

REOVIRUSES HAVING MODIFIED SEQUENCES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. 119(e) to U.S. Application No. 60/894,425 filed on March 12, 2007 and U.S. Application No. 60/989,568 filed on November 21, 2007, both of which are incorporated herein by reference.

TECHNICAL FIELD

This invention relates to viruses, and more particularly to reoviruses having modified sequences.

BACKGROUND

The name reovirus derives from an acronym for respiratory and enteric orphan virus, reflecting that the initial isolates came from human respiratory and enteric tracts but were not associated with serious disease. Reoviruses have a double-stranded, segmented RNA genome. The virions measure 60-80 nm in diameter and possess two concentric capsid shells, each of which is icosahedral. The mammalian reovirus genome consists of double-stranded RNA in 10 discrete segments with a total genome size of ~23.5 kbp. The individual RNA segments vary in size.

Three serologically distinct but related types of reovirus have been recovered from mammalian species: type 1 (representative strains include, for example, Lang (T1L)), type 2 (representative strains include, for example, Jones (T2J)) and type 3 (representative strains include, for example, Dearing or Abney (T3D or T3A, respectively)). The three serotypes are easily identifiable on the basis of neutralization and hemagglutinin-inhibition assays (see, for example, Sabin, 1959, *Science*, 130:966; Fields, et al., 1996, *Fundamental Virology*, 3rd Ed., Lippincott-Raven; Rosen, 1960, *Am. J. Hyg.*, 71:242; and Stanley, 1967, *Br. Med. Bull.*, 23:150).

SUMMARY

Provided herein are reoviruses having modified nucleic acid and polypeptide sequences. Sequence modifications include, for example, modifications in one or more of the reovirus genome segments. Also provided are pharmaceutical compositions that include reoviruses having a modified sequence as well as methods of using such reoviruses.

In one aspect, there is provided a reovirus comprising (i) a lambda-3 polypeptide having an amino acid modification which is a Leu at residue 979, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1; (ii) a lambda-3 polypeptide having an amino acid modification which is an Arg at residue 1045, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1.

In a second aspect, there is provided a reovirus comprising (i) a L1 genome segment having a nucleic acid substitution which is a C at position 2953, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, an A at position 3153, a G at position 3231, numbered relative to SEQ ID NO:22 (GenBank Accession No. M24734.1); (ii) a L1 genome segment having a nucleic acid substitution which is an A at position 3153, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, a G at position 3231, numbered relative to SEQ ID NO:22 (GenBank Accession No. M24734.1).

In a third aspect, there is provided a polypeptide comprising (i) an amino acid sequence of a reovirus lambda-3 polypeptide, wherein the sequence of the reovirus lambda-3 polypeptide comprises an amino acid modification which is a Leu at residue 979, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1; (ii) an amino acid sequence of a reovirus lambda-3 polypeptide, wherein the sequence of the reovirus lambda-3 polypeptide comprises an amino acid modification

which is a Arg at residue 1045, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1.

In a fourth aspect, there is provided a reovirus comprising one or more of the polypeptides as defined above.

In a fifth aspect, there is provided a nucleic acid molecule comprising (i) a nucleic acid sequence of a reovirus L1 genome segment, wherein the nucleic acid sequence of the reovirus L1 genome segment comprises a nucleic acid substitution which is a C at position 2953, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, an A at position 3153, a G at position 3231, numbered relative to GenBank Accession No. M24734.1; (ii) a nucleic acid sequence of a reovirus L1 genome segment, wherein the nucleic acid sequence of the reovirus L1 genome segment comprises a nucleic acid substitution which is an A at position 3153, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, a G at position 3231, numbered relative to GenBank Accession No. M24734.1.

In a sixth aspect, there is provided a reovirus comprising one or more of the nucleic acid molecules as defined above.

In a seventh aspect, there is provided a reovirus, wherein the reovirus comprises genomic segments having the sequences as set forth in SEQ ID NOs:1-3 and 7-10.

In an eighth aspect, there is provided a reovirus, wherein the reovirus comprises polypeptides as set forth in SEQ ID NOs:11, 12, and 18-21, and at least one of SEQ ID NO:13 or 14.

In a ninth aspect, there is provided a pharmaceutical composition comprising the reovirus as defined above and a pharmaceutically acceptable carrier.

In a tenth aspect, there is provided the use of the reovirus as defined above or the pharmaceutical composition as defined above in the manufacture of a medicament for treating a proliferative disorder in a patient wherein said patient is to be administered with said medication.

In an eleventh aspect, there is provided the reovirus as defined above or the pharmaceutical composition as defined above for use in treating a proliferative disorder.

In one embodiment, the disclosure provides a reovirus that has a lambda-3 polypeptide having one or more amino acid modifications; a sigma-3 polypeptide having one or more amino acid modifications; a mu-1 polypeptide having one or more amino acid modifications; and/or a mu-2

polypeptide having one or more amino acid modifications. Such a reovirus can be, for example, non-naturally occurring. In another embodiment, the disclosure provides a reovirus lambda-3 polypeptide having one or more amino acid modifications; a reovirus sigma-3 polypeptide having one or more amino acid modifications; a reovirus mu-1 polypeptide having one or more amino acid
5 modifications; and/or a reovirus mu-2 polypeptide having one or more amino acid modifications.

By way of example, the one or more amino acid modifications in the lambda-3 polypeptide can be a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession
10 No. M24734.1. It is noted that, when the amino acid sequence is a Val at residue 214 or a Val at residue 1071, the amino acid sequence further includes at least one additional change in the amino acid sequence. In one embodiment, the lambda-3 polypeptide includes the sequence shown in SEQ ID NO:19.

Further by way of example, the one or more amino acid modifications in the sigma-3
15 polypeptide can be a Leu at residue 14, a Lys at residue 198, or any combination thereof, numbered relative to GenBank Accession No. K02739. It is noted that, when the amino acid sequence is a Leu at residue 14, the amino acid sequence further includes at least one additional change in the amino acid sequence. In one embodiment, the sigma-3 polypeptide includes the sequence shown in SEQ ID NO:15.

Further by way of example, the one or more amino acid modifications in the mu-1
20 polypeptide can be an Asp at residue 73 numbered relative to GenBank Accession No. M20161.1. In one embodiment, the mu-1 polypeptide includes the sequence shown in SEQ ID NO:17.

Also by way of example, the amino acid modification mu-2 polypeptide can be a Ser at residue 528 numbered relative to GenBank Accession No. AF461684.1. In one embodiment, the
25 mu-2 polypeptide includes the sequence shown in SEQ ID NO:16.

A reovirus as described herein having one or more modifications can further include a reovirus sigma-2 polypeptide. Such a sigma-2 polypeptide can have a Cys at one or more of position 70, 127, 195, 241, 255, 294, 296, or 340, numbered relative to GenBank Accession No. NP_694684.1. In one embodiment, the sigma-2 polypeptide includes the sequence shown in SEQ
30 ID NO:12.

In another embodiment, the disclosure provides a reovirus that has a L1 genome segment having one or more nucleic acid modifications; a S4 genome segment having one or more nucleic acid modifications; a M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications. Such a reovirus can be, for example, non-
35 naturally occurring. In another embodiment, the disclosure provides a L1 genome segment

having one or more nucleic acid modifications; a S4 genome segment having one or more nucleic acid modifications; a M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications.

5 By way of example, the one or more nucleic acid modifications in the L1 genome segment can be a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, an A at position 3153, or a G at position 3231, numbered relative to GenBank Accession No. M24734.1. In one embodiment, the L1 genome segment includes the sequence shown in SEQ ID NO:8.

10 Further by way of example, the one or more nucleic acid modifications in the S4 genome segment can be an A at position 74 and an A at position 624, numbered relative to GenBank Accession No. K02739. In one embodiment, the S4 genome segment includes the sequence shown in SEQ ID NO:4.

15 Further by way of example, the nucleic acid modification in the M2 genome segment can be a C at position 248, numbered relative to GenBank Accession No. M20161.1. In one embodiment, the M2 genome segment includes the sequence shown in SEQ ID NO:6.

Also by way of example, the nucleic acid modification in the M1 genome segment can be a T at position 1595, numbered relative to GenBank Accession No. AF461684.1. In one embodiment, the M1 genome segment includes the sequence shown in SEQ ID NO:5.

20 A reovirus as described herein can include any modification or combination of modifications disclosed herein. In some embodiments, a reovirus as described herein is a reassortant. In certain embodiments, a reovirus as described herein includes genomic segments having the sequences shown in SEQ ID NOs:1-10 or the polypeptides shown in SEQ ID NOs:11, 12, and 16-21, and either or both SEQ ID NO:13 or 14. In one embodiment, a reovirus as disclosed herein is identified as IDAC Accession No. 190907-01.

25 A reovirus as disclosed herein generally exhibits a growth advantage over a reovirus that does not contain a corresponding modification. Representative growth advantages include, but are not limited to, an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release
35 effective tumor epitopes.

A reovirus as described herein can be included, along with a pharmaceutically acceptable carrier, in a pharmaceutical composition. Such pharmaceutical compositions can include, for example, one or more chemotherapeutic agents and/or one or more immunosuppressive agents.

In still another embodiment, the disclosure provides for methods of making an improved reovirus. Such methods generally include the steps of modifying the nucleic acid sequence of the reovirus, and selecting one or more improved reoviruses. In some embodiments, the modifying step includes, for example, mutagenizing the reovirus. Representative types of mutagenesis include, without limitation, site-directed mutagenesis and chemical mutagenesis. In other embodiments, the modifying step includes culturing the reovirus in a human cell line.

An improved reovirus made according to the methods disclosed herein can be selected for an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes.

In yet another embodiment, the disclosure provides methods of treating a proliferative disorder in a patient. Such methods generally include administering a modified reovirus as described herein or a pharmaceutical composition containing such a modified reovirus to the patient. Typically, the reovirus is administered in an amount effective to cause oncolysis, and can be administered more than once. Representative routes of administration include, for example, direct injection, intravenously, intravascularly, intrathecally, intramuscularly, subcutaneously, intraperitoneally, topically, orally, rectally, vaginally, nasally, or by inhalation. The methods of treating a proliferative disorder as described herein can be accompanied by one of more procedures such as surgery, chemotherapy, radiation therapy, and immunosuppressive therapy.

In another embodiment, the disclosure provides a kit (or article of manufacture) that includes a reovirus having a modified sequence or any combination of genome segments having a modified sequence as disclosed herein. A kit also can include one or more agents as disclosed herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described

below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The details of one or more embodiments of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of this disclosure will be apparent from the drawings and detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is the nucleotide sequence of a representative S1 segment (SEQ ID NO:1), S2 segment (SEQ ID NO:2), S3 segment (SEQ ID NO:3) and S4 segment (SEQ ID NO:4).

Figure 2 is the nucleotide sequence of a representative M1 segment (SEQ ID NO:5), M2 segment (SEQ ID NO:6) and M3 segment (SEQ ID NO:7).

Figure 3 is the nucleotide sequence of a representative L1 segment (SEQ ID NO:8), L2 segment (SEQ ID NO:9) and L3 segment (SEQ ID NO:10).

Figure 4 is the amino acid sequence of a representative sigma-1 polypeptide (SEQ ID NO:11), sigma-2 polypeptide (SEQ ID NO:12), sigma-NS polypeptide (putative coding sequence 1, SEQ ID NO:13; putative coding sequence 2, SEQ ID NO:14) and sigma-3 polypeptide (SEQ ID NO:15).

Figure 5 is the amino acid sequence of a representative mu-2 polypeptide (SEQ ID NO:16), mu-1 polypeptide (SEQ ID NO:17) and mu-NS polypeptide (SEQ ID NO:18).

Figure 6 is the amino acid sequence of a representative lambda-3 polypeptide (SEQ ID NO:19), lambda-2 polypeptide (SEQ ID NO:20) and lambda-1 polypeptide (SEQ ID NO:21).

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

This disclosure describes modifications in the nucleotide and amino acid sequence of a reovirus. Such modifications are optionally selected to affect the virus's ability to replicate and/or package itself and, therefore, alter the infectivity and/or rate of replication of a reovirus.

Reovirus Having Modified Sequences and Methods of Making

Any of the genomic segments from any type 3 mammalian orthoreovirus (referred to herein simply as "reovirus") can be modified as disclosed herein. Representative type 3 mammalian orthoreoviruses include, without limitation, Dearing and Abney strains. See, for example, ATCC Accession Nos. VR-232 and VR-824. Reoviruses that can be modified as disclosed herein include

naturally-occurring reoviruses (e.g., isolated from a source in nature such as from a patient) and reassortant reoviruses (see, e.g., U.S. Patent No. 7,163,678).

Representative modifications to the different genomic segments of a reovirus and their manifestations in the encoded polypeptide are shown in Table 1. The modifications shown in Table 1 show modifications (both in the number of modifications and in the non-conservative nature of many of the modifications) in the sequence of segments encoding polypeptides associated with RNA-dependent RNA polymerase, transcriptional activities and/or RNA binding. For example, many of the novel modifications disclosed herein are located in the L1 genome segment. The wild-type L1 genome segment encodes a 1,267 amino acid (142 kDa) protein designated lambda-3.

Lambda-3 represents the catalytic subunit of the reovirus RNA-dependent RNA polymerase, which mediates both plus- and minus-strand RNA synthesis within reovirus particles. Further modifications were observed in the M2 genome segment. The wild-type M2 genome segment encodes a 708 amino acid (76 kDa) protein designated mu-1, which is involved in the regulation of particle-bound transcription. In addition, modifications also were observed in the S4 and M1 genomic segments, which encode sigma-3 and mu-2, respectively, and play a role in transcription or single-stranded or double-stranded RNA binding.

Thus, this disclosure provides for L1, S4, M1, M2 or any combination of such genome segments that contain one or more nucleic acid modifications in the respective genome segment. Provided herein is a reovirus L1 genome segment having one or more nucleic acid modifications; a reovirus S4 genome segment having one or more nucleic acid modifications; a reovirus M1 genome segment having one or more nucleic acid modifications; and/or a M2 genome segment having one or more nucleic acid modifications.

A reovirus L1 genome segment has, for example, any combination of one or more of the following nucleotides: a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, an A at position 3153, or a G at position 3231 (numbered relative to GenBank Accession No. M24734.1). A reovirus S4 genome segment has, for example, any combination of one or more of the following nucleotides: an A at position 74 or an A at position 624 (numbered relative to GenBank Accession No. K02739). A reovirus M1 genome segment has, for example, a T nucleotide at position 1595 (numbered relative to GenBank Accession No. AF461684.1). A reovirus M2 genome segment has, for example, a C nucleotide at position 248 (numbered relative to GenBank Accession No. M20161.1). The indicated nucleotide at the indicated position represents modifications when compared to other corresponding sequences available in public databases (e.g., GenBank Accession Nos. M24734.1, K02739, AF461684.1, and M20161.1).

A reovirus lambda-3 polypeptide has, for example, any combination of one or more amino acid residues: a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, an Arg at residue 1045, or a Val at residue 1071 (numbered relative to GenBank Accession No. M24734.1).

5 It is noted that, when the polypeptide sequence comprises a Val at residue 214 or a Val at residue 1071, the polypeptide sequence further comprises at least one additional change in the amino acid sequence. A reovirus sigma-3 polypeptide has, for example, any combination of one or more amino acid residues: a Leu at residue 14 or a Lys at residue 198 (numbered relative to GenBank Accession No. K02739). It is noted that, when the polypeptide sequence comprises a Leu at residue 14, the
10 polypeptide sequence further comprises at least one additional change in the amino acid sequence. A reovirus mu-1 polypeptide has, for example, an Asp at residue 73 (numbered relative to GenBank Accession No. AF461684.1). A reovirus mu-2 polypeptide has, for example, a Ser at residue 528 (numbered relative to GenBank Accession No. M20161.1). The indicated amino acid at the indicated position represents modifications when compared to other corresponding sequences in
15 public databases (e.g., GenBank Accession Nos. M24734.1, K02739, AF461684.1, and M20161.1).

As used herein, a "non-naturally occurring" reovirus is a reovirus that has at least one nucleic acid or amino acid modification as compared to wild type sequences derived from, for example, a field isolate (e.g., a patient). "Non-naturally occurring" reovirus refers to a virus which has been manipulated or modified in the laboratory. Such manipulated or modified reoviruses
20 include laboratory strains or mutagenized versions. These versions are distinguishable, in nucleic acid and/or amino acid sequence, from, for example, Dearing and Abney strains (e.g., ATCC VR-824 and VF-232, respectively). Representative modifications to one or more of the genome segments, the encoded polypeptide, or both are disclosed herein. In addition to a genome segment or polypeptide containing one or more of the modifications described herein, a reovirus optionally
25 contains an S2 genome segment, which encodes the sigma-2 polypeptide. A sigma-2 polypeptide, for example, has a Cys at one or more or all of the following positions: 70, 127, 195, 241, 255, 294, 296 or 340 (numbered relative to GenBank Accession No. NP_694684.1).

A modification generally occurs at the nucleic acid level, which may or may not manifest itself in the encoded polypeptide. Modifications to a nucleic acid include, without limitation, single
30 or multiple nucleotide transitions (purine to purine or pyrimidine to pyrimidine) or transversions (purine to pyrimidine or *vice versa*) and single- or multiple-nucleotide deletions or insertions. A modification in a nucleic acid can result in one or more conservative or non-conservative amino acid substitutions in the encoded polypeptide, a shift in the reading frame of translation ("frame-shift") resulting in an entirely different polypeptide encoded from that point on, a premature stop
35 codon resulting in a truncated polypeptide ("truncation"), or a modification in a reovirus nucleic

acid may not change the encoded polypeptide at all ("silent" or "nonsense"). See, for example, Johnson & Overington, 1993, *J. Mol. Biol.*, 233:716-38; Henikoff & Henikoff, 1992, *Proc. Natl. Acad. Sci. USA*, 89:10915-19; and U.S. Patent No. 4,554,101 for disclosure on conservative and non-conservative amino acid substitutions.

