotracheitis virus genomic DNA, which comprises a double stranded DNA molecule consisting essentially of a double-stranded DNA to be deleted, which is flanked on each side by a double stranded DNA homologous to the infectious laryngotracheitis virus glycoprotein gG gene, glycoprotein gI gene, US2 gene, or UL-47 like gene.

75. The homology vector of claim 74, designated Homology Vector 544-55.12.

76. The homology vector of claim 74, designated Homology Vector 562-61.1F.

77. The homology vector of claim 74, designated Homology Vector 472-73.27.

78. The homology vector of claim 74, designated Homology Vector 560-52.F1.

TCAGTTGCGAC TTGTACAGCT ACATGTACGA TGAAGCGTTC GACTGGAAG 1800
ACAGTCCAAAT GCTTAACAGC ACTAGACGCA TCATGAAGCA GCTCATGTCG 1850
GGCGGTCTCTGT ATATCCATTC AGAAGAAGCT ATGCACAGGG ACATCAACT 1900
CGAAAATATTT TTCTTAAAATT GCGAGGCGGA GACAGTCTGT GGCAGCTTTG 1950
GAACGTGCAC GCGTTTTGAA AATGAGCGGG AGGCCCTTCGA ATATGGATGG 2000
GGGGTGGCAC TGGCCTTACTAA CTCCTCCGAGA ATATCGTGCA GGGGTTCGTA 2050
CTGTAATATT ACAGACAATTT GAGACATGCG AGTAGTATTT CTGGAAATGG 2100
TAAGGCACTAGA ATTTGCGCCG ATCGGGCATG GCCGGGAGAA TCGGACACAG 2150
CAATTGCTGAA AGTATTACGA CTCTCTCTCA GTTTGTGATG AAGAGTCCC 2200
AGACCCCGGG TGTGAATCTGT ACAATTATTT GCATATTGCG ACAGTCGATC 2250
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8/29

FIGURE 1-8

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### FIGURE 4-1

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![Diagram](image-url)
FIGURE 5-2

Junction A

GAA TAC AAG CTT AGA TGC ATA TTT ACT CGA GCC
pSP 64/65 → ILTV 2.4 kb Hind III

Junction B

GGT TTG GCG GAG CGG ATA TGA TCT CGA CCT GCA GTG AAT AAT AAA ATG TGT
[ Bcl I, Sal I ]
ILTV 2.4 kb Hind III → PRV BamH I #7

Junction C

TGT CCG TCG AGA TCC TCT AGA GTC GAG ATC AGC AAA ATG TTC ACG GGG
[ Sal I , Bcl I ]
HCMV 2.1 kb Pst I → ILTV 2.4 kb Hind III

Junction D

ILTV 2.4 kb Hind III → pSP 64/65

Hind III
Figure 6-1

DNA Vector

Fragment 1
- pSP 1819
- ILTV 2.5 kb
- Asp7181

Fragment 2
- PRV, E. coli, HSV-1
- Asp7181
- XbaI

Fragment 3
- ILTV 1097 bp
- Asp7181
- XbaI

Origin
- pSP 1819
- ILTV 2.5 kb

Sites
- Asp7181
- Asp7181
- XbaI

Size
- ~2958 BP
- ~3300 BP
- ~3039 BP
- ~809 BP

PRV, E. coli, HSV
uidA
PRV gX Promoter
HSV-1 poly A
800 BP
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<td>ILTV 8.0 kb Asp718 I</td>
<td>Hind III—Hind III</td>
<td>~2700 BP</td>
</tr>
</tbody>
</table>

†Restriction enzyme site introduced by PCR cloning
<table>
<thead>
<tr>
<th>DNA</th>
<th>Origin</th>
<th>Sites</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector</td>
<td>pSP18/19</td>
<td>Asp718 I—Asp718 I</td>
<td>~2958 BP</td>
</tr>
<tr>
<td>Fragment 1</td>
<td>ILTV 5164 bp Asp718I</td>
<td>Asp718 I—BssH II</td>
<td>~1066 BP</td>
</tr>
<tr>
<td>Fragment 2</td>
<td>ILTV 5164 bp Asp718I</td>
<td>Sal I—Bcl I</td>
<td>~123 BP</td>
</tr>
<tr>
<td>Fragment 3</td>
<td>HSV-1, E. coli, PRV</td>
<td>BamH I—BamH I</td>
<td>~3027 BP</td>
</tr>
<tr>
<td>Fragment 4</td>
<td>ILTV 5164 bp Asp718I</td>
<td>Bcl I—Asp718 I</td>
<td>~1334 BP</td>
</tr>
</tbody>
</table>

**Diagram:**

- `ΔUL47` and `ΔORF4` near the start of Fragment 1.
- `ΔgG` near the end of Fragment 1.
- `HSV-1 poly A` and `uidA` between Fragment 1 and Fragment 3.
- `PRV gX Promoter` near the end of Fragment 3.
- `800 BP` between Fragment 3 and Fragment 4.
**FIGURE 8-2**

**Junction A**
- Eco RI
- Sac I
- Asp718 I

pSP18/19 → ILTV 5164 bp Asp718 I

**Junction B**
- ATC TAT TGG AGC GTT TAG
- CGC GCG TCG ACG AAA GGT CAG AGA CGA

ILTV 5164 bp Asp718 I
(ILTV UL47) → ILTV 5164 bp Asp718 I
(ILTV gG)