5 Nucleic acids from reovirus particles are isolated, for example, using standard methodologies, which are commercially available. See also, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins. As used herein, "isolated" nucleic acids refer to nucleic acids that are substantially separated from other nucleic acids with which they are usually associated. Thus,
10 an "isolated" nucleic acid includes, without limitation, reoviral nucleic acid that is essentially free of non-reoviral (e.g., host cell) nucleic acid, or a reoviral genomic segment that is essentially free of nucleic acid corresponding to other genomic segments. In addition, an isolated nucleic acid includes an engineered nucleic acid such as recombinant or synthetic nucleic acids.

Modifications are generated in the nucleic acid of a reovirus using any number of methods
15 known in the art. For example, site directed mutagenesis can be used to modify a reovirus nucleic acid sequence. One of the most common methods of site-directed mutagenesis is oligonucleotide-directed mutagenesis. In oligonucleotide-directed mutagenesis, an oligonucleotide encoding the desired change(s) in sequence is annealed to one strand of the DNA of interest and serves as a primer for initiation of DNA synthesis. In this manner, the oligonucleotide containing the sequence
20 change is incorporated into the newly synthesized strand. See, for example, Kunkel, 1985, *Proc. Natl. Acad. Sci. USA*, 82:488; Kunkel et al., 1987, *Meth. Enzymol.*, 154:367; Lewis & Thompson, 1990, *Nucl. Acids Res.*, 18:3439; Bohnsack, 1996, *Meth. Mol. Biol.*, 57:1; Deng & Nickoloff, 1992, *Anal. Biochem.*, 200:81; and Shimada, 1996, *Meth. Mol. Biol.*, 57:157.

Other methods are routinely used in the art to introduce a modification into a sequence. For
25 example, modified nucleic acids are generated using PCR or chemical synthesis, or polypeptides having the desired change in amino acid sequence can be chemically synthesized. See, for example, Bang & Kent, 2005, *Proc. Natl. Acad. Sci. USA*, 102:5014-9 and references therein. Selection on a cell type on which reovirus is not usually grown (e.g., human cells) and/or chemical mutagenesis (see, for example, Rudd & Lemay, 2005, *J. Gen. Virology*, 86:1489-97) also can be
30 used to generate modifications in the nucleic acid of a reovirus. For example, the modifications shown in Table 1 were generated by culturing reovirus on human cells (e.g., human embryonic kidney (HEK) 293 cells), which are not typically used in the art of culturing reovirus. In contrast, cells that are commonly used to culture reovirus are described in, for example, Tyler, "Mammalian Reoviruses," Ch 53, page 1731-2, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott
35 Williams & Wilkins. The modifications described herein represent an adaptation by the reovirus to

human cells. There was also a selection step at each of these plaque purification steps by selection the largest plaque (triple plaque purification), thus a growth or virulence advantage in these cells.

After one or more modifications have been introduced into a reovirus nucleic acid or polypeptide, virus particles are reconstituted using methods known in the art. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins; Smith et al., 1969, *Virology*, 39(4):791-810; and U.S. Patent Nos. 7,186,542; 7,049,127; 6,808,916; and 6,528,305. Reoviruses having one or more modifications in their sequence are cultured in, for example, mouse L929 cells or neoplastic cells (e.g., MCF7 (ATCC Accession No. HTB-22), SKBR3 (ATCC Accession No. HTB-30), or MDA MB 468 (ATCC Accession No. HTB 132) cells), and selected based on any number of characteristics that may indicate, for example, a growth advantage over a reovirus that does not contain one or more modifications. Reoviruses are selected following culturing in a cell line (neoplastic or otherwise) and/or following infection of an animal model system.

Such characteristics include, without limitation, an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cell lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes. Additionally, reoviruses having a modified sequence are selected, for example, for the ability to lytically infect a mammalian cell having an active Ras pathway. See, for example, U.S. Patent No. 7,052,832.

Reovirus particles are obtained using any number of methods known in the art. For example, reoviruses are cultured in L929 mouse fibroblast cells or human cells (e.g., HEK 293), and the viral particles purified using standard methodology. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe & Howley, eds., 2006, Lippincott Williams & Wilkins; Smith et al., 1969, *Virology*, 39(4):791-810; and U.S. Patent Nos. 7,186,542; 7,049,127; 6,808,916; and 6,528,305. As used herein, "purified" viral particles refers to virus particles that have been substantially separated from cellular components that naturally accompany it. Typically, virus particles are considered "purified" when they are at least 70% (e.g., at least 75%, 80%, 85%, 90%, 95%, or 99%) by dry weight, free from the proteins and other cellular components with which the viruses are naturally associated.

A reovirus having the nucleic acid sequence shown in Figures 1, 2 and 3 (SEQ ID NOs: 1-10) and the amino acid sequence shown in Figures 4, 5, and 6 (SEQ ID NOs: 11-21), which contain the nucleotide and amino acid modifications shown in Table 1, was deposited with the International Depositary Authority of Canada (IDAC, National Microbiology Laboratory, Public Health Agency of Canada, 1015 Arlington St., Winnipeg, Manitoba Canada R3E 3R2) on September 19, 2007, and assigned Accession No. 190907-01. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit is exemplary and was made merely as a convenience for those of skill in the art and is not an admission that a deposit is required for patentability (e.g., under 35 U.S.C. §112).

Methods of Using Reoviruses Having Modified Sequences

As described previously (see, for example, U.S. Patent Nos. 6,110,461; 6,136,307; 6,261,555; 6,344,195; 6,576,234; and 6,811,775), reoviruses use a host cell's Ras pathway machinery to downregulate double-stranded RNA-activated protein kinase (PKR) and thus replicate in the cell. Based upon these discoveries, methods have been developed for using reovirus to treat proliferative disorders in mammals. Representative mammals include mice, dogs, cats, sheep, goats, cows, horses, pigs, non-human primates, and humans. As used herein, a "patient" includes any mammal with a proliferative disorder.

A "proliferative disorder" is any cellular disorder in which the cells proliferate more rapidly than normal tissue growth. Thus a "proliferating cell" is a cell that is proliferating more rapidly than normal cells. A proliferative disorder includes, but is not limited to, neoplasms, which are also referred to as tumors. A neoplasm includes, but is not limited to, pancreatic cancer, breast cancer, brain cancer (e.g., glioblastoma), lung cancer, prostate cancer, colorectal cancer, thyroid cancer, renal cancer, adrenal cancer, liver cancer, neurofibromatosis, and leukemia. A neoplasm includes a solid neoplasm (e.g. sarcoma or carcinoma) or a cancerous growth affecting the hematopoietic system (e.g., lymphoma or leukemia). Other proliferative disorders include, but are not limited to neurofibromatosis.

Generally, in proliferative disorders for which reovirus is used as a treatment, at least some of the proliferating cells have a mutation in which the Ras gene (or an element of the Ras signaling pathway) is activated, either directly (e.g., by an activating mutation in Ras) or indirectly (e.g., by activation of an upstream or downstream element in the Ras pathway). Activation of an upstream element in the Ras pathway includes, for example, transformation with epidermal growth factor receptor (EGFR) or Sos. See, for example, Wiessmuller & Wittinghofer, 1994, *Cellular Signaling*, 6(3):247-267; and Barbacid, 1987, *Ann. Rev. Biochem.*, 56, 779-827. Activation of a downstream

element in the Ras pathway includes, for example, a mutation within B-Raf. See, for example, Brose et al., 2002, *Cancer Res.*, 62:6997-7000. In addition, reovirus is useful for treating proliferative disorders caused by mutations or dysregulation of PKR. See, for example, Strong et al., 1998, *EMBO J.*, 17:3351-662.

5 A reovirus having a modified sequence as disclosed herein is administered to a mammal that has a proliferative disorder. As used herein, administration refers to delivery of a reovirus such that the reovirus contacts the proliferating cells. The route by which a reovirus is administered depends on the type of disorder and the location of the proliferating cells. A wide variety of administration routes can be employed. For example, for a solid neoplasm that is accessible, a reovirus is
10 administered by direct injection. For a hematopoietic neoplasm, for example, a reovirus is administered intravenously or intravascularly. For certain neoplasms, e.g., those not easily accessible within the body such as metastases or brain tumors, a reovirus is administered in a manner such that it is transported systemically through the body of the mammal to thereby reach the neoplasm (e.g., intrathecally, intravenously, intramuscularly, subcutaneously, or intra-
15 peritoneally). A reovirus also is administered locally including, for example, topically (e.g., for melanoma), orally (e.g., for oral or esophageal neoplasm), rectally (e.g., for colorectal neoplasm), vaginally (e.g., for cervical or vaginal neoplasm), nasally or by inhalation (e.g., for lung neoplasm). A reovirus is optionally administered by more than one route and/or to more than one location in an individual.

20 Targeted administration may be used to administer a reovirus. For example, dendritic cells containing a reovirus may be administered to a subject. See, for example, US Publication No. 2008/0014183. In another example of targeted delivery, carrier cells may be used to target cells of a proliferative disorder and prevent immune recognition of a reovirus which they carry. See, for example, Qiao et al., 2008, *Nature Med.*, 14:37-44; and WO 2008/009115.

25 A reovirus having a modified sequence as disclosed herein is administered in an amount that is sufficient to treat the proliferative disorder (e.g., an "effective amount"). A proliferative disorder is "treated" when administration of a reovirus having a modified sequence to proliferating cells affects one or more symptoms or clinical signs of the disorder including, e.g., increasing lysis (e.g., "oncolysis") of the cells, reducing the number of proliferating cells, reducing the size or
30 progression of a neoplasm, reducing pain associated with the neoplasm, as compared to the signs or symptoms in the absence of the treatment. As used herein, the term "oncolysis" means at least 10% of the proliferating cells are lysed (e.g., at least 20%, 30%, 40%, 50%, or 75% of the cells are lysed). The percentage of lysis can be determined, for example, by measuring the reduction in the size of a neoplasm or in the number of proliferating cells in a mammal, or by measuring the amount
35 of lysis of cells *in vitro* (e.g., from a biopsy of the proliferating cells).

An effective amount of a reovirus having a modified sequence is determined on an individual basis and is based, at least in part, on the particular reovirus used; the individual's size, age, gender; and the size and other characteristics of the proliferating cells. For example, for treatment of a human, approximately 10^3 to 10^{12} plaque forming units (PFU) of a reovirus is used, depending on the type, size and number of proliferating cells or neoplasms present. The effective amount can be from about 1.0 PFU/kg body weight to about 10^{15} PFU /kg body weight (e.g., from about 10^2 PFU /kg body weight to about 10^{13} PFU /kg body weight). A reovirus is administered in a single dose or in multiple doses (e.g., two, three, four, six, or more doses). Multiple doses are administered concurrently or consecutively (e.g., over a period of days or weeks). Treatment with a reovirus having a modified sequence lasts from several days to several months or until diminution of the disease is achieved.

It is contemplated that a reovirus having a modified sequence as disclosed herein is optionally administered in conjunction with surgery or removal of proliferating cells (e.g., a neoplasm). It also is contemplated that a reovirus having a modified sequence is optionally administered in conjunction with or in addition to radiation therapy. It is further contemplated that a reovirus having a modified sequence is optionally administered in conjunction with or in addition to known anticancer compounds, chemotherapeutic agents, and/or immunosuppressive agents. Such agents, include, but are not limited to, 5-fluorouracil, mitomycin C, methotrexate, hydroxyurea, gemcitabine, cyclophosphamide, dacarbazine, mitoxantrone, anthracyclins (Epirubicin, Irinotecan, and Doxorubicin), antibodies to receptors such as herceptin, topoisomerase inhibitors such as etoposide or camptothecin, pregnasome, platinum compounds such as carboplatin and cisplatin, taxanes such as taxol and taxotere, hormone therapies such as tamoxifen and anti-estrogens, interleukins, interferons, aromatase inhibitors, progestational agents, LHRH analogs, mTOR inhibitors (e.g., rapamycin and derivatives thereof; see, for example, Homicsko et al., 2005, *Cancer Res.*, 65:6882-90; and Rao et al., 2004, *Curr. Cancer Drug Targets*, 4:621-35), and combinations thereof.

It is further contemplated that a reovirus having a modified sequence is administered in conjunction with an agent that can increase endothelial permeability and/or decrease interstitial fluid pressure. Such agents include, for example, TNF- α . See, for example, Sacchi et al., 2006, *Clin. Cancer Res.*, 12:175-182. It is contemplated that a reovirus having a modified sequence can be administered in conjunction with any combination of the therapies and agents described herein.

Pharmaceutical Compositions

Pharmaceutical compositions that include one or more reoviruses, at least one of which has a modified sequence as described herein, are provided. See, for example, U.S. Patent No.

6,576,234. In addition to one or more reoviruses, at least one of which has a modified sequence, a pharmaceutical composition typically includes a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier includes a solid, semi-solid, or liquid material that acts as a vehicle, carrier or medium for the reovirus. Thus, for example, compositions containing a reovirus having a modified sequence are in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers include phosphate-buffered saline or another physiologically acceptable buffer, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. A pharmaceutical composition additionally can include, without limitation, lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. Pharmaceutical compositions of the invention can be formulated to provide quick, sustained or delayed release of a reovirus having a modified sequence after administration by employing procedures known in the art. In addition to the representative formulations described below, other suitable formulations for use in a pharmaceutical composition are found in *Remington: The Science and Practice of Pharmacy* (2003, Gennaro & Gennaro, eds., Lippincott Williams & Wilkens).

For preparing solid compositions such as tablets, a reovirus having a modified sequence is mixed with a pharmaceutical carrier to form a solid composition. Optionally, tablets or pills are coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, a tablet or pill comprises an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components, for example, are separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials are used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

Liquid formulations that include a reovirus having a modified sequence for oral administration or for injection generally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. These liquid or solid compositions optionally contain suitable pharmaceutically acceptable excipients as described herein. Such compositions are administered, for example, by the oral or nasal respiratory route for local or systemic effect. Compositions in pharmaceutically acceptable solvents are nebulized by use of inert gases. Nebulized solutions are inhaled, for example, directly from the nebulizing device, from an attached face mask tent, or from an intermittent positive pressure breathing machine. Solution, suspension, or powder compositions are administered, orally or nasally, for example, from devices which deliver the formulation in an appropriate manner.

Another formulation that is employed in the methods taught herein employs transdermal delivery devices ("patches"). Such transdermal patches are used to provide continuous or discontinuous infusion of a reovirus having a modified sequence. The construction and use of transdermal patches for the delivery of pharmaceutical agents are performed according to methods known in the art. See, for example, U.S. Patent No. 5,023,252. Such patches are constructed for continuous, pulsatile, or on-demand delivery of a reovirus having a modified sequence.

A reovirus having a modified sequence is optionally chemically or biochemically pretreated (e.g., by treatment with a protease such as chymotrypsin or trypsin) prior to administration (e.g., prior to inclusion in the pharmaceutical composition). Pretreatment with a protease removes the outer coat or capsid of the virus and can be used to increase the infectivity of the virus.

Additionally or alternatively, a reovirus having a modified sequence is coated in a liposome or micelle to reduce or prevent an immune response in a mammal that has developed immunity toward a reovirus. Such reoviruses are referred to as "immunoprotected reoviruses." See, for example, U.S. Patent Nos. 6,565,831 and 7,014,847.

A reovirus having a modified sequence or a pharmaceutical composition comprising such a reovirus can be packaged into a kit. It is contemplated that a kit optionally includes one or more chemotherapeutic agents and/or immunosuppressive agents (e.g., anti-antireovirus antibodies). A pharmaceutical composition, for example, is formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of a reovirus having a modified sequence calculated to produce the desired therapeutic effect in association with a suitable pharmaceutically acceptable carrier.

In accordance with the present invention, there may be employed conventional molecular biology, microbiology, biochemical, and recombinant DNA techniques within the skill of the art.

Such techniques are explained fully in the literature. The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

5 Example 1—Sequencing and Analysis

Cultures for production of reovirus were initiated from a suspension-adapted HEK 293 S Master Cell Bank (MCB). HEK 293 cells were maintained in Serum Free Medium (HEK 293 SFM II) supplemented with L-glutamine. HEK 293 cells were expanded and seeded into three 15 L spinner flasks, and further expanded until there was 12 L in each of the three flasks. Infection of
10 the HEK 293 cells by reovirus was performed by direct inoculation of the virus into the cell culture. The virus was harvested when the viability of the HEK 293 S cells had decreased by 20-50% post-infection. The virus material from all three spinners was pooled in a single sterile container and agitated to create a homogeneous mixture. Three liters of the pooled cell suspension was removed, transferred to conical tubes, and centrifuged at ~3000 rpm for 15 minutes. The cells were then
15 resuspended with 100 mL of clarified conditioned medium, snap frozen in an alcohol-dry ice bath three times, and then filled into sterile, labeled cryovials for use as a seed stock.

A viral stock was prepared by performing a three-time plaque purification. Adherent HEK 293 S cells were plated onto 6-well tissue culture plates, infected with the seed stock described above, and two of the largest plaques were picked. These two plaques were separately amplified
20 and harvested and two of the largest plaques were picked again. This procedure was repeated again for a total of three times. Of the two plaques, one was selected as seed stock for subsequent expansions.

Cultures were initiated from the same suspension adapted HEK 293 S MCB described above and were maintained in the same HEK 293 Serum Free Medium (HEK 293 SFM II)
25 supplemented with L-glutamine. Cells were expanded from T-flasks up to multiple 3 L spinner flasks. The infection was performed by first diluting the plaque-purified virus in HEK 293 SFM media and then adding 8 to 12 mL of the diluted virus into the cell culture. The virus was harvested when the viability of the HEK 293 S cells had decreased by 20-50% following infection, and microscopic examination of each of the spinners confirmed the lack of microbial contamination and
30 that a cytopathic effect (CPE) was present in the cells. CPE was indicated by cells having a swollen and granular appearance. The material from the spinners was pooled in a single sterile container, agitated to create a homogeneous mixture, and a bulk harvest sample removed. The remaining pooled cell suspension was transferred to conical tubes and centrifuged at ~3000 rpm for 15 minutes. The cells were then resuspended with 400 mL of clarified conditioned medium, and

the concentrated cell suspension was snap-frozen in an alcohol-dry ice bath three times to lyse the cells and then filled into sterile, labeled cryovials for use in sequencing reactions.

Both RNA strands were sequenced from both directions, and the sequence of each of the 10 genomic segments was assembled from the overlapping contigs. The assembled sequence of each genomic segment was used in a BLAST search of the NCBI database (ncbi.nlm.nih.gov on the World Wide Web). Alignments with three or four different reovirus sequences found in the NCBI database were examined and the alignment having the highest amount of homology was used for further analysis. The polymorphisms or modifications compared to other reported sequences are shown in Table 1. Those modifications that are unique to the selected reovirus strain are indicated with an asterisk in Table 1.

Table 1. Modifications Identified

Genomic Segment	Position (nucleotide; amino acid)	Published Sequence (nucleotide; amino acid)	Novel Polymorphism (nucleotide; amino acid)
S1		GenBank Accession No. M10262.1	SEQ ID NO:1
	499; 163	A; Thr	T; Ser
S3		GenBank Accession No. X01627.1	SEQ ID NO:3
	1057; 344	T; <i>Leu</i>	C; <i>Leu</i>
S4		GenBank Accession No. K02739	SEQ ID NO:4
*	74; 14	G; <i>Leu</i>	A; <i>Leu</i>
*	624; 198	G; Glu	A; Lys
	719; 229	G; Glu	T; Asp
M1		GenBank Accession No. AF461684.1	SEQ ID NO:5
	1129; 372	G; Met	T; Ile
*	1595; 528	G; Ala	T; Ser
M2		GenBank Accession No. M20161.1	SEQ ID NO:6
*	248; 73	A; Glu	C; Asp
	302; 91	G; <i>Ala</i>	C; <i>Ala</i>
	303; 92	C; <i>Leu</i>	T; <i>Leu</i>
	305; 92	T; <i>Leu</i>	G; <i>Leu</i>
	709-10; 227	CG; Thr	GC; Ser
	1173; 382	T; <i>Leu</i>	C; <i>Leu</i>
L1		GenBank Accession No. M24734.1	SEQ ID NO:8
*	660; 214	A; <i>Val</i>	T; <i>Val</i>
*	817; 267	T; Ser	G; Ala
*	1687; 557	C; Pro	A; Thr
*	2283; 755	C; Asn	G; Lys
*	2284-6; 756	GAT; Asp	ATG; Met
*	2794; 926	A; Thr	C; Pro

*	2905; 963	T; Ser	C; Pro
*	2953; 979	A; Met	C; Leu
*	3153; 1045	C; Ser	A; Arg
*	3231; 1071	T; <i>Val</i>	G; <i>Val</i>
L2		GenBank Accession No. J03488.1	SEQ ID NO:9
	1838-40; 609	TTT; Phe	GGG; Gly
	3703; 1230	A; <i>Leu</i>	G; <i>Leu</i>
L3		GenBank Accession No. AF129822	SEQ ID NO:10
	1512; 500	T; Ile	G; Ser
	2569; 852	G; Gln	T; His

* designates unique modifications; italicized residues indicate silent modifications; position numbers are with respect to the indicated GenBank Accession No.

5 It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

10 Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed method and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular modification of a reovirus or treatment regime is disclosed and
15 discussed and a number of modifications that can be made to the reovirus or regime are discussed, each and every combination and permutation of the reovirus and the regime are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed.

WHAT IS CLAIMED IS:

1. A reovirus comprising (i) a lambda-3 polypeptide having an amino acid modification which is a Leu at residue 979, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1; (ii) a lambda-3 polypeptide having an amino acid modification which is an Arg at residue 1045, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1.
2. The reovirus of claim 1, wherein the lambda-3 polypeptide comprises SEQ ID NO:19.

3. The reovirus of claim 1, where the reovirus further comprises a reovirus sigma-2 polypeptide.
4. The reovirus of claim 3, wherein the sigma-2 polypeptide comprises a Cys at one or more of position 70, 127, 195, 241, 255, 294, 296, or 340, numbered relative to SEQ ID NO:30 (GenBank Accession No. NP_694684.1).
5. The reovirus of claim 4, wherein the sigma-2 polypeptide comprises SEQ ID NO:12.
6. The reovirus of any of claims 1-5, wherein the reovirus is a reassortant.
7. A reovirus comprising
 - (i) a L1 genome segment having a nucleic acid substitution which is a C at position 2953, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, an A at position 3153, a G at position 3231, numbered relative to SEQ ID NO:22 (GenBank Accession No. M24734.1);
 - (ii) a L1 genome segment having a nucleic acid substitution which is an A at position 3153, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, a G at position 3231, numbered relative to SEQ ID NO:22 (GenBank Accession No. M24734.1).
8. The reovirus of claim wherein the L1 genome segment comprises SEQ ID NO:8.

9. The reovirus of any of claims 7-8, wherein the reovirus is a reassortant.
10. A polypeptide comprising
 - (i) an amino acid sequence of a reovirus lambda-3 polypeptide, wherein the sequence of the reovirus lambda-3 polypeptide comprises an amino acid modification which is a Leu at residue 979, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, an Arg at residue 1045, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1;
 - (ii) an amino acid sequence of a reovirus lambda-3 polypeptide, wherein the sequence of the reovirus lambda-3 polypeptide comprises an amino acid modification which is a Arg at residue 1045, and optionally one or more further amino acid modifications, wherein the one or more amino acid modifications are selected from the group consisting of a Val at residue 214, an Ala at residue 267, a Thr at residue 557, a Lys at residue 755, a Met at residue 756, a Pro at residue 926, a Pro at residue 963, a Leu at residue 979, a Val at residue 1071, or any combination thereof, numbered relative to GenBank Accession No. M24734.1.
11. The polypeptide of claim 10, wherein the lambda-3 polypeptide comprises SEQ ID NO:19.

12. A reovirus comprising one or more of the polypeptides of claims 10-11.
13. The reovirus of claim 12, wherein the reovirus further comprises a sigma-2 polypeptide comprising a Cys at one or more of position 70,127,195,241,255,294,296, or 340, numbered relative to GenBank Accession No. NP 694684.1.
14. The reovirus of claim 13, wherein the sigma-2 polypeptide comprises SEQ ID NO:12.
15. The reovirus of any of claims 12-14, wherein the reovirus is a reassortant.
16. A nucleic acid molecule comprising
 - (i) a nucleic acid sequence of a reovirus L1 genome segment, wherein the nucleic acid sequence of the reovirus L1 genome segment comprises a nucleic acid substitution which is a C at position 2953, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, an A at position 3153, a G at position 3231, numbered relative to GenBank Accession No. M24734.1;
 - (ii) a nucleic acid sequence of a reovirus L1 genome segment, wherein the nucleic acid sequence of the reovirus L1 genome segment comprises a nucleic acid substitution which is an A at position 3153, and optionally one or more further nucleic acid modifications, wherein the one or more nucleic acid modifications are selected from the group consisting of a T at position 660, a G at position 817, an A at position 1687, a G at position 2283, an ATG at positions 2284-2286, a C at position 2794, a C at position 2905, a C at position 2953, a G at position 3231, numbered relative to GenBank Accession No. M24734.1
17. The nucleic acid molecule of claim 16, wherein the L1 genome segment comprises SEQ ID NO:8.

18. A reovirus comprising one or more of the nucleic acid molecules of claim 16-17.
19. The reovirus of claim 18, wherein the reovirus is a reassortant.
20. A reovirus, wherein the reovirus comprises genomic segments having the sequences as set forth in SEQ ID NOs:1-3 and 7-10.
21. A reovirus, wherein the reovirus comprises polypeptides as set forth in SEQ ID NOs:11, 12, and 18-21, and at least one of SEQ ID NO:13 or 14.

22. The reovirus of claim 20 or 21 having IDAC Accession No. 190907-01.

23. The reovirus of any of claims 1-9, 12-15, 18-22, wherein the reovirus exhibits a growth advantage over a reovirus that does not contain a modification.

24. The reovirus of claim 23, wherein the growth advantage is selected from the group consisting of an increased rate of lysis; an increased size of plaque formation; an increased rate of RNA replication; an increased rate of RNA transcription; an increased rate of translation; an increased rate of virus assembly and/or packaging; an increased number of viral progeny; an increased ability of a reovirus to be taken up by a host cell; an increased or enhanced ability to uncoat; enhanced cell lysis or inducement to cell death including apoptosis, necrosis or autophagy; an enhanced ability to infect, lyse and kill human neoplastic cells lines; decreased immunogenicity in mammalian cells; differential susceptibility to interferon sensitivity; decreased toxicity toward the host; enhanced drug interaction; enhanced radiotherapy interaction; or the ability to release effective tumor epitopes.

25. A pharmaceutical composition comprising the reovirus of any one of claims 1-9, 12-15, or 18-24 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising one or more chemotherapeutic agents and/or one or more immunosuppressive agents.

27. The use of the reovirus of any of claims 1-9, 12-15, or 18-24 or the pharmaceutical composition of claim 49 or 50 in the manufacture of a medicament for treating a proliferative disorder in a patient wherein said patient is to be administered with said medication.

28. The use of claim 27, wherein the reovirus is to be administered in an amount effective to cause oncolysis.

29. The use of claim 27, further comprising at least one of the procedures selected from the group consisting of surgery, chemotherapy, radiation therapy, and immunosuppressive therapy.

30. The use of claim 27, wherein the reovirus or pharmaceutical composition is to be administered more than once.

31. The use of claim 27, wherein the reovirus or pharmaceutical composition is to be administered intravenously, intravascularly, intrathecally, intramuscularly, subcutaneously, intraperitoneally, topically, orally, rectally, vaginally, nasally, by direct injection, or by inhalation.

32. The reovirus of any of claims 1-9, 12-15 or 18-24 or the pharmaceutical composition of claim 25 or 26 for use in treating a proliferative disorder.

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SEQUENCE LISTING

<110> Oncolytics Biotech Inc.; Matthew C. COFFEY

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<211> 1331

<212> DNA

<213> Reovirus

<400> 2

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1331

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<211> 1198

<212> DNA

<213> Reovirus

<400> 3

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<211> 1196

<212> DNA

<213> Reovirus

<400> 4

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 <211> 2304
 <212> DNA
 <213> Reovirus

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 <211> 2204
 <212> DNA
 <213> Reovirus

<400> 6
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 <211> 2241
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 <213> Reovirus

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2241

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<211> 3854
<212> DNA
<213> Reovirus

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 Met Ala Ser Ser Leu Arg Ala Ala Ile Ser Lys Ile Lys Arg Asp Asp
 1 5 10 15
 Val Gly Gln Gln Val Cys Pro Asn Tyr Val Met Leu Arg Ser Ser Val
 20 25 30
 Thr Thr Lys Val Val Arg Asn Val Val Glu Tyr Gln Ile Arg Thr Gly
 35 40 45
 Gly Phe Phe Ser Cys Leu Ala Met Leu Arg Pro Leu Gln Tyr Ala Lys
 50 55 60
 Arg Glu Arg Leu Leu Gly Gln Arg Asn Leu Glu Arg Ile Ser Thr Arg
 65 70 75 80
 Asp Ile Leu Gln Thr Arg Asp Leu His Ser Leu Cys Met Pro Thr Pro
 85 90 95
 Asp Ala Pro Met Ser Asn His Gln Ala Ser Thr Met Arg Glu Leu Ile
 100 105 110
 Cys Ser Tyr Phe Lys Val Asp His Ala Asp Gly Leu Lys Tyr Ile Pro
 115 120 125
 Met Asp Glu Arg Tyr Ser Pro Ser Ser Leu Ala Arg Leu Phe Thr Met
 130 135 140
 Gly Met Ala Gly Leu His Ile Thr Thr Glu Pro Ser Tyr Lys Arg Val
 145 150 155 160
 Pro Ile Met His Leu Ala Ala Asp Leu Asp Cys Met Thr Leu Ala Leu
 165 170 175
 Pro Tyr Met Ile Thr Leu Asp Gly Asp Thr Val Val Pro Val Ala Pro
 180 185 190
 Thr Leu Ser Ala Glu Gln Leu Leu Asp Asp Gly Leu Lys Gly Leu Ala
 195 200 205
 Cys Met Asp Met Asp Val Arg Trp Thr Arg Ile Ala Gly Arg Leu Val
 210 215 220

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Ile Arg Val Trp Thr Leu His Ala Ala Ser Thr Ser Cys Ile Ala Arg
 225 230 235 240
 Arg Gln Gln Lys Pro Ser Val Cys Leu Arg His Ala Leu Cys
 245 250

<210> 14
 <211> 366
 <212> PRT
 <213> Reovirus

<400> 14
 Met Ala Ser Ser Leu Arg Ala Ala Ile Ser Lys Ile Lys Arg Asp Asp
 1 5 10 15
 Val Gly Gln Gln Val Cys Pro Asn Tyr Val Met Leu Arg Ser Ser Val
 20 25 30
 Thr Thr Lys Val Val Arg Asn Val Val Glu Tyr Gln Ile Arg Thr Gly
 35 40 45
 Gly Phe Phe Ser Cys Leu Ala Met Leu Arg Pro Leu Gln Tyr Ala Lys
 50 55 60
 Arg Glu Arg Leu Leu Gly Gln Arg Asn Leu Glu Arg Ile Ser Thr Arg
 65 70 75 80
 Asp Ile Leu Gln Thr Arg Asp Leu His Ser Leu Cys Met Pro Thr Pro
 85 90 95
 Asp Ala Pro Met Ser Asn His Gln Ala Ser Thr Met Arg Glu Leu Ile
 100 105 110
 Cys Ser Tyr Phe Lys Val Asp His Ala Asp Gly Leu Lys Tyr Ile Pro
 115 120 125
 Met Asp Glu Arg Tyr Ser Pro Ser Ser Leu Ala Arg Leu Phe Thr Met
 130 135 140
 Gly Met Ala Gly Leu His Ile Thr Thr Glu Pro Ser Tyr Lys Arg Val
 145 150 155 160
 Pro Ile Met His Leu Ala Ala Asp Leu Asp Cys Met Thr Leu Ala Leu
 165 170 175
 Pro Tyr Met Ile Thr Leu Asp Gly Asp Thr Val Val Pro Val Ala Pro
 180 185 190
 Thr Leu Ser Ala Glu Gln Leu Leu Asp Asp Gly Leu Lys Gly Leu Ala
 195 200 205
 Cys Met Asp Ile Ser Tyr Gly Cys Glu Val Asp Ala Asn Ser Arg Pro
 210 215 220
 Ala Gly Asp Gln Ser Met Asp Ser Ser Arg Cys Ile Asn Glu Leu Tyr
 225 230 235 240
 Cys Glu Glu Thr Ala Glu Ala Ile Cys Val Leu Lys Thr Cys Leu Val
 245 250 255
 Leu Asn Cys Met Gln Phe Lys Leu Glu Met Asp Asp Leu Ala His Asn
 260 265 270
 Ala Ala Glu Leu Asp Lys Ile Gln Met Met Ile Pro Phe Ser Glu Arg
 275 280 285
 Val Phe Arg Met Ala Ser Ser Phe Ala Thr Ile Asp Ala Gln Cys Phe
 290 295 300
 Arg Phe Cys Val Met Met Lys Asp Lys Asn Leu Lys Ile Asp Met Arg
 305 310 315 320
 Glu Thr Thr Arg Leu Trp Thr Arg Ser Ala Ser Asp Asp Ser Val Ala
 325 330 335
 Thr Ser Ser Leu Ser Ile Ser Leu Asp Arg Gly Arg Trp Val Ala Ala
 340 345 350
 Asp Ala Ser Asp Ala Arg Leu Leu Val Phe Pro Ile Arg Val
 355 360 365

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<210> 15
 <211> 365
 <212> PRT
 <213> Reovirus