[ BssH II ]

**Junction C**
- CTG CTT CAT TTC TGA TCC CCG GGA ACG

ILTV 5164 bp Asp718 I → HSV-1 BamHI #Q

[Bcl I, BamHI]
FIGURE 9-1

<table>
<thead>
<tr>
<th>DNA</th>
<th>Origin</th>
<th>Sites</th>
<th>Size</th>
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<tr>
<td>Vector</td>
<td>pUC19</td>
<td>Asp718 I—BamH I</td>
<td>~2677 BP</td>
</tr>
<tr>
<td>Fragment 1</td>
<td>ILTV 5164 bp Asp718I</td>
<td>Asp718 I—Nhe I</td>
<td>~2830 BP</td>
</tr>
<tr>
<td>Fragment 2</td>
<td>PRV, E. coli, HSV-1</td>
<td>Sal I—Sal I</td>
<td>~3051 BP</td>
</tr>
<tr>
<td>Fragment 3</td>
<td>ILTV 4545 bp BamH I</td>
<td>Sal I—BamH I</td>
<td>~1709 BP</td>
</tr>
</tbody>
</table>

[Diagram showing DNA fragments A to D, with PRV gX Promoter, uidA, HSV-1 poly A, and 800 BP]
<table>
<thead>
<tr>
<th>DNA</th>
<th>Vector</th>
<th>Origin</th>
<th>pSP 71</th>
<th>PRV BamHI #10</th>
<th>pRAJ 260</th>
<th>PRV gX Promoter</th>
<th>Fragment 1</th>
<th>Fragment 2</th>
<th>Fragment 3</th>
<th>Fragment 3</th>
<th>Fragment 3</th>
<th>Fragment 3</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Site</td>
<td></td>
<td>Sma I</td>
<td>EcoRI f</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Xma I</td>
<td>EcoRI f</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Xma I</td>
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<tr>
<td></td>
<td></td>
<td>Size</td>
<td></td>
<td>~3066 BP</td>
<td>~422 BP</td>
<td>~18226 BP</td>
<td>~784 BP</td>
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</tr>
</tbody>
</table>

† Restriction enzyme site introduced by PCR cloning

 poly A  E. coli  Fragment 2  C  Fragment 3  D  Fragment 1

uidA
FIGURE 11-2

Junction A

Xba I
Sal I
Pst I

TCT AGA GTC GAC CTG CAG TGA ATA ATA AAA TGT GTG TTT GTC CGA AAT

pSP 72 → HCMV 2.1 kb Pst I

Junction B

Ava II Nco I BamH I

CTC CAT AGA AGA CAC CGG GAC CAT GGA TCC CGT CGT TTT ACA ACG

HCMV 2.1 kb Pst I → pJF 751
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPCI(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
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)
U.S. : 435/235.1, 69.1, 69.3; 424/184.1, 204.1, 229.1; 436/507, 517; 935/55, 65, 66

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)
APS, CABA, VETB, BIOSIS, MEDLINE, EMBASE, WIPDS, BIOTECHDS, CA, DIALOG, CRIS/USDA, AGRICOLA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

[X] Further documents are listed in the continuation of Box C. | | See patent family annex. |

| * | Special categories of cited documents: | "T" |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | | |
| "E" | earlier document published on or after the international filing date | "X" |
| "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) | "Y" |
| "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 data claimed | |

Date of the actual completion of the international search
01 DECEMBER 1994

Date of mailing of the international search report
12 JAN 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
NITA M. MINNIFIELD
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*
## INTERNATIONAL SEARCH REPORT

### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>Y</td>
<td>Avian Diseases, Volume 27, No. 4, issued 1983, T. Izuchi et al., &quot;Studies on a live virus vaccine against infectious laryngotracheitis of chickens. I. Biological properties of attenuated strain C7&quot;, pages 918-926, see entire document.</td>
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<td>Y</td>
<td>US, A, 4,980,162 (HONDA ET AL.) 25 December 1990, see entire document.</td>
<td>45-66</td>
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<td>WO, A, 92/03554 (SHEPPARD ET AL.) 05 March 1992, see entire document.</td>
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<tr>
<td>Y</td>
<td>WO, A, 90/02802 (GRIFFIN ET AL.) 22 March 1990, see entire document.</td>
<td>1-79</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. □ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.:
   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:

   Please See Extra Sheet.

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying 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.
A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):
C12N 7/00, 15/00; A61K 39/00, 39/12, 39/27, 39/38, 39/245, 39/255, 39/265; G01N 33/564, 33/557; C12P 21/06

A. CLASSIFICATION OF SUBJECT MATTER:
US CL:
435/235.1, 69.1, 69.3; 424/184.1, 204.1, 229.1; 436/507, 517; 935/55, 65, 66

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-43, is drawn to a recombinant infectious laryngotracheitis virus.

Group II, claims 44-66, is drawn to a vaccine and method of immunizing.

Group III, claims 67-70, is drawn to a method of diagnosis.

Group IV, claims 71-79, is drawn to a homology vector for producing a virus.

The inventions listed as Groups I, II, III, and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The inventions can not be used for the same purpose and the inventions can be used for other purposes than what is claimed, for example the homology vector can be used to produce any virus. For example the special technical feature of Group II, the vaccine composition and the method of using the vaccine composition to immunize an animal are not found in the other Groups.