<400> 15

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Met Glu Val Cys Leu Pro Asn Gly His Gln Val Val Asp Leu Ile Asn
 1          5          10          15
Asn Ala Phe Glu Gly Arg Val Ser Ile Tyr Ser Ala Gln Glu Gly Trp
      20          25          30
Asp Lys Thr Ile Ser Ala Gln Pro Asp Met Met Val Cys Gly Gly Ala
      35          40          45
Val Val Cys Met His Cys Leu Gly Val Val Gly Ser Leu Gln Arg Lys
 50          55          60
Leu Lys His Leu Pro His His Arg Cys Asn Gln Gln Ile Arg His Gln
 65          70          75          80
Asp Tyr Val Asp Val Gln Phe Ala Asp Arg Val Thr Ala His Trp Lys
      85          90          95
Arg Gly Met Leu Ser Phe Val Ala Gln Met His Glu Met Met Asn Asp
      100          105          110
Val Ser Pro Asp Asp Leu Asp Arg Val Arg Thr Glu Gly Gly Ser Leu
      115          120          125
Val Glu Leu Asn Arg Leu Gln Val Asp Pro Asn Ser Met Phe Arg Ser
 130          135          140
Ile His Ser Ser Trp Thr Asp Pro Leu Gln Val Val Asp Asp Leu Asp
 145          150          155          160
Thr Lys Leu Asp Gln Tyr Trp Thr Ala Leu Asn Leu Met Ile Asp Ser
      165          170          175
Ser Asp Leu Ile Pro Asn Phe Met Met Arg Asp Pro Ser His Ala Phe
      180          185          190
Asn Gly Val Lys Leu Lys Gly Asp Ala Arg Gln Thr Gln Phe Ser Arg
      195          200          205
Thr Phe Asp Ser Arg Ser Ser Leu Glu Trp Gly Val Met Val Tyr Asp
 210          215          220
Tyr Ser Glu Leu Asp His Asp Pro Ser Lys Gly Arg Ala Tyr Arg Lys
 225          230          235          240
Glu Leu Val Thr Pro Ala Arg Asp Phe Gly His Phe Gly Leu Ser His
      245          250          255
Tyr Ser Arg Ala Thr Thr Pro Ile Leu Gly Lys Met Pro Ala Val Phe
      260          265          270
Ser Gly Met Leu Thr Gly Asn Cys Lys Met Tyr Pro Phe Ile Lys Gly
      275          280          285
Thr Ala Lys Leu Lys Thr Val Arg Lys Leu Val Glu Ala Val Asn His
 290          295          300
Ala Trp Gly Val Glu Lys Ile Arg Tyr Ala Leu Gly Pro Gly Gly Met
 305          310          315          320
Thr Gly Trp Tyr Asn Arg Thr Met Gln Gln Ala Pro Ile Val Leu Thr
      325          330          335
Pro Ala Ala Leu Thr Met Phe Pro Asp Thr Ile Lys Phe Gly Asp Leu
      340          345          350
Asn Tyr Pro Val Met Ile Gly Asp Pro Met Ile Leu Gly
      355          360          365

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<210> 16
 <211> 736
 <212> PRT
 <213> Reovirus

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<400> 16

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Met Ala Tyr Ile Ala Val Pro Ala Val Val Asp Ser Arg Ser Ser Glu
 1           5           10           15
Ala Ile Gly Leu Leu Glu Ser Phe Gly Val Asp Ala Gly Ala Asp Ala
      20           25           30
Asn Asp Val Ser Tyr Gln Asp His Asp Tyr Val Leu Asp Gln Leu Gln
      35           40           45
Tyr Met Leu Asp Gly Tyr Glu Ala Gly Asp Val Ile Asp Ala Leu Val
      50           55           60
His Lys Asn Trp Leu His His Ser Val Tyr Cys Leu Leu Pro Pro Lys
65           70           75           80
Ser Gln Leu Leu Glu Tyr Trp Lys Ser Asn Pro Ser Ala Ile Pro Asp
      85           90           95
Asn Val Asp Arg Arg Leu Arg Lys Arg Leu Met Leu Lys Lys Asp Leu
      100          105          110
Arg Lys Asp Asp Glu Tyr Asn Gln Leu Ala Arg Ala Phe Lys Ile Ser
      115          120          125
Asp Val Tyr Ala Pro Leu Ile Ser Ser Thr Thr Ser Pro Met Thr Met
      130          135          140
Ile Gln Asn Leu Asn Arg Gly Glu Ile Val Tyr Thr Thr Thr Asp Arg
145          150          155          160
Val Ile Gly Ala Arg Ile Leu Leu Tyr Ala Pro Arg Lys Tyr Tyr Ala
      165          170          175
Ser Thr Leu Ser Phe Thr Met Thr Lys Cys Ile Ile Pro Phe Gly Lys
      180          185          190
Glu Val Gly Arg Val Pro His Ser Arg Phe Asn Val Gly Thr Phe Pro
      195          200          205
Ser Ile Ala Thr Pro Lys Cys Phe Val Met Ser Gly Val Asp Ile Glu
210          215          220
Ser Ile Pro Asn Glu Phe Ile Lys Leu Phe Tyr Gln Arg Val Lys Ser
225          230          235          240
Val His Ala Asn Ile Leu Asn Asp Ile Ser Pro Gln Ile Val Ser Asp
      245          250          255
Met Ile Asn Arg Lys Arg Leu Arg Val His Thr Pro Ser Asp Arg Arg
      260          265          270
Ala Ala Gln Leu Met His Leu Pro Tyr His Val Lys Arg Gly Ala Ser
      275          280          285
His Val Asp Val Tyr Lys Val Asp Val Val Asp Met Leu Phe Glu Val
290          295          300
Val Asp Val Ala Asp Gly Leu Arg Asn Val Ser Arg Lys Leu Thr Met
305          310          315          320
His Thr Val Pro Val Cys Ile Leu Glu Met Leu Gly Ile Glu Ile Ala
      325          330          335
Asp Tyr Cys Ile Arg Gln Glu Asp Gly Met Leu Thr Asp Trp Phe Leu
      340          345          350
Leu Leu Thr Met Leu Ser Asp Gly Leu Thr Asp Arg Arg Thr His Cys
      355          360          365
Gln Tyr Leu Ile Asn Pro Ser Ser Val Pro Pro Asp Val Ile Leu Asn
370          375          380
Ile Ser Ile Thr Gly Phe Ile Asn Arg His Thr Ile Asp Val Met Pro
385          390          395          400
Asp Ile Tyr Asp Phe Val Lys Pro Ile Gly Ala Val Leu Pro Lys Gly
      405          410          415
Ser Phe Lys Ser Thr Ile Met Arg Val Leu Asp Ser Ile Ser Ile Leu
      420          425          430
Gly Ile Gln Ile Met Pro Arg Ala His Val Val Asp Ser Asp Glu Val
435          440          445
Gly Glu Gln Met Glu Pro Thr Phe Glu Gln Ala Val Met Glu Ile Tyr

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450		455		460
Lys Gly Ile Ala Gly Val Asp Ser Leu Asp Asp Leu Ile Lys Trp Val				
465		470		475
Leu Asn Ser Asp Leu Ile Pro His Asp Asp Arg Leu Gly Gln Leu Phe				
	485		490	495
Gln Ala Phe Leu Pro Leu Ala Lys Asp Leu Leu Ala Pro Met Ala Arg				
	500		505	510
Lys Phe Tyr Asp Asn Ser Met Ser Glu Gly Arg Leu Leu Thr Phe Ser				
	515		520	525
His Ala Asp Ser Glu Leu Leu Asn Ala Asn Tyr Phe Gly His Leu Leu				
	530		535	540
Arg Leu Lys Ile Pro Tyr Ile Thr Glu Val Asn Leu Met Ile Arg Lys				
545		550		555
Asn Arg Glu Gly Gly Glu Leu Phe Gln Leu Val Leu Ser Tyr Leu Tyr				
	565		570	575
Lys Met Tyr Ala Thr Ser Ala Gln Pro Lys Trp Phe Gly Ser Leu Leu				
	580		585	590
Arg Leu Leu Ile Cys Pro Trp Leu His Met Glu Lys Leu Ile Gly Glu				
	595		600	605
Ala Asp Pro Ala Ser Thr Ser Ala Glu Ile Gly Trp His Ile Pro Arg				
	610		615	620
Glu Gln Leu Met Gln Asp Gly Trp Cys Gly Cys Glu Asp Gly Phe Ile				
625		630		635
Pro Tyr Val Ser Ile Arg Ala Pro Arg Leu Val Ile Glu Glu Leu Met				
	645		650	655
Glu Lys Asn Trp Gly Gln Tyr His Ala Gln Val Ile Val Thr Asp Gln				
	660		665	670
Leu Val Val Gly Glu Pro Arg Arg Val Ser Ala Lys Ala Val Ile Lys				
	675		680	685
Gly Asn His Leu Pro Val Lys Leu Val Ser Arg Phe Ala Cys Phe Thr				
	690		695	700
Leu Thr Ala Lys Tyr Glu Met Arg Leu Ser Cys Gly His Ser Thr Gly				
705		710		715
Arg Gly Ala Ala Tyr Ser Ala Arg Leu Ala Phe Arg Ser Asp Leu Ala				
	725		730	735

<210> 17
 <211> 708
 <212> PRT
 <213> Reovirus

<400> 17

Met Gly Asn Ala Ser Ser Ile Val Gln Thr Ile Asn Val Thr Gly Asp				
1	5	10	15	
Gly Asn Val Phe Lys Pro Ser Ala Glu Thr Ser Ser Thr Ala Val Pro				
	20	25	30	
Ser Leu Ser Leu Ser Pro Gly Met Leu Asn Pro Gly Gly Val Pro Trp				
	35	40	45	
Ile Ala Val Gly Asp Glu Thr Ser Val Thr Ser Pro Gly Ala Leu Arg				
	50	55	60	
Arg Met Thr Ser Lys Asp Ile Pro Asp Thr Ala Ile Ile Asn Thr Asp				
65	70	75	80	
Asn Ser Ser Gly Ala Val Pro Ser Glu Ser Ala Leu Val Pro Tyr Ile				
	85	90	95	
Asp Glu Pro Leu Val Val Val Thr Glu His Ala Ile Thr Asn Phe Thr				
	100	105	110	
Lys Ala Glu Met Ala Leu Glu Phe Asn Arg Glu Phe Leu Asp Lys Met				
	115	120	125	

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Arg	Val	Leu	Ser	Val	Ser	Pro	Lys	Tyr	Ser	Asp	Leu	Leu	Thr	Tyr	Val
130						135					140				
Asp	Cys	Tyr	Val	Gly	Val	Ser	Ala	Arg	Gln	Ala	Leu	Asn	Asn	Phe	Gln
145						150				155					160
Lys	Gln	Val	Pro	Val	Ile	Thr	Pro	Thr	Arg	Gln	Thr	Met	Tyr	Val	Asp
				165					170						175
Ser	Ile	Gln	Ala	Ala	Leu	Lys	Ala	Leu	Glu	Lys	Trp	Glu	Ile	Asp	Leu
			180						185					190	
Arg	Val	Ala	Gln	Thr	Leu	Leu	Pro	Thr	Asn	Val	Pro	Ile	Gly	Glu	Val
		195					200					205			
Ser	Cys	Pro	Met	Gln	Ser	Val	Val	Lys	Leu	Leu	Asp	Asp	Gln	Leu	Pro
	210					215					220				
Asp	Asp	Ser	Leu	Ile	Arg	Arg	Tyr	Pro	Lys	Glu	Ala	Ala	Val	Ala	Leu
225					230					235					240
Ala	Lys	Arg	Asn	Gly	Gly	Ile	Gln	Trp	Met	Asp	Val	Ser	Glu	Gly	Thr
			245						250					255	
Val	Met	Asn	Glu	Ala	Val	Asn	Ala	Val	Ala	Ala	Ser	Ala	Leu	Ala	Pro
			260					265					270		
Ser	Ala	Ser	Ala	Pro	Pro	Leu	Glu	Glu	Lys	Ser	Lys	Leu	Thr	Glu	Gln
	275						280					285			
Ala	Met	Asp	Leu	Val	Thr	Ala	Ala	Glu	Pro	Glu	Ile	Ile	Ala	Ser	Leu
	290					295					300				
Ala	Pro	Val	Pro	Ala	Pro	Val	Phe	Ala	Ile	Pro	Pro	Lys	Pro	Ala	Asp
305					310					315					320
Tyr	Asn	Val	Arg	Thr	Leu	Arg	Ile	Asp	Glu	Ala	Thr	Trp	Leu	Arg	Met
				325					330					335	
Ile	Pro	Lys	Ser	Met	Asn	Thr	Pro	Phe	Gln	Ile	Gln	Val	Thr	Asp	Asn
			340					345					350		
Thr	Gly	Thr	Asn	Trp	His	Leu	Asn	Leu	Arg	Gly	Gly	Thr	Arg	Val	Val
	355						360					365			
Asn	Leu	Asp	Gln	Ile	Ala	Pro	Met	Arg	Phe	Val	Leu	Asp	Leu	Gly	Gly
	370					375					380				
Lys	Ser	Tyr	Lys	Glu	Thr	Ser	Trp	Asp	Pro	Asn	Gly	Lys	Lys	Val	Gly
385				390					395						400
Phe	Ile	Val	Phe	Gln	Ser	Lys	Ile	Pro	Phe	Glu	Leu	Trp	Thr	Ala	Ala
			405						410					415	
Ser	Gln	Ile	Gly	Gln	Ala	Thr	Val	Val	Asn	Tyr	Val	Gln	Leu	Tyr	Ala
			420					425					430		
Glu	Asp	Ser	Ser	Phe	Thr	Ala	Gln	Ser	Ile	Ile	Ala	Thr	Thr	Ser	Leu
	435					440					445				
Ala	Tyr	Asn	Tyr	Glu	Pro	Glu	Gln	Leu	Asn	Lys	Thr	Asp	Pro	Glu	Met
	450					455					460				
Asn	Tyr	Tyr	Leu	Leu	Ala	Thr	Phe	Ile	Asp	Ser	Ala	Ala	Ile	Thr	Pro
465					470					475					480
Thr	Asn	Met	Thr	Gln	Pro	Asp	Val	Trp	Asp	Ala	Leu	Leu	Thr	Met	Ser
			485						490					495	
Pro	Leu	Ser	Ala	Gly	Glu	Val	Thr	Val	Lys	Gly	Ala	Val	Val	Ser	Glu
			500					505					510		
Val	Val	Pro	Ala	Asp	Leu	Ile	Gly	Ser	Tyr	Thr	Pro	Glu	Ser	Leu	Asn
	515						520					525			
Ala	Ser	Leu	Pro	Asn	Asp	Ala	Ala	Arg	Cys	Met	Ile	Asp	Arg	Ala	Ser
	530					535					540				
Lys	Ile	Ala	Glu	Ala	Ile	Lys	Ile	Asp	Asp	Asp	Ala	Gly	Pro	Asp	Glu
545					550				555						560
Tyr	Ser	Pro	Asn	Ser	Val	Pro	Ile	Gln	Gly	Gln	Leu	Ala	Ile	Ser	Gln
			565						570					575	
Leu	Glu	Thr	Gly	Tyr	Gly	Val	Arg	Ile	Phe	Asn	Pro	Lys	Gly	Ile	Leu
			580					585					590		
Ser	Lys	Ile	Ala	Ser	Arg	Ala	Met	Gln	Ala	Phe	Ile	Gly	Asp	Pro	Ser

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595 600 605
 Thr Ile Ile Thr Gln Ala Ala Pro Val Leu Ser Asp Lys Asn Asn Trp
 610 615 620
 Ile Ala Leu Ala Gln Gly Val Lys Thr Ser Leu Arg Thr Lys Ser Leu
 625 630 635 640
 Ser Ala Gly Val Lys Thr Ala Val Ser Lys Leu Ser Ser Ser Glu Ser
 645 650 655
 Ile Gln Asn Trp Thr Gln Gly Phe Leu Asp Lys Val Ser Ala His Phe
 660 665 670
 Pro Ala Pro Lys Pro Asp Cys Pro Thr Ser Gly Asp Ser Gly Glu Ser
 675 680 685
 Ser Asn Arg Arg Val Lys Arg Asp Ser Tyr Ala Gly Val Val Lys Arg
 690 695 700
 Gly Tyr Thr Arg
 705

<210> 18
 <211> 721
 <212> PRT
 <213> Reovirus

<400> 18
 Met Ala Ser Phe Lys Gly Phe Ser Ala Asn Thr Val Pro Val Ser Lys
 1 5 10 15
 Ala Lys Arg Asp Ile Ser Ser Leu Ala Ala Thr Pro Gly Leu Arg Ser
 20 25 30
 Gln Ser Phe Thr Pro Ser Val Asp Met Ser Gln Ser Arg Glu Phe Leu
 35 40 45
 Thr Lys Ala Ile Glu Gln Gly Ser Met Ser Ile Pro Tyr Gln His Val
 50 55 60
 Asn Val Pro Lys Val Asp Arg Lys Val Val Ser Leu Val Val Arg Pro
 65 70 75 80
 Phe Ser Ser Gly Ala Phe Ser Ile Ser Gly Val Ile Ser Pro Ala His
 85 90 95
 Ala Tyr Leu Leu Glu Cys Leu Pro Gln Leu Glu Gln Ala Met Ala Phe
 100 105 110
 Val Ala Ser Pro Glu Ser Phe Gln Ala Ser Asp Val Ala Lys Arg Phe
 115 120 125
 Ala Ile Lys Pro Gly Met Ser Leu Gln Asp Ala Ile Thr Ala Phe Ile
 130 135 140
 Asn Phe Val Ser Ala Met Leu Lys Met Thr Val Thr Arg Gln Asn Phe
 145 150 155 160
 Asp Val Ile Val Ala Glu Ile Glu Arg Leu Ala Ser Thr Ser Val Ser
 165 170 175
 Val Arg Thr Glu Glu Ala Lys Val Ala Asp Glu Glu Leu Met Leu Phe
 180 185 190
 Gly Leu Asp His Arg Gly Pro Gln Gln Leu Asp Val Ser Asp Ala Lys
 195 200 205
 Gly Ile Met Lys Ala Ala Asp Ile Gln Thr Thr His Asp Val His Leu
 210 215 220
 Ala Pro Gly Val Gly Asn Ile Asp Pro Glu Ile Tyr Asn Glu Gly Arg
 225 230 235 240
 Phe Met Phe Met Gln His Lys Pro Leu Ala Ala Asp Gln Ser Tyr Phe
 245 250 255
 Thr Leu Glu Thr Ala Asp Tyr Phe Lys Ile Tyr Pro Thr Tyr Asp Glu
 260 265 270
 His Asp Gly Arg Met Ala Asp Gln Lys Gln Ser Gly Leu Ile Leu Cys
 275 280 285

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Thr Lys Asp Glu Val Leu Ala Glu Gln Thr Ile Phe Lys Leu Asp Ala
 290 295 300
 Pro Asp Asp Lys Thr Val His Leu Leu Asp Arg Asp Asp Asp His Val
 305 310 315 320
 Val Ala Arg Phe Thr Lys Val Phe Ile Glu Asp Val Ala Pro Gly His
 325 330 335
 His Ala Ala Gln Arg Ser Gly Gln Arg Ser Val Leu Asp Asp Leu Tyr
 340 345 350
 Ala Asn Thr Gln Val Ile Ser Ile Thr Ser Ala Ala Leu Lys Trp Val
 355 360 365
 Val Lys His Gly Val Ser Asp Gly Ile Val Asn Arg Lys Asn Val Lys
 370 375 380
 Val Cys Val Gly Phe Asp Pro Leu Tyr Thr Leu Ser Thr His Asn Gly
 385 390 395 400
 Val Ser Leu Cys Ala Leu Leu Met Asp Glu Lys Leu Ser Val Leu Asn
 405 410 415
 Ser Ala Cys Arg Met Thr Leu Arg Ser Leu Met Lys Thr Gly Arg Asp
 420 425 430
 Val Asp Ala His Arg Ala Phe Gln Arg Val Leu Ser Gln Gly Tyr Thr
 435 440 445
 Ser Leu Met Cys Tyr Tyr His Pro Ser Arg Lys Leu Ala Tyr Gly Glu
 450 455 460
 Val Leu Phe Leu Glu Arg Ser Asn Asp Val Thr Asp Gly Ile Lys Leu
 465 470 475 480
 Gln Leu Asp Ala Ser Arg Gln Cys His Glu Cys Pro Val Leu Gln Gln
 485 490 495
 Lys Val Val Glu Leu Glu Lys Gln Ile Ile Met Gln Lys Ser Ile Gln
 500 505 510
 Ser Asp Pro Thr Pro Val Ala Leu Gln Pro Leu Leu Ser Gln Leu Arg
 515 520 525
 Glu Leu Ser Ser Glu Val Thr Arg Leu Gln Met Glu Leu Ser Arg Ala
 530 535 540
 Gln Ser Leu Asn Ala Gln Leu Glu Ala Asp Val Lys Ser Ala Gln Ser
 545 550 555 560
 Cys Ser Leu Asp Met Tyr Leu Arg His His Thr Cys Ile Asn Gly His
 565 570 575
 Ala Lys Glu Asp Glu Leu Leu Asp Ala Val Arg Val Ala Pro Asp Val
 580 585 590
 Arg Arg Glu Ile Met Glu Lys Arg Ser Glu Val Arg Gln Gly Trp Cys
 595 600 605
 Glu Arg Ile Ser Lys Glu Ala Ala Ala Lys Cys Gln Thr Val Ile Asp
 610 615 620
 Asp Leu Thr Leu Met Asn Gly Lys Gln Ala Gln Glu Ile Thr Glu Leu
 625 630 635 640
 Arg Asp Ser Ala Glu Lys Tyr Glu Lys Gln Ile Ala Glu Leu Val Ser
 645 650 655
 Thr Ile Thr Gln Asn Gln Ile Thr Tyr Gln Gln Glu Leu Gln Ala Leu
 660 665 670
 Val Ala Lys Asn Val Glu Leu Asp Ala Leu Asn Gln Arg Gln Ala Lys
 675 680 685
 Ser Leu Arg Ile Thr Pro Ser Leu Leu Ser Ala Thr Pro Ile Asp Ser
 690 695 700
 Val Asp Asp Val Ala Asp Leu Ile Asp Phe Ser Val Pro Thr Asp Glu
 705 710 715 720
 Leu

<210> 19

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<211> 1267
 <212> PRT
 <213> Reovirus

<400> 19

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Met Ser Ser Met Ile Leu Thr Gln Phe Gly Pro Phe Ile Glu Ser Ile
 1           5           10           15
Ser Gly Ile Thr Asp Gln Ser Asn Asp Val Phe Glu Asp Ala Ala Lys
      20           25           30
Ala Phe Ser Met Phe Thr Arg Ser Asp Val Tyr Lys Ala Leu Asp Glu
      35           40           45
Ile Pro Phe Ser Asp Asp Ala Met Leu Pro Ile Pro Pro Thr Ile Tyr
      50           55           60
Thr Lys Pro Ser His Asp Ser Tyr Tyr Tyr Ile Asp Ala Leu Asn Arg
65           70           75           80
Val Arg Arg Lys Thr Tyr Gln Gly Pro Asp Val Tyr Val Pro Asn
      85           90           95
Cys Ser Ile Val Glu Leu Leu Glu Pro His Glu Thr Leu Thr Ser Tyr
      100          105          110
Gly Arg Leu Ser Glu Ala Ile Glu Asn Arg Ala Lys Asp Gly Asp Ser
      115          120          125
Gln Ala Arg Ile Ala Thr Thr Tyr Gly Arg Ile Ala Glu Ser Gln Ala
      130          135          140
Arg Gln Ile Lys Ala Pro Leu Glu Lys Phe Val Leu Ala Leu Leu Val
145          150          155          160
Ala Glu Ala Gly Gly Ser Leu Tyr Asp Pro Val Leu Gln Lys Tyr Asp
      165          170          175
Glu Ile Pro Asp Leu Ser His Asn Cys Pro Leu Trp Cys Phe Arg Glu
      180          185          190
Ile Cys Arg His Ile Ser Gly Pro Leu Pro Asp Arg Ala Pro Tyr Leu
      195          200          205
Tyr Leu Ser Ala Gly Val Phe Trp Leu Met Ser Pro Arg Met Thr Ser
      210          215          220
Ala Ile Pro Pro Leu Leu Ser Asp Leu Val Asn Leu Ala Ile Leu Gln
225          230          235          240
Gln Thr Ala Gly Leu Asp Pro Ser Leu Val Lys Leu Gly Val Gln Ile
      245          250          255
Cys Leu His Ala Ala Ala Ser Ser Ser Tyr Ala Trp Phe Ile Leu Lys
      260          265          270
Thr Lys Ser Ile Phe Pro Gln Asn Thr Leu His Ser Met Tyr Glu Ser
      275          280          285
Leu Glu Gly Gly Tyr Cys Pro Asn Leu Glu Trp Leu Glu Pro Arg Ser
      290          295          300
Asp Tyr Lys Phe Met Tyr Met Gly Val Met Pro Leu Ser Ala Lys Tyr
305          310          315          320
Ala Arg Ser Ala Pro Ser Asn Asp Lys Lys Ala Arg Glu Leu Gly Glu
      325          330          335
Lys Tyr Gly Leu Ser Ser Val Val Gly Glu Leu Arg Lys Arg Thr Lys
      340          345          350
Thr Tyr Val Lys His Asp Phe Ala Ser Val Arg Tyr Ile Arg Asp Ala
      355          360          365
Met Ala Cys Thr Ser Gly Ile Phe Leu Val Arg Thr Pro Thr Glu Thr
      370          375          380
Val Leu Gln Glu Tyr Thr Gln Ser Pro Glu Ile Lys Val Pro Ile Pro
385          390          395          400
Gln Lys Asp Trp Thr Gly Pro Ile Gly Glu Ile Arg Ile Leu Lys Asp
      405          410          415
Thr Thr Ser Ser Ile Ala Arg Tyr Leu Tyr Arg Thr Trp Tyr Leu Ala
      420          425          430

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Ala Ala Arg Met Ala Ala Gln Pro Arg Thr Trp Asp Pro Leu Phe Gln
 435 440 445
 Ala Ile Met Arg Ser Gln Tyr Val Thr Ala Arg Gly Gly Ser Gly Ala
 450 455 460
 Ala Leu Arg Glu Ser Leu Tyr Ala Ile Asn Val Ser Leu Pro Asp Phe
 465 470 475 480
 Lys Gly Leu Pro Val Lys Ala Ala Thr Lys Ile Phe Gln Ala Ala Gln
 485 490 495
 Leu Ala Asn Leu Pro Phe Ser His Thr Ser Val Ala Ile Leu Ala Asp
 500 505 510
 Thr Ser Met Gly Leu Arg Asn Gln Val Gln Arg Arg Pro Arg Ser Ile
 515 520 525
 Met Pro Leu Asn Val Pro Gln Gln Gln Val Ser Ala Pro His Thr Leu
 530 535 540
 Thr Ala Asp Tyr Ile Asn Tyr His Met Asn Leu Ser Thr Thr Ser Gly
 545 550 555 560
 Ser Ala Val Ile Glu Lys Val Ile Pro Leu Gly Val Tyr Ala Ser Ser
 565 570 575
 Pro Pro Asn Gln Ser Ile Asn Ile Asp Ile Ser Ala Cys Asp Ala Ser
 580 585 590
 Ile Thr Trp Asp Phe Phe Leu Ser Val Ile Met Ala Ala Ile His Glu
 595 600 605
 Gly Val Ala Ser Ser Ser Ile Gly Lys Pro Phe Met Gly Val Pro Ala
 610 615 620
 Ser Ile Val Asn Asp Glu Ser Val Val Gly Val Arg Ala Ala Arg Pro
 625 630 635 640
 Ile Ser Gly Met Gln Asn Met Ile Gln His Leu Ser Lys Leu Tyr Lys
 645 650 655
 Arg Gly Phe Ser Tyr Arg Val Asn Asp Ser Phe Ser Pro Gly Asn Asp
 660 665 670
 Phe Thr His Met Thr Thr Thr Phe Pro Ser Gly Ser Thr Ala Thr Ser
 675 680 685
 Thr Glu His Thr Ala Asn Asn Ser Thr Met Met Glu Thr Phe Leu Thr
 690 695 700
 Val Trp Gly Pro Glu His Thr Asp Asp Pro Asp Val Leu Arg Leu Met
 705 710 715 720
 Lys Ser Leu Thr Ile Gln Arg Asn Tyr Val Cys Gln Gly Asp Asp Gly
 725 730 735
 Leu Met Ile Ile Asp Gly Thr Thr Ala Gly Lys Val Asn Ser Glu Thr
 740 745 750
 Ile Gln Lys Met Leu Glu Leu Ile Ser Lys Tyr Gly Glu Glu Phe Gly
 755 760 765
 Trp Lys Tyr Asp Ile Ala Tyr Asp Gly Thr Ala Glu Tyr Leu Lys Leu
 770 775 780
 Tyr Phe Ile Phe Gly Cys Arg Ile Pro Asn Leu Ser Arg His Pro Ile
 785 790 795 800
 Val Gly Lys Glu Arg Ala Asn Ser Ser Ala Glu Glu Pro Trp Pro Ala
 805 810 815
 Ile Leu Asp Gln Ile Met Gly Val Phe Phe Asn Gly Val His Asp Gly
 820 825 830
 Leu Gln Trp Gln Arg Trp Ile Arg Tyr Ser Trp Ala Leu Cys Cys Ala
 835 840 845
 Phe Ser Arg Gln Arg Thr Met Ile Gly Glu Ser Val Gly Tyr Leu Gln
 850 855 860
 Tyr Pro Met Trp Ser Phe Val Tyr Trp Gly Leu Pro Leu Val Lys Ala
 865 870 875 880
 Phe Gly Ser Asp Pro Trp Ile Phe Ser Trp Tyr Met Pro Thr Gly Asp
 885 890 895
 Leu Gly Met Tyr Ser Trp Ile Ser Leu Ile Arg Pro Leu Met Thr Arg

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<400> 20
Met Ala Asn Val Trp Gly Val Arg Leu Ala Asp Ser Leu Ser Ser Pro
 1             5             10             15
Thr Ile Glu Thr Arg Thr Arg Gln Tyr Thr Leu His Asp Leu Cys Ser
      20             25             30

```

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Asp Leu Asp Ala Asn Pro Gly Arg Glu Pro Trp Lys Pro Leu Arg Asn
 35 40 45
 Gln Arg Thr Asn Asn Ile Val Ala Val Gln Leu Phe Arg Pro Leu Gln
 50 55 60
 Gly Leu Val Leu Asp Thr Gln Leu Tyr Gly Phe Pro Gly Ala Phe Asp
 65 70 75 80
 Asp Trp Glu Arg Phe Met Arg Glu Lys Leu Arg Val Leu Lys Tyr Glu
 85 90 95
 Val Leu Arg Ile Tyr Pro Ile Ser Asn Tyr Ser Asn Glu His Val Asn
 100 105 110
 Val Phe Val Ala Asn Ala Leu Val Gly Ala Phe Leu Ser Asn Gln Ala
 115 120 125
 Phe Tyr Asp Leu Leu Pro Leu Leu Ile Ile Asn Asp Thr Met Ile Gly
 130 135 140
 Asp Leu Leu Gly Thr Gly Ala Ser Leu Ser Gln Phe Phe Gln Ser His
 145 150 155 160
 Gly Asp Val Leu Glu Val Ala Ala Gly Arg Lys Tyr Leu Gln Met Glu
 165 170 175
 Asn Tyr Ser Asn Asp Asp Asp Asp Pro Pro Leu Phe Ala Lys Asp Leu
 180 185 190
 Ser Asp Tyr Ala Lys Ala Phe Tyr Ser Asp Thr Tyr Glu Val Leu Asp
 195 200 205
 Arg Phe Thr Trp Thr His Asp Ser Ser Ala Gly Val Leu Val His Tyr
 210 215 220
 Asp Lys Pro Thr Asn Gly His His Tyr Leu Leu Gly Thr Leu Thr Gln
 225 230 235 240
 Met Val Ser Ala Pro Pro Tyr Ile Ile Asn Ala Thr Asp Ala Met Leu
 245 250 255
 Leu Glu Ser Cys Leu Glu Gln Phe Ser Ala Asn Val Arg Ala Arg Pro
 260 265 270
 Ala Gln Pro Val Thr Arg Leu Asp Gln Cys Tyr His Leu Arg Trp Gly
 275 280 285
 Ala Gln Tyr Val Gly Glu Asp Ser Leu Thr Tyr Arg Leu Gly Val Leu
 290 295 300
 Ser Leu Leu Ala Thr Asn Gly Tyr Gln Leu Ala Arg Pro Ile Pro Arg
 305 310 315 320
 Gln Leu Thr Asn Arg Trp Leu Ser Ser Phe Val Ser Gln Ile Met Ser
 325 330 335
 Asp Gly Val Asn Glu Thr Pro Leu Trp Pro Gln Glu Arg Tyr Val Gln
 340 345 350
 Ile Ala Tyr Asp Ser Pro Ser Val Val Asp Gly Ala Thr Gln Tyr Gly
 355 360 365
 Tyr Val Arg Lys Asn Gln Leu Arg Leu Gly Met Arg Ile Ser Ala Leu
 370 375 380
 Gln Ser Leu Ser Asp Thr Pro Ser Pro Val Gln Trp Leu Pro Gln Tyr
 385 390 395 400
 Thr Ile Asp Gln Ala Ala Met Asp Glu Gly Asp Leu Met Val Ser Arg
 405 410 415
 Leu Thr Gln Leu Pro Leu Arg Pro Asp Tyr Gly Asn Ile Trp Val Gly
 420 425 430
 Asp Ala Leu Ser Tyr Tyr Val Asp Tyr Asn Arg Ser His Arg Val Val
 435 440 445
 Leu Ser Ser Glu Leu Pro Gln Leu Pro Asp Thr Tyr Phe Asp Gly Asp
 450 455 460
 Glu Gln Tyr Gly Arg Ser Leu Phe Ser Leu Ala Arg Lys Ile Gly Asp
 465 470 475 480
 Arg Ser Leu Val Lys Asp Thr Ala Val Leu Lys His Ala Tyr Gln Ala
 485 490 495
 Ile Asp Pro Asn Thr Gly Lys Glu Tyr Leu Arg Ser Arg Gln Ser Val

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500					505					510					
Ala	Tyr	Phe	Gly	Ala	Ser	Ala	Gly	His	Ser	Gly	Ala	Asp	Gln	Pro	Leu
		515					520					525			
Val	Ile	Glu	Pro	Trp	Ile	Gln	Gly	Lys	Ile	Ser	Gly	Val	Pro	Pro	Pro
	530					535					540				
Ser	Ser	Val	Arg	Gln	Phe	Gly	Tyr	Asp	Val	Ala	Arg	Gly	Ala	Ile	Val
545					550					555					560
Asp	Leu	Ala	Arg	Pro	Phe	Pro	Ser	Gly	Asp	Tyr	Gln	Phe	Val	Tyr	Ser
			565						570					575	
Asp	Val	Asp	Gln	Val	Val	Asp	Gly	His	Asp	Asp	Leu	Ser	Ile	Ser	Ser
			580					585					590		
Gly	Leu	Val	Glu	Ser	Leu	Leu	Ser	Ser	Cys	Met	His	Ala	Thr	Ala	Pro
	595					600					605				
Gly	Gly	Ser	Phe	Val	Val	Lys	Ile	Asn	Phe	Pro	Thr	Arg	Pro	Val	Trp
	610					615					620				
His	Tyr	Ile	Glu	Gln	Lys	Ile	Leu	Pro	Asn	Ile	Thr	Ser	Tyr	Met	Leu
625					630					635					640
Ile	Lys	Pro	Phe	Val	Thr	Asn	Asn	Val	Glu	Leu	Phe	Phe	Val	Ala	Phe
			645						650					655	
Gly	Val	His	Gln	His	Ser	Ser	Leu	Thr	Trp	Thr	Ser	Gly	Val	Tyr	Phe
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Phe	Leu	Val	Asp	His	Phe	Tyr	Arg	Tyr	Glu	Thr	Leu	Ser	Thr	Ile	Ser
	675					680					685				
Arg	Gln	Leu	Pro	Ser	Phe	Gly	Tyr	Val	Asp	Asp	Gly	Ser	Ser	Val	Thr
	690					695				700					
Gly	Ile	Glu	Thr	Ile	Ser	Ile	Glu	Asn	Pro	Gly	Phe	Ser	Asn	Met	Thr
705					710					715					720
Gln	Ala	Ala	Arg	Ile	Gly	Ile	Ser	Gly	Leu	Cys	Ala	Asn	Val	Gly	Asn
			725						730					735	
Ala	Arg	Lys	Ser	Ile	Ala	Ile	Tyr	Glu	Ser	His	Gly	Ala	Arg	Val	Leu
			740					745					750		
Thr	Ile	Thr	Ser	Arg	Arg	Ser	Pro	Ala	Ser	Ala	Arg	Arg	Lys	Ser	Arg
	755					760						765			
Leu	Arg	Tyr	Leu	Pro	Leu	Ile	Asp	Pro	Arg	Ser	Leu	Glu	Val	Gln	Ala
	770					775					780				
Arg	Thr	Ile	Leu	Pro	Ala	Asp	Pro	Val	Leu	Phe	Glu	Asn	Val	Ser	Gly
785					790					795					800
Ala	Ser	Pro	His	Val	Cys	Leu	Thr	Met	Met	Tyr	Asn	Phe	Glu	Val	Ser
			805						810					815	
Ser	Ala	Val	Tyr	Asp	Gly	Asp	Val	Val	Leu	Asp	Leu	Gly	Thr	Gly	Pro
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Glu	Ala	Lys	Ile	Leu	Glu	Leu	Ile	Pro	Ala	Thr	Ser	Pro	Val	Thr	Cys
	835						840					845			
Val	Asp	Ile	Arg	Pro	Thr	Ala	Gln	Pro	Ser	Gly	Cys	Trp	Asn	Val	Arg
	850					855					860				
Thr	Thr	Phe	Leu	Glu	Leu	Asp	Tyr	Leu	Ser	Asp	Gly	Trp	Ile	Thr	Gly
865					870					875					880
Val	Arg	Gly	Asp	Ile	Val	Thr	Cys	Met	Leu	Ser	Leu	Gly	Ala	Ala	Ala
			885						890					895	
Ala	Gly	Lys	Ser	Met	Thr	Phe	Asp	Ala	Ala	Phe	Gln	Gln	Leu	Ile	Lys
			900					905					910		
Val	Leu	Ser	Lys	Ser	Thr	Ala	Asn	Val	Val	Leu	Val	Gln	Val	Asn	Cys
	915						920					925			
Pro	Thr	Asp	Val	Val	Arg	Ser	Ile	Lys	Gly	Tyr	Leu	Glu	Ile	Asp	Ser
	930					935					940				
Thr	Asn	Lys	Arg	Tyr	Arg	Phe	Pro	Lys	Phe	Gly	Arg	Asp	Glu	Pro	Tyr
945					950					955					960
Ser	Asp	Met	Asp	Ala	Leu	Glu	Lys	Ile	Cys	Arg	Thr	Ala	Trp	Pro	Asn
			965						970					975	

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Cys Ser Ile Thr Trp Val Pro Leu Ser Tyr Asp Leu Arg Trp Thr Arg
 980 985 990
 Leu Ala Leu Leu Glu Ser Thr Thr Leu Ser Ser Ala Ser Ile Arg Ile
 995 1000 1005
 Ala Glu Leu Met Tyr Lys Tyr Met Pro Ile Met Arg Ile Asp Ile His
 1010 1015 1020
 Gly Leu Pro Met Glu Lys Arg Gly Asn Phe Ile Val Gly Gln Asn Cys
 1025 1030 1035 1040
 Ser Leu Val Ile Pro Gly Phe Asn Ala Gln Asp Val Phe Asn Cys Tyr
 1045 1050 1055
 Phe Asn Ser Ala Leu Ala Phe Ser Thr Glu Asp Val Asn Ala Ala Met
 1060 1065 1070
 Ile Pro Gln Val Ser Ala Gln Phe Asp Ala Thr Lys Gly Glu Trp Thr
 1075 1080 1085
 Leu Asp Met Val Phe Ser Asp Ala Gly Ile Tyr Thr Met Gln Ala Leu
 1090 1095 1100
 Val Gly Ser Asn Ala Asn Pro Val Ser Leu Gly Ser Phe Val Val Asp
 1105 1110 1115 1120
 Ser Pro Asp Val Asp Ile Thr Asp Ala Trp Pro Ala Gln Leu Asp Phe
 1125 1130 1135
 Thr Ile Ala Gly Thr Asp Val Asp Ile Thr Val Asn Pro Tyr Tyr Arg
 1140 1145 1150
 Leu Met Thr Phe Val Arg Ile Asp Gly Gln Trp Gln Ile Ala Asn Pro
 1155 1160 1165
 Asp Lys Phe Gln Phe Phe Ser Ser Ala Ser Gly Thr Leu Val Met Asn
 1170 1175 1180
 Val Lys Leu Asp Ile Ala Asp Lys Tyr Leu Leu Tyr Tyr Ile Arg Asp
 1185 1190 1195 1200
 Val Gln Ser Arg Asp Val Gly Phe Tyr Ile Gln His Pro Leu Gln Leu
 1205 1210 1215
 Leu Asn Thr Ile Thr Leu Pro Thr Asn Glu Asp Leu Phe Leu Ser Ala
 1220 1225 1230
 Pro Asp Met Arg Glu Trp Ala Val Lys Glu Ser Gly Asn Thr Ile Cys
 1235 1240 1245
 Ile Leu Asn Ser Gln Gly Phe Val Leu Pro Gln Asp Trp Asp Val Leu
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 Thr Asp Thr Ile Ser Trp Ser Pro Ser Ile Pro Thr Tyr Ile Val Pro
 1265 1270 1275 1280
 Pro Gly Asp Tyr Thr Leu Thr Pro Leu
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 <211> 1275
 <212> PRT
 <213> Reovirus

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 Lys Gln Asn Asn Lys Ala Gly Pro Ala Thr Thr Glu Pro Gly Thr Ser
 35 40 45
 Asn Arg Glu Gln Tyr Lys Ala Arg Pro Gly Ile Ala Ser Val Gln Arg
 50 55 60
 Ala Thr Glu Ser Ala Glu Met Pro Met Lys Asn Asn Asp Glu Gly Thr
 65 70 75 80
 Pro Asp Lys Lys Gly Asn Thr Lys Gly Asp Leu Val Asn Glu His Ser

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Glu	Ala	Lys	Asp	Glu	Ala	Asp	Glu	Ala	Thr	Lys	Lys	Gln	Ala	Lys	Asp																	
				100					105					110																		
Thr	Asp	Lys	Ser	Lys	Ala	Gln	Val	Thr	Tyr	Ser	Asp	Thr	Gly	Ile	Asn																	
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Asn	Ala	Asn	Glu	Leu	Ser	Arg	Ser	Gly	Asn	Val	Asp	Asn	Glu	Gly	Gly																	
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Ser	Asn	Gln	Lys	Pro	Met	Ser	Thr	Arg	Ile	Ala	Glu	Ala	Thr	Ser	Ala																	
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Ile	Val	Ser	Lys	His	Pro	Ala	Arg	Val	Gly	Leu	Pro	Pro	Thr	Ala	Ser																	
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Ser	Gly	His	Gly	Tyr	Gln	Cys	His	Val	Cys	Ser	Ala	Val	Leu	Phe	Ser																	
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Pro	Leu	Asp	Leu	Asp	Ala	His	Val	Ala	Ser	His	Gly	Leu	His	Gly	Asn																	
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Met	Thr	Leu	Thr	Ser	Ser	Asp	Ile	Gln	Arg	His	Ile	Thr	Glu	Phe	Ile																	
				210					215					220																		
Ser	Ser	Trp	Gln	Asn	His	Pro	Ile	Val	Gln	Val	Ser	Ala	Asp	Val	Glu																	
225					230					235					240																	
Asn	Lys	Lys	Thr	Ala	Gln	Leu	Leu	His	Ala	Asp	Thr	Pro	Arg	Leu	Val																	
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Thr	Trp	Asp	Ala	Gly	Leu	Cys	Thr	Ser	Phe	Lys	Ile	Val	Pro	Ile	Val																	
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Pro	Ala	Gln	Val	Pro	Gln	Asp	Val	Leu	Ala	Tyr	Thr	Phe	Phe	Thr	Ser																	
				275					280					285																		
Ser	Tyr	Ala	Ile	Gln	Ser	Pro	Phe	Pro	Glu	Ala	Ala	Val	Ser	Arg	Ile																	
				290					295					300																		
Val	Val	His	Thr	Arg	Trp	Ala	Ser	Asn	Val	Asp	Phe	Asp	Arg	Asp	Ser																	
305					310					315					320																	
Ser	Val	Ile	Met	Ala	Pro	Pro	Thr	Glu	Asn	Asn	Ile	His	Leu	Phe	Lys																	
				325					330					335																		
Gln	Leu	Leu	Asn	Thr	Glu	Thr	Leu	Ser	Val	Arg	Gly	Ala	Asn	Pro	Leu																	
				340					345					350																		
Met	Phe	Arg	Ala	Asn	Val	Leu	His	Met	Leu	Leu	Glu	Phe	Val	Leu	Asp																	
				355					360					365																		
Asn	Leu	Tyr	Leu	Asn	Arg	His	Thr	Gly	Phe	Ser	Gln	Asp	His	Thr	Pro																	
				370					375					380																		
Phe	Thr	Glu	Gly	Ala	Asn	Leu	Arg	Ser	Leu	Pro	Gly	Pro	Asp	Ala	Glu																	
385					390					395					400																	
Lys	Trp	Tyr	Ser	Ile	Met	Tyr	Pro	Thr	Arg	Met	Gly	Thr	Pro	Asn	Val																	
				405					410					415																		
Ser	Lys	Ile	Cys	Asn	Phe	Val	Ala	Ser	Cys	Val	Arg	Asn	Arg	Val	Gly																	
				420					425					430																		
Arg	Phe	Asp	Arg	Ala	Gln	Met	Met	Asn	Gly	Ala	Met	Ser	Glu	Trp	Val																	
				435					440					445																		
Asp	Val	Phe	Glu	Thr	Ser	Asp	Ala	Leu	Thr	Val	Ser	Ile	Arg	Gly	Arg																	
				450					455					460																		
Trp	Met	Ala	Arg	Leu	Ala	Arg	Met	Asn	Ile	Asn	Pro	Thr	Glu	Ile	Glu																	
465																																

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Ser Thr Val Ser Glu Ser Thr Thr Gln Thr Leu Ser Pro Ala Ser Ser
 565 570 575
 Ile Leu Gly Lys Leu Arg Pro Ser Asn Ser Asp Phe Ser Ser Phe Arg
 580 585 590
 Val Ala Leu Ala Gly Trp Leu Tyr Asn Gly Val Val Thr Thr Val Ile
 595 600 605
 Asp Asp Ser Ser Tyr Pro Lys Asp Gly Gly Ser Val Thr Ser Leu Glu
 610 615 620
 Asn Leu Trp Asp Phe Phe Ile Leu Ala Leu Ala Leu Pro Leu Thr Thr
 625 630 635 640
 Asp Pro Cys Ala Pro Val Lys Ala Phe Met Thr Leu Ala Asn Met Met
 645 650 655
 Val Gly Phe Glu Thr Ile Pro Met Asp Asn Gln Ile Tyr Thr Gln Ser
 660 665 670
 Arg Arg Ala Ser Ala Phe Ser Thr Pro His Thr Trp Pro Arg Cys Phe
 675 680 685
 Met Asn Ile Gln Leu Ile Ser Pro Ile Asp Ala Pro Ile Leu Arg Gln
 690 695 700
 Trp Ala Glu Ile Ile His Arg Tyr Trp Pro Asn Pro Ser Gln Ile Arg
 705 710 715 720
 Tyr Gly Ala Pro Asn Val Phe Gly Ser Ala Asn Leu Phe Thr Pro Pro
 725 730 735
 Glu Val Leu Leu Leu Pro Ile Asp His Gln Pro Ala Asn Val Thr Thr
 740 745 750
 Pro Thr Leu Asp Phe Thr Asn Glu Leu Thr Asn Trp Arg Ala Arg Val
 755 760 765
 Cys Glu Leu Met Lys Asn Leu Val Asp Asn Gln Arg Tyr Gln Pro Gly
 770 775 780
 Trp Thr Gln Ser Leu Val Ser Ser Met Arg Gly Thr Leu Asp Lys Leu
 785 790 795 800
 Lys Leu Ile Lys Ser Met Thr Pro Met Tyr Leu Gln Gln Leu Ala Pro
 805 810 815
 Val Glu Leu Ala Val Ile Ala Pro Met Leu Pro Phe Pro Pro Phe Gln
 820 825 830
 Val Pro Tyr Val Arg Leu Asp Arg Asp Arg Val Pro Thr Met Val Gly
 835 840 845
 Val Thr Arg His Ser Arg Asp Thr Ile Thr Gln Pro Ala Leu Ser Leu
 850 855 860
 Ser Thr Thr Asn Thr Thr Val Gly Val Pro Leu Ala Leu Asp Ala Arg
 865 870 875 880
 Ala Ile Thr Val Ala Leu Leu Ser Gly Lys Tyr Pro Pro Asp Leu Val
 885 890 895
 Thr Asn Val Trp Tyr Ala Asp Ala Ile Tyr Pro Met Tyr Ala Asp Thr
 900 905 910
 Glu Val Phe Ser Asn Leu Gln Arg Asp Met Ile Thr Cys Glu Ala Val
 915 920 925
 Gln Thr Leu Val Thr Leu Val Ala Gln Ile Ser Glu Thr Gln Tyr Pro
 930 935 940
 Val Asp Arg Tyr Leu Asp Trp Ile Pro Ser Leu Arg Ala Ser Ala Ala
 945 950 955 960
 Thr Ala Ala Thr Phe Ala Glu Trp Val Asn Thr Ser Met Lys Thr Ala
 965 970 975
 Phe Asp Leu Ser Asp Met Leu Leu Glu Pro Leu Leu Ser Gly Asp Pro
 980 985 990
 Arg Met Thr Gln Leu Ala Ile Gln Tyr Gln Gln Tyr Asn Gly Arg Thr
 995 1000 1005
 Phe Asn Ile Ile Pro Glu Met Pro Gly Ser Val Ile Ala Asp Cys Val
 1010 1015 1020
 Gln Leu Thr Ala Glu Val Phe Asn His Glu Tyr Asn Leu Phe Gly Ile

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1025 1030 1035 1040
 Ala Arg Gly Asp Ile Ile Ile Gly Arg Val Gln Ser Thr His Leu Trp
 1045 1050 1055
 Ser Pro Leu Ala Pro Pro Pro Asp Leu Val Phe Asp Arg Asp Thr Pro
 1060 1065 1070
 Gly Val His Ile Phe Gly Arg Asp Cys Arg Ile Ser Phe Gly Met Asn
 1075 1080 1085
 Gly Ala Ala Pro Met Ile Arg Asp Glu Thr Gly Leu Met Val Pro Phe
 1090 1095 1100
 Glu Gly Asn Trp Ile Phe Pro Leu Ala Leu Trp Gln Met Asn Thr Arg
 1105 1110 1115 1120
 Tyr Phe Asn Gln Gln Phe Asp Ala Trp Ile Lys Thr Gly Glu Leu Arg
 1125 1130 1135
 Ile Arg Ile Glu Met Gly Ala Tyr Pro Tyr Met Leu His Tyr Tyr Asp
 1140 1145 1150
 Pro Arg Gln Tyr Ala Asn Ala Trp Asn Leu Thr Ser Ala Trp Leu Glu
 1155 1160 1165
 Glu Ile Thr Pro Thr Ser Ile Pro Ser Val Pro Phe Met Val Pro Ile
 1170 1175 1180
 Ser Ser Asp His Asp Ile Ser Ser Ala Pro Ala Val Gln Tyr Ile Ile
 1185 1190 1195 1200
 Ser Thr Glu Tyr Asn Asp Arg Ser Leu Phe Cys Thr Asn Ser Ser Ser
 1205 1210 1215
 Pro Gln Thr Ile Ala Gly Pro Asp Lys His Ile Pro Val Glu Arg Tyr
 1220 1225 1230
 Asn Ile Leu Thr Asn Pro Asp Ala Pro Pro Thr Gln Ile Gln Leu Pro
 1235 1240 1245
 Glu Val Val Asp Leu Tyr Asn Val Val Thr Arg Tyr Ala Tyr Glu Thr
 1250 1255 1260
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 <213> Reovirus

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 tatgatgaga ttccagatct atcgcataat tgccctttat ggtgttttag agagatctgt 600
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 aatttagcta ttttgcaaca aactgogggt ttagatccat cattagtga attgggagta 780
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 gttaaacatg actttgcttc agtgaggtac attcgtgacg ctatggcatg tactagcggg 1140
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gcgtatctgc tcgtgaaatg gcgaatgtgc gagggccgcg aaccgtcggg tgatttgoga 3240
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gttggaacca tgctccagag tacgagaaag tactttgtc agacactatt catggcaaa 3360
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ggagttgctg tcgacatcta tctggaggat atacatggcg gtggtcgggc acttgacag 3840
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<210> 23

<211> 1297

<212> PRT

<213> Reovirus

<400> 23

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Met Ser Ser Met Ile Leu Thr Gln Phe Gly Pro Phe Ile Glu Ser Ile
1           5           10           15
Ser Gly Ile Thr Asp Gln Ser Asn Asp Val Phe Glu Asp Ala Ala Lys
20           25           30
Ala Phe Ser Met Phe Thr Arg Ser Asp Val Tyr Lys Ala Leu Asp Glu
35           40           45

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Ile Pro Phe Ser Asp Asp Ala Met Leu Pro Ile Pro Pro Thr Ile Tyr
 50 55 60
 Thr Lys Pro Ser His Asp Ser Tyr Tyr Tyr Ile Asp Ala Leu Asn Arg
 65 70 75 80
 Val Arg Arg Lys Thr Tyr Gln Gly Pro Asp Asp Val Tyr Val Pro Asn
 85 90 95
 Cys Ser Ile Val Glu Leu Leu Glu Pro His Glu Thr Leu Thr Ser Tyr
 100 105 110
 Gly Arg Leu Ser Glu Ala Ile Glu Asn Arg Ala Lys Asp Gly Asp Ser
 115 120 125
 Gln Ala Arg Ile Ala Thr Thr Tyr Gly Arg Ile Ala Glu Ser Gln Ala
 130 135 140
 Arg Gln Ile Lys Ala Pro Leu Glu Lys Phe Val Leu Ala Leu Leu Val
 145 150 155 160
 Ala Glu Ala Gly Gly Ser Leu Tyr Asp Pro Val Leu Gln Lys Tyr Asp
 165 170 175
 Glu Ile Pro Asp Leu Ser His Asn Cys Pro Leu Trp Cys Phe Arg Glu
 180 185 190
 Ile Cys Arg His Ile Ser Gly Pro Leu Pro Asp Arg Ala Pro Tyr Leu
 200 205 210
 Tyr Leu Ser Ala Gly Val Phe Trp Leu Met Ser Pro Arg Met Thr Ser
 215 220 225
 Ala Ile Pro Pro Leu Leu Ser Asp Leu Val Asn Leu Ala Ile Leu Gln
 230 235 240 245
 Gln Thr Ala Gly Leu Asp Pro Ser Leu Val Lys Leu Gly Val Gln Ile
 250 255 260
 Cys Leu His Ala Ala Ala Ser Ser Ser Tyr Ser Trp Phe Ile Leu Lys
 265 270 275
 Thr Lys Ser Ile Phe Pro Gln Asn Thr Leu His Ser Met Tyr Glu Ser
 280 285 290
 Leu Glu Gly Gly Tyr Cys Pro Asn Leu Glu Trp Leu Glu Pro Arg Ser
 295 300 305
 Asp Tyr Lys Phe Met Tyr Met Gly Val Met Pro Leu Ser Ala Lys Tyr
 310 315 320 325
 Ala Arg Ser Ala Pro Ser Asn Asp Lys Lys Ala Arg Glu Leu Gly Glu
 330 335 340
 Lys Tyr Gly Leu Ser Ser Val Val Gly Glu Leu Arg Lys Arg Thr Lys
 345 350 355
 Thr Tyr Val Lys His Asp Phe Ala Ser Val Arg Tyr Ile Arg Asp Ala
 360 365 370
 Met Ala Cys Thr Ser Gly Ile Phe Leu Val Arg Thr Pro Thr Glu Thr
 375 380 385
 Val Leu Gln Glu Tyr Thr Gln Ser Pro Glu Ile Lys Val Pro Ile Pro
 390 395 400 405
 Gln Lys Asp Trp Thr Gly Pro Ile Gly Glu Ile Arg Ile Leu Lys Asp
 410 415 420
 Thr Thr Ser Ser Ile Ala Arg Tyr Leu Tyr Arg Thr Trp Tyr Leu Ala
 425 430 435
 Ala Ala Arg Met Ala Ala Gln Pro Arg Thr Trp Asp Pro Leu Phe Gln
 440 445 450
 Ala Ile Met Arg Ser Gln Tyr Val Thr Ala Arg Gly Gly Ser Gly Ala
 455 460 465
 Ala Leu Arg Glu Ser Leu Tyr Ala Ile Asn Val Ser Leu Pro Asp Phe
 470 475 480 485
 Lys Gly Leu Pro Val Lys Ala Ala Thr Lys Ile Phe Gln Ala Ala Gln
 490 495 500
 Leu Ala Asn Leu Pro Phe Ser His Thr Ser Val Ala Ile Leu Ala Asp
 505 510 515
 Thr Ser Met Gly Leu Arg Asn Gln Val Gln Arg Arg Pro Arg Ser Ile

30/38

520	525	530
Met Pro Leu Asn Val Pro Gln Gln Val Ser Ala Pro His Thr Leu		
535	540	545
Thr Ala Asp Tyr Ile Asn Tyr His Met Asn Leu Ser Pro Thr Ser Gly		
550	555	560
Ser Ala Val Ile Glu Lys Val Ile Pro Leu Gly Val Tyr Ala Ser Ser		
570	575	580
Pro Pro Asn Gln Ser Ile Asn Ile Asp Ile Ser Ala Cys Asp Ala Ser		
585	590	595
Ile Thr Trp Asp Phe Phe Leu Ser Val Ile Met Ala Ala Ile His Glu		
600	605	610
Gly Val Ala Ser Ser Ser Ile Gly Lys Pro Phe Met Gly Val Pro Ala		
615	620	625
Ser Ile Val Asn Asp Glu Ser Val Val Gly Val Arg Ala Ala Arg Pro		
630	635	640
Ile Ser Gly Met Gln Asn Met Ile Gln His Leu Ser Lys Leu Tyr Lys		
650	655	660
Arg Gly Phe Ser Tyr Arg Val Asn Asp Ser Phe Ser Pro Gly Asn Asp		
665	670	670
Phe Thr His Met Thr Thr Thr Phe Pro Ser Gly Ser Thr Ala Thr Ser		
675	680	685
Thr Glu His Thr Ala Asn Asn Ser Thr Met Met Glu Thr Phe Leu Thr		
690	700	705
Val Trp Gly Pro Glu His Thr Asp Asp Pro Asp Val Leu Arg Leu Met		
710	715	720
Lys Ser Leu Thr Ile Gln Arg Asn Tyr Val Cys Gln Gly Asp Asp Gly		
730	735	740
Leu Met Ile Ile Asp Gly Thr Thr Ala Gly Lys Val Asn Ser Glu Thr		
745	750	755
Ile Gln Asn Asp Leu Glu Leu Ile Ser Lys Tyr Gly Glu Glu Phe Gly		
760	765	770
Trp Lys Tyr Asp Ile Ala Tyr Asp Gly Thr Ala Glu Tyr Leu Lys Leu		
775	780	785
Tyr Phe Ile Phe Gly Cys Arg Ile Pro Asn Leu Ser Arg His Pro Ile		
790	795	800
Val Gly Lys Glu Arg Ala Asn Ser Ser Ala Glu Glu Pro Trp Pro Ala		
810	815	820
Ile Leu Asp Gln Ile Met Gly Val Phe Phe Asn Gly Val His Asp Gly		
825	830	835
Leu Gln Trp Gln Arg Trp Ile Arg Tyr Ser Trp Ala Leu Cys Cys Ala		
840	845	850
Phe Ser Arg Gln Arg Thr Met Ile Gly Glu Ser Val Gly Tyr Leu Gln		
855	890	895
Tyr Pro Met Trp Ser Phe Val Tyr Trp Gly Leu Pro Leu Val Lys Ala		
900	905	910
Phe Gly Ser Asp Pro Trp Ile Phe Ser Trp Tyr Met Pro Thr Gly Asp		
920	925	930
Leu Gly Met Tyr Ser Trp Ile Ser Leu Ile Arg Pro Leu Met Thr Arg		
935	940	945
Trp Met Val Ala Asn Gly Tyr Val Thr Asp Arg Cys Ser Thr Val Phe		
950	955	960
Gly Asn Ala Asp Tyr Arg Arg Cys Phe Asn Glu Leu Lys Leu Tyr Gln		
965	970	975
Gly Tyr Tyr Met Ala Gln Leu Pro Arg Asn Pro Lys Lys Ser Gly Arg		
980	985	990
Ala Ala Ser Arg Glu Val Arg Glu Gln Phe Thr Gln Ala Leu Ser Asp		
1000	1005	1010
Tyr Leu Met Gln Asn Pro Glu Leu Lys Ser Arg Val Leu Arg Gly Arg		
1015	1020	1025

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Ser Glu Trp Glu Lys Tyr Gly Ala Gly Ile Ile His Asn Pro Pro Ser
 1030 1035 1040
 Leu Phe Asp Val Pro His Lys Trp Tyr Gln Gly Ala Gln Glu Ala Ala
 1045 1050 1055
 Ile Ala Thr Arg Glu Glu Leu Ala Glu Met Asp Glu Thr Leu Met Arg
 1055 1060 1065 1070
 Ala Arg Arg His Ser Tyr Ser Ser Phe Ser Lys Leu Leu Glu Ala Tyr
 1075 1080 1085
 Leu Leu Val Lys Trp Arg Met Cys Glu Ala Arg Glu Pro Ser Val Asp
 1090 1095 1100
 Leu Arg Leu Pro Leu Cys Ala Gly Ile Asp Pro Leu Asn Ser Asp Pro
 1105 1110 1115
 Phe Leu Lys Met Val Ser Val Gly Pro Met Leu Gln Ser Thr Arg Lys
 1120 1125 1130
 Tyr Phe Ala Gln Thr Leu Phe Met Ala Lys Thr Val Ser Gly Leu Asp
 1135 1140 1145 1150
 Val Asn Ala Ile Asp Ser Ala Leu Leu Arg Leu Arg Thr Leu Gly Ala
 1155 1160 1165
 Asp Lys Lys Ala Leu Thr Ala Gln Leu Leu Met Val Gly Leu Gln Glu
 1170 1175 1180
 Ser Glu Ala Asp Ala Leu Ala Gly Lys Ile Met Leu Gln Asp Val Asn
 1185 1190 1195
 Thr Val Gln Leu Ala Arg Val Asn Leu Ala Val Pro Asp Thr Trp
 1200 1205 1210
 Met Ser Leu Asp Phe Asp Ser Met Phe Lys His His Val Lys Leu Leu
 1215 1220 1225 1230
 Pro Lys Asp Gly Arg His Leu Asn Thr Asp Ile Pro Pro Arg Met Gly
 1235 1240 1245
 Trp Leu Arg Ala Ile Leu Arg Phe Leu Gly Ala Gly Met Val Met Thr
 1250 1255 1260
 Ala Thr Gly Val Ala Val Asp Ile Tyr Leu Glu Asp Ile His Gly Gly
 1265 1270 1275
 Gly Arg Ser Leu Gly Gln Arg Phe Met Thr Trp Met Arg Gln Glu Gly
 1280 1285 1290
 Arg Ser Ala
 1295

<210> 24
 <211> 1196
 <212> DNA
 <213> Reovirus

<400> 24
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 agggatggga caaaacaatc tcagcacagc cagatatgat ggtatgtggt ggcgccgtcg 180
 tttgcatgca ttgtctaggt gttgttggt ctctacaacg caagctgaag catttgccctc 240
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 gtgttactgc tcaactggaag cgggggtatgc tgtccttcgt tgcgcagatg cagcagatga 360
 tgaatgacgt gtcgccagat gacctggatc gtgtgcgtac tgagggaggt tcaactagtgg 420
 agctgaaccg gcttcaggtt gacccaaatt caatgtttag atcaatacac tcaagttgga 480
 cagatccttt gcaggtggtg gacgaccttg acactaagct ggatcagtac tggacagcct 540
 taaacctgat gatcgactca tccgacttga taccctaact tatgatgaga gacccatcac 600
 acgcgttcaa tgggtgtgaaa ctggaggag atgctcgtca aacccaattc tccaggactt 660
 ttgattcgag atcgagtttg gaatgggggtg tgatggttta tgattactct gagctggagc 720
 atgatccatc gaagggccgt gcttacagaa aggaattggt gacgccagct cgagatttcg 780
 gtcacttttg attatcccat tattctaggg cgactacccc aatccttgga aagatgccgg 840
 ccgtattctc aggaatgttg actgggaact gtaaaatgta tccattcatt aaaggaacgg 900

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ctaagctgaa gacagtgcgc aagctagtgg aggcagtcaa tcatgcttgg ggtgtcgaga 960
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 aggcccccatt tgtgctaact cctgctgctc tcacaatgtt cccagatacc atcaagtttg 1080
 gggatttgaa ttatccagtg atgattggcg atccgatgat tcttggttaa acacccccat 1140
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<210> 25

<211> 370

<212> PRT

<213> Reovirus

<400> 25

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Asn	Ala	Phe	Glu	Gly	Arg	Val	Ser	Ile	Tyr	Ser	Ala	Gln	Glu	Gly	Trp
			20					25					30		
Asp	Lys	Thr	Ile	Ser	Ala	Gln	Pro	Asp	Met	Met	Val	Cys	Gly	Gly	Ala
			35				40					45			
Val	Val	Cys	Met	His	Cys	Leu	Gly	Val	Val	Gly	Ser	Leu	Gln	Arg	Lys
			50				55				60				
Leu	Lys	His	Leu	Pro	His	His	Arg	Cys	Asn	Gln	Gln	Ile	Arg	His	Gln
65					70					75				80	
Asp	Tyr	Val	Asp	Val	Gln	Phe	Ala	Asp	Arg	Val	Thr	Ala	His	Trp	Lys
				85					90					95	
Arg	Gly	Met	Leu	Ser	Phe	Val	Ala	Gln	Met	His	Glu	Met	Met	Asn	Asp
			100					105					110		
Val	Ser	Pro	Asp	Asp	Leu	Asp	Arg	Val	Arg	Thr	Glu	Gly	Gly	Ser	Leu
			115				120					125			
Val	Glu	Leu	Asn	Arg	Leu	Gln	Val	Asp	Pro	Asn	Ser	Met	Phe	Arg	Ser
			130				135				140				
Ile	His	Ser	Ser	Trp	Thr	Asp	Pro	Leu	Gln	Val	Val	Asp	Asp	Leu	Asp
145					150					155				160	
Thr	Lys	Leu	Asp	Gln	Tyr	Trp	Thr	Ala	Leu	Asn	Leu	Met	Ile	Asp	Ser
				165					170					175	
Ser	Asp	Leu	Ile	Pro	Asn	Phe	Met	Met	Arg	Asp	Pro	Ser	His	Ala	Phe
			180					185					190		
Asn	Gly	Val	Lys	Leu	Glu	Gly	Asp	Ala	Arg	Gln	Thr	Gln	Phe	Ser	Arg
			195				200					205			
Thr	Phe	Asp	Ser	Arg	Ser	Ser	Leu	Glu	Trp	Gly	Val	Met	Val	Tyr	Asp
			210				215				220				
Tyr	Ser	Glu	Leu	Glu	His	Asp	Pro	Ser	Lys	Gly	Arg	Ala	Tyr	Arg	Lys
225					230					235				240	
Glu	Leu	Val	Thr	Pro	Ala	Arg	Asp	Phe	Gly	His	Phe	Gly	Leu	Ser	His
245				250					255					260	
Tyr	Ser	Arg	Ala	Thr	Thr	Pro	Ile	Leu	Gly	Lys	Met	Pro	Ala	Val	Phe
			265					270					275		
Ser	Gly	Met	Leu	Thr	Gly	Asn	Cys	Lys	Met	Tyr	Pro	Phe	Ile	Lys	Gly
			280			285						290			
Thr	Ala	Lys	Leu	Lys	Thr	Val	Arg	Lys	Leu	Val	Glu	Ala	Val	Asn	His
			295			300					305				
Ala	Trp	Gly	Val	Glu	Lys	Ile	Arg	Tyr	Ala	Leu	Gly	Pro	Gly	Gly	Met
310					315					320				325	
Thr	Gly	Trp	Tyr	Asn	Arg	Thr	Met	Gln	Gln	Ala	Pro	Ile	Val	Leu	Thr
				330					335					340	
Pro	Ala	Ala	Leu	Thr	Met	Phe	Pro	Asp	Thr	Ile	Lys	Phe	Gly	Asp	Leu
			345					350					355		
Asn	Tyr	Pro	Val	Met	Ile	Gly	Asp	Pro	Met	Ile	Leu	Gly			
			360				365					370			

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<210> 26
 <211> 2203
 <212> DNA
 <213> Reovirus

<400> 26
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 taccatcggt aagcttatca cctggaatgc tgaatcccgg aggggtacca tggattgctg 180
 ttggagatga gacatctgtg acttcaccag gcgcattacg tcgaatgacg tcaaaggaca 240
 tcccggaaac ggcaataatc aacacagaca attcatcagg cgcctgacca agcgaatcag 300
 cgcttgtgcc ctacatcgat gagccgctgg tagtgggttac agagcatgct attaccaact 360
 tcaccaaagc tgagatggca cttgaattca atcgtgagtt ccttgacaag atgcgtgtgc 420
 tgtcagtgtc accaaaatat tcggatcttc tgacctatgt tgactgctac gtcggtgtgt 480
 ctgctcgtaac ggcttttaaac aattttcaga aacaagtgcc tgtgattaca cctactaggc 540
 agacgatgta tgtcgactcg atacaagcgg ccttgaaaagc tttagaaaag tgggagattg 600
 atctgagagt ggctcaaacg ttgctgccta cgaacgttcc gattggagaa gtctcttgtc 660
 caatgcagtc ggtagtgaac ctgctggatg atcagctgcc agatgacacg ctgatacggg 720
 ggtatcccaa ggaagccgcc gtcgctttgg ctaaaccgaa cgggggaata caatggatgg 780
 acgtatcaga aggcaccgtg atgaacgagg ctgtcaacgc tgttgacgct agtgcactgg 840
 caccttcagc atcagcccca cccttagaag agaagtcaaa gttaaccgaa caagcgatgg 900
 atctcgtgac cgcggtcgag cctgagataa ttgcctcact cgcgccagtt cccgcacccg 960
 tgtttgcat accacctaata ccagcagatt ataattgtgcg tactctgagg atcgcagagg 1020
 ccacttggtc gcgaatgatt ccaaaatcaa tgaacacacc ttttcaaact cagggtgactg 1080
 ataacacagg aactaattgg catctcaatt tgaggggggg gactcgtgta gtgaatctgg 1140
 accaaatcgc tccgatgcgg tttgtattag atttaggggg aaagagttat aaagagacga 1200
 gctgggatcc aaacggcaag aaggctcgat tcatcgtttt tcaatcgaag ataccattcg 1260
 aactttggac tgctgcttca cagatcggtc aagccacggg gggttaactat gtccaactat 1320
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 actatgagcc tgagcagttg aataagactg accctgagat gaattattat cttttggcga 1440
 cttttataga ctcagccgct ataacgcca cgaatatgac acagcctgat gtttgggatg 1500
 ctttgctgac gatgtcccca ctatcagctg gcgaggtgac agtgaagggt gcggtagtga 1560
 gtgaagtatg cctgcagac ttgatagta gctacactcc agaatcccta aacgcctcac 1620
 ttccgaatga tgctgctaga tgcattgatc atagagcttc gaagatagcc gaagcaatca 1680
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 tgaaaactag tctgcgtact aaaagtctat cagcgggagt gaagactgca gtgagtaagc 1980
 tgagctcatc tgagtctatc cagaattgga ctcaaggatt cttggataaa gtgtcagcgc 2040
 attttccagc accaaagccc gattgtccga ctagcggaga tagtgggtgaa tcgtctaate 2100
 gccgagtga ggcgcactca tacgcaggag tgggtcaaacg tgggtacaca cgttaggccg 2160
 ctgcacctgg tgacgcgggg ttaagggatg caggcaaatc atc 2203

<210> 27
 <211> 708
 <212> PRT
 <213> Reovirus

<400> 27
 Met Gly Asn Ala Ser Ser Ile Val Gln Thr Ile Asn Val Thr Gly Asp
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 Gly Asn Val Phe Lys Pro Ser Ala Glu Thr Ser Ser Thr Ala Val Pro
 20 25 30
 Ser Leu Ser Leu Ser Pro Gly Met Leu Asn Pro Gly Gly Val Pro Trp
 35 40 45

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Ile Ala Val Gly Asp Glu Thr Ser Val Thr Ser Pro Gly Ala Leu Arg
 50                      55                      60
Arg Met Thr Ser Lys Asp Ile Pro Glu Thr Ala Ile Ile Asn Thr Asp
65                      70                      75                      80
Asn Ser Ser Gly Ala Val Pro Ser Glu Ser Ala Leu Val Pro Tyr Ile
                      85                      90                      95
Asp Glu Pro Leu Val Val Val Thr Glu His Ala Ile Thr Asn Phe Thr
                      100                      105                      110
Lys Ala Glu Met Ala Leu Glu Phe Asn Arg Glu Phe Leu Asp Lys Met
                      115                      120                      125
Arg Val Leu Ser Val Ser Pro Lys Tyr Ser Asp Leu Leu Thr Tyr Val
                      130                      135                      140
Asp Cys Tyr Val Gly Val Ser Ala Arg Gln Ala Leu Asn Asn Phe Gln
145                      150                      155                      160
Lys Gln Val Pro Val Ile Thr Pro Thr Arg Gln Thr Met Tyr Val Asp
                      165                      170                      175
Ser Ile Gln Ala Ala Leu Lys Ala Leu Glu Lys Trp Glu Ile Asp Leu
                      180                      185                      190
Arg Val Ala Gln Thr Leu Leu Pro Thr Asn Val Pro Ile Gly Glu Val
                      195                      200                      205
Ser Cys Pro Met Gln Ser Val Val Lys Leu Leu Asp Asp Gln Leu Pro
210                      215                      220
Asp Asp Thr Leu Ile Arg Arg Tyr Pro Lys Glu Ala Ala Val Ala Leu
225                      230                      235                      240
Ala Lys Arg Asn Gly Gly Ile Gln Trp Met Asp Val Ser Glu Gly Thr
                      245                      250                      255
Val Met Asn Glu Ala Val Asn Ala Val Ala Ala Ser Ala Leu Ala Pro
                      260                      265                      270
Ser Ala Ser Ala Pro Pro Leu Glu Glu Lys Ser Lys Leu Thr Glu Gln
                      275                      280                      285
Ala Met Asp Leu Val Thr Ala Ala Glu Pro Glu Ile Ile Ala Ser Leu
290                      295                      295
Ala Pro Val Pro Ala Pro Val Phe Ala Ile Pro Pro Lys Pro Ala Asp
300                      305                      310                      315
Tyr Asn Val Arg Thr Leu Arg Ile Asp Glu Ala Thr Trp Leu Arg Met
                      320                      325                      330
Ile Pro Lys Ser Met Asn Thr Pro Phe Gln Ile Gln Val Thr Asp Asn
                      335                      340                      345
Thr Gly Thr Asn Trp His Leu Asn Leu Arg Gly Gly Thr Arg Val Val
                      350                      355                      360
Asn Leu Asp Gln Ile Ala Pro Met Arg Phe Val Leu Asp Leu Gly Gly
365                      370                      375
Lys Ser Tyr Lys Glu Thr Ser Trp Asp Pro Asn Gly Lys Lys Val Gly
380                      385                      390                      400
Phe Ile Val Phe Gln Ser Lys Ile Pro Phe Glu Leu Trp Thr Ala Ala
                      405                      410                      415
Ser Gln Ile Gly Gln Ala Thr Val Val Asn Tyr Val Gln Leu Tyr Ala
                      420                      425                      430
Glu Asp Ser Ser Phe Thr Ala Gln Ser Ile Ile Ala Thr Thr Ser Leu
435                      440                      445
Ala Tyr Asn Tyr Glu Pro Glu Gln Leu Asn Lys Thr Asp Pro Glu Met
450                      455                      460
Asn Tyr Tyr Leu Leu Ala Thr Phe Ile Asp Ser Ala Ala Ile Thr Pro
465                      470                      475                      480
Thr Asn Met Thr Gln Pro Asp Val Trp Asp Ala Leu Leu Thr Met Ser
                      485                      490                      495
Pro Leu Ser Ala Gly Glu Val Thr Val Lys Gly Ala Val Val Ser Glu
                      500                      505                      510
Val Val Pro Ala Asp Leu Ile Gly Ser Tyr Thr Pro Glu Ser Leu Asn

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515	520	525
Ala Ser Leu Pro Asn Asp	Ala Ala Arg Cys Met	Ile Asp Arg Ala Ser
530	535	540
Lys Ile Ala Glu Ala Ile	Lys Ile Asp Asp Asp	Ala Gly Pro Asp Glu
545	550	555
Tyr Ser Pro Asn Ser Val	Pro Ile Gln Gly Gln	Leu Ala Ile Ser Gln
565	570	575
Leu Glu Thr Gly Tyr Gly	Val Arg Ile Phe Asn	Pro Lys Gly Ile Leu
580	585	590
Ser Lys Ile Ala Ser Arg	Ala Met Gln Ala Phe	Ile Gly Asp Pro Ser
595	600	605
Thr Ile Ile Thr Gln Ala	Ala Pro Val Leu Ser	Asp Lys Asn Asn Trp
610	615	620
Ile Ala Leu Ala Gln Gly	Val Lys Thr Ser Leu	Arg Thr Lys Ser Leu
625	630	635
Ser Ala Gly Val Lys Thr	Ala Val Ser Lys Leu	Ser Ser Ser Glu Ser
645	650	655
Ile Gln Asn Trp Thr Gln	Gly Phe Leu Asp Lys	Val Ser Ala His Phe
660	665	670
Pro Ala Pro Lys Pro Asp	Cys Pro Thr Ser Gly	Asp Ser Gly Glu Ser
675	680	685
Ser Asn Arg Arg Val Lys	Arg Asp Ser Tyr Ala	Gly Val Val Lys Arg
690	695	700
Gly Tyr Thr Arg		
705		

<210> 28

<211> 2304

<212> DNA

<213> Reovirus

<400> 28

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taactcaatg agtgagggtg gattgctaac attcgctcat gccgacagtg agttgctgaa 1620
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<210> 29
 <211> 731
 <212> PRT
 <213> Reovirus

<400> 29

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Met Ala Tyr Ile Ala Val Pro Ala Val Val Asp Ser Arg Ser Ser Glu
1           5           10           15
Ala Ile Gly Leu Leu Glu Ser Phe Gly Val Asp Ala Gly Ala Asp Ala
20          25          30
Asn Asp Val Ser Tyr Gln Asp His Asp Tyr Val Leu Asp Gln Leu Gln
35          40          45
Tyr Met Leu Asp Gly Tyr Glu Ala Gly Asp Val Ile Asp Ala Leu Val
50          55          55
His Lys Asn Trp Leu His His Ser Val Tyr Cys Leu Leu Pro Pro Lys
60          65          70          75
Ser Gln Leu Leu Glu Tyr Trp Lys Ser Asn Pro Ser Ala Ile Pro Asp
80          85          90
Asn Val Asp Arg Arg Leu Arg Lys Arg Leu Met Leu Lys Lys Asp Leu
95          100         105
Arg Lys Asp Asp Glu Tyr Asn Gln Leu Ala Arg Ala Phe Lys Ile Ser
110         115         120
Asp Val Tyr Ala Pro Leu Ile Ser Ser Thr Thr Ser Pro Met Thr Met
125         130         135
Ile Gln Asn Leu Asn Arg Gly Glu Ile Val Tyr Thr Thr Thr Asp Arg
140         145         150         155
Val Ile Gly Ala Arg Ile Leu Leu Tyr Ala Pro Arg Lys Tyr Tyr Ala
160         165         170
Ser Thr Leu Ser Phe Thr Met Thr Lys Cys Ile Ile Pro Phe Gly Lys
175         180         185
Glu Val Gly Arg Val Pro His Ser Arg Phe Asn Val Gly Thr Phe Pro
190         195         200
Ser Ile Ala Thr Pro Lys Cys Phe Val Met Ser Gly Val Asp Ile Glu
205         210         215
Ser Ile Pro Asn Glu Phe Ile Lys Leu Phe Tyr Gln Arg Val Lys Ser
220         225         230         235
Val His Ala Asn Ile Leu Asn Asp Ile Ser Pro Gln Ile Val Ser Asp
240         245         250
Met Ile Asn Arg Lys Arg Leu Arg Val His Thr Pro Ser Asp Arg Arg
255         260         265
Ala Ala Gln Leu Met His Leu Pro Tyr His Val Lys Arg Gly Ala Ser
270         275         280
His Val Asp Val Tyr Lys Val Asp Val Val Asp Met Leu Phe Glu Val
285         290         295

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Val Asp Val Ala Asp Gly Leu Arg Asn Val Ser Arg Lys Leu Thr Met
 300 305 310 315
 His Thr Val Pro Val Cys Ile Leu Glu Met Leu Gly Ile Glu Ile Ala
 320 325 330
 Asp Tyr Cys Ile Arg Gln Glu Asp Gly Met Leu Thr Asp Trp Phe Leu
 335 340 345
 Leu Leu Thr Met Leu Ser Asp Gly Leu Thr Asp Arg Arg Thr His Cys
 350 355 360
 Gln Tyr Leu Met Asn Pro Ser Ser Val Pro Pro Asp Val Ile Leu Asn
 365 370 375
 Ile Ser Ile Thr Gly Phe Ile Asn Arg His Thr Ile Asp Val Met Pro
 380 385 390 395
 Asp Ile Tyr Asp Phe Val Lys Pro Ile Gly Ala Val Leu Pro Lys Gly
 400 405 410
 Ser Phe Lys Ser Thr Ile Met Arg Val Leu Asp Ser Ile Ser Ile Leu
 415 420 425
 Gly Ile Gln Ile Met Pro Arg Ala His Val Val Asp Ser Asp Glu Val
 430 435 440
 Gly Glu Gln Met Glu Pro Thr Phe Glu Gln Ala Val Met Glu Ile Tyr
 445 450 455
 Lys Gly Ile Ala Gly Val Asp Ser Leu Asp Asp Leu Ile Lys Trp Val
 460 465 470 475
 Leu Asn Ser Asp Leu Ile Pro His Asp Asp Arg Leu Gly Gln Leu Phe
 480 485 490
 Gln Ala Phe Leu Pro Leu Ala Lys Asp Leu Leu Ala Pro Met Ala Arg
 495 500 505
 Lys Phe Tyr Asp Asn Ser Met Ser Glu Gly Arg Leu Leu Thr Phe Ala
 510 515 520
 His Ala Asp Ser Glu Leu Leu Asn Ala Asn Tyr Phe Gly His Leu Leu
 525 530 535
 Arg Leu Lys Ile Pro Tyr Ile Thr Glu Val Asn Leu Met Ile Arg Lys
 540 545 550 555
 Asn Arg Glu Gly Gly Glu Leu Phe Gln Leu Val Leu Ser Tyr Leu Tyr
 560 565 570
 Lys Met Tyr Ala Thr Ser Ala Gln Pro Lys Trp Phe Gly Ser Leu Leu
 575 580 585
 Arg Leu Leu Ile Cys Pro Trp Leu His Met Glu Lys Leu Ile Gly Glu
 590 595 600
 Ala Asp Pro Ala Ser Thr Ser Ala Glu Ile Gly Trp His Ile Pro Arg
 605 610 615
 Glu Gln Leu Met Gln Asp Gly Trp Cys Gly Cys Glu Asp Gly Phe Ile
 620 625 630 635
 Pro Tyr Val Ser Ile Arg Ala Pro Arg Leu Val Ile Glu Glu Leu Met
 640 645 650
 Glu Lys Asn Trp Gly Gln Tyr His Ala Gln Val Ile Val Thr Asp Gln
 655 660 665
 Leu Val Val Gly Glu Pro Arg Arg Val Ser Ala Lys Ala Val Ile Lys
 670 675 680
 Gly Asn His Leu Pro Val Lys Leu Val Ser Arg Phe Ala Cys Phe Thr
 685 690 695
 Leu Thr Ala Lys Tyr Glu Met Arg Leu Ser Cys Gly His Ser Thr Gly
 700 705 710 715
 Arg Gly Ala Ala Tyr Ser Ala Arg Leu Ala Phe Arg Ser Asp Leu Ala
 720 725 730

<210> 30

<211> 423

<212> PRT

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<213> Reovirus

<400> 30

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Met Ala Arg Ala Ala Phe Leu Phe Lys Thr Val Gly Phe Gly Gly Leu
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Gln Asn Val Pro Ile Asn Asp Glu Leu Ser Ser His Leu Leu Arg Ala
          20          25          30
Gly Asn Ser Pro Trp Gln Leu Thr Gln Phe Leu Asp Trp Ile Ser Leu
          35          40          45
Gly Arg Gly Leu Ala Thr Ser Ala Leu Val Pro Thr Ala Gly Ser Arg
          50          55          60
Tyr Tyr Gln Met Ser Cys Leu Leu Ser Gly Thr Leu Gln Ile Pro Phe
65          70          75          80
Arg Pro Asn His Arg Trp Gly Asp Ile Arg Phe Leu Arg Leu Val Trp
          85          90          95
Ser Ala Pro Thr Leu Asp Gly Leu Val Val Ala Pro Pro Gln Val Leu
          100          105          110
Ala Gln Pro Ala Leu Gln Ala Gln Ala Asp Arg Val Tyr Asp Cys Asp
          115          120          125
Asp Tyr Pro Phe Leu Ala Arg Asp Pro Arg Phe Lys His Arg Val Tyr
130          135          140
Gln Gln Leu Ser Ala Val Thr Leu Leu Asn Leu Thr Gly Phe Gly Pro
145          150          155          160
Ile Ser Tyr Val Arg Val Asp Glu Asp Met Trp Ser Gly Asp Val Asn
          165          170          175
Gln Leu Leu Met Asn Tyr Phe Gly His Thr Phe Ala Glu Ile Ala Tyr
          180          185          190
Thr Leu Cys Gln Ala Ser Ala Asn Arg Pro Trp Glu Tyr Asp Gly Thr
          195          200          205
Tyr Ala Arg Met Thr Gln Ile Val Leu Ser Leu Phe Trp Leu Ser Tyr
          210          215          220
Val Gly Val Ile His Gln Gln Asn Thr Tyr Arg Thr Phe Tyr Phe Gln
225          230          235          240
Cys Asn Arg Arg Gly Asp Ala Ala Glu Val Trp Ile Leu Ser Cys Ser
          245          255          260
Leu Asn His Ser Ala Gln Ile Arg Pro Gly Asn Arg Ser Leu Phe Val
          265          270          275
Met Pro Thr Ser Pro Asp Trp Asn Met Asp Val Asn Leu Ile Leu Ser
          280          285          290
Ser Thr Leu Thr Gly Cys Leu Cys Ser Gly Ser Gln Leu Pro Leu Ile
          295          300          305
Asp Asn Asn Ser Val Pro Ala Val Ser Arg Asn Ile His Gly Trp Thr
310          315          320          325
Gly Arg Ala Gly Asn Gln Leu His Gly Phe Gln Val Arg Arg Met Val
          330          335          340
Thr Glu Phe Cys Asp Arg Leu Arg Arg Asp Gly Val Met Thr Gln Ala
          345          350          355
Gln Gln Asn Gln Val Glu Ala Leu Ala Asp Gln Thr Gln Gln Phe Lys
          360          365          370
Arg Asp Lys Leu Glu Thr Trp Ala Arg Glu Asp Asp Gln Tyr Asn Gln
          375          380          385
Ala His Pro Asn Ser Thr Met Phe Arg Thr Lys Pro Phe Thr Asn Ala
390          395          400          405
Gln Trp Gly Arg Gly Asn Thr Gly Ala Thr Ser Ala Ala Ile Ala Ala
          410          415          420
Leu Ile

